The Impact of Genetic Study on Radiological Diagnosis of Osteochondrodysplasias

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Ordered Approach to Diagnosis

• Assessment of disproportion
• Epiphyseal ossification
• Physes and metaphyses
• Diaphyses
• Vertebral bodies and ribs
• Bone density
• Dislocations, missing things, extra things
Assessment of disproportion

Rhizomelia

Mesomelia

Acromelia
Epiphyseal Ossification

- Target sites
  - Talus and Calcaneus
    - 24-28 weeks gest
  - Proximal tibial epiphysis and distal femoral
    - At full term birth
  - Proximal humeral epiphysis
    - By 42 weeks GA
  - Femoral heads
    - 4-7 months

18 months old, Kniest
Physes and Metaphyses

- Irregularity at the physis is frequently indicative of a metaphyseal chondrodysplasia

Schmid Metaphyseal Chondrodysplasia
2 yo
Diaphyses

- Gracile and thin doesn’t help
- Thick cortices or other findings does!

Camurati-Engelmann Syndrome

*J Med Genet* 2006;43:1-11
Bone Density

• Markedly increased density
  – Craniotubular disorder
  – Osteopetrosis
  – Pyknodysostosis

• Decreased density
  – Osteogenesis imperfecta
  – nonspecific
Dislocations, Missing and Extra Things

- Usually an easy trait to focus on
- Multiple dislocation syndromes
  - Larsen
  - Desbuquois
- Disordered carpus
  - Includes OPD
• Find something to hang your hat on and follow that into the wormhole
Recent advances in molecular genetics have led to a revolution in the diagnosis of skeletal dysplasias
• They are not floating in space isolated from each other
Radiographic and clinical similarities combined with genetic study now shows us that these dysplasias are related
Role of Radiology

- Since many dysplasias are related, it is more important for us to diagnose the general “family”
- Identifying familial relationships helps us to a more specific diagnosis
- Provides direction for the geneticist for possible sequencing
Familial Nature of Genetic Disease

• As the study of genetics has progressed, we now recognize several “families” of dysplasias
  – As a result, nomenclature has been largely restructured.
Familial Nature of Genetic Disease

- Sulfatase abnormalities - Mucopolysaccaridoses
- Fibroblast growth receptor (FGFR) 3- achondroplasia
- Sulfate transporter - diastrophic dysplasia
- Aryl Sulfatase E - chondrodysplasia punctata
- FGFR 2 - crouzon's, Aperts
- Filamin - OPD, Larsen’s
- Collagen 2 - SED-c, Kniest
Familial Nature of Genetic Disease

- Sulfatase abnormalities
- Fibroblast growth receptor 3
- Sulfate transporter
Sulfatase Abnormalities

- Includes most of the mucopolysaccharidoses
- Site of action of these sulfatases is lysosomal and is mostly involved with degradation of proteoglycans
Glycosaminoglycans

- Glycosaminoglycan = mucopolysaccharide
- Chondroitin sulfate - cartilage, tendons, ligaments, aorta - Sly’s
- Dermatan sulfate - skin, blood vessels, valves - Maroteaux-Lamy, Hurler’s, Hunter’s
- Heparan sulfate - vessel walls, brain, cell surface - Hurler’s, Hunter’s, San Filippo
- Keratan sulfate - cornea, cartilage - Morquio’s
Hurler’s Disease
Hunter’s Disease
Hunter’s Disease
Hurler’s Disease
Morquio’s Disease
Tongues Central vs Inferior
Sophisticated Approach

- A molecular based approach with an understanding of causes of dysplasia and avoids baby talk
Familial Nature of Genetic Disease

- Sulfatase abnormalities
- Fibroblast growth receptor 3
- Sulfate transporter
Fibroblast Growth Factor Receptor 3 Function

- Decreases velocity of endochondral ossification
- Causes slowing of chondrocyte division at physis
- Increases chondrocyte proliferation at perichondrium
• Too much FGFR3 is made which slows the velocity of endochondral ossification
• Acts through upmodulation of tyrosine kinase switch
• Same switch affected by gleevec and related drugs
Fibroblast Growth Factor Receptor 3 Abnormalities

- Thanatophoric dysplasia
- Homozygous achondroplasia
- Achondroplasia
- Hypochondroplasia
• Constitute a spectrum of abnormalities characterized by short thick bones with metaphyseal splaying
• Short skull base
• Vertebral abnormalities ranging from platyspondyly to pediculate shortening
Thanatophoric Dysplasia

- Short skull base
- +/- cloverleaf skull
- Frontal bossing
- Severe platyspondyly
- Severe micromelia
- Metaphyseal splaying
Homozygous Achondroplasia

- Similar to heterozygous achondroplasia but findings are more severe
- Lies between achondroplasia and thanatophoria on the spectrum of abnormalities
Achondroplasia

- Short skull base
- Frontal bossing
- Rhizomelia
- Metaphyseal splaying
- Pediculate shortening
- Trident hands with brachydactyly
Hypochondroplasia

- Similar to achondroplasia but less severe
- Very variable
Homozygous Achondroplasia
Achondroplasia
Thanatophoric Dysplasia
Homozygous Achondroplasia
Achondroplasia
Familial Nature of Genetic Disease

- Sulfatase abnormalities
- Fibroblast growth receptor 3
- Sulfate transporter
Sulfate Transporter Gene

- transports sulfate into the cell for use in the sulfation of proteoglycans
Sulfate Transporter Abnormalities

- Achondroplasia type IB
- Atelosteogenesis type II
- Diastrophic dysplasia
• Describe a spectrum of abnormality from little sulfation of proteoglycans
• To moderate decrease
• To mild decrease in sulfation
Sulfation Rates

- Achondroplasia Ib 34%
- Atelosteogenesis II 50%
- Diastrophic dysplasia 70%
- Normal 95%
Clinical findings

Achondroplasia 1b
- Micromelia
- Cleft palate
- Short trunk
- Lethal
- Cryptorchidism
- Inguinal hernias
- Ear deformities
- Hitchhiker thumb

Atelosteogenesis 2
- Micromelia
- Cleft palate
- Radial/ulnar finger deviation
- Joint dislocations
- Midface hypoplasia
- Clubfoot
- Hitchhiker thumb

Diastrophic Dysplasia
- Micromelia
- Cleft palate
- Ulnar hand deviation
- Ear deformities
- Joint dislocations
- Cryptorchidism
- Inguinal hernia
- Clubfoot
- Hitchhiker thumb
Radiologic findings

Achondrogenesis 1b
- poorly mineralized skull
- Poorly ossified vertebral bodies
- Absent pubic, ischial ossification
- Short, thick, bowed bones
- Proximal placement of first metacarpal

Atelosteogenesis 2
- Vertebral hypoplasia and clefts
- Short bowed bones
- Proximal placement of first metacarpal

Diastrophic dysplasia
- Hypoplasia of cervical vertebral bodies
- Posterior process clefting
- Platyspondyly
- Scoliosis
- Proximal placement of first metacarpal
- Short thick bones
Achondrogenesis 1B

- poorly mineralized skull
- Poorly ossified vertebral bodies
- Absent pubic, ischial ossification
- Short, thick, bowed bones
- Concave ends of tubular bones with multiple spurs
- Hitchhiker thumb
Atelosteogenesis Type 2

- Vertebral hypoplasia and clefts
- Short bowed bones
- Dumbbell femurs
- Gap between digits 1 & 2
- Hitchhiker thumb
- Clubfoot
Diastrophic Dysplasia

- Vertebral hypoplasia and clefts
- Scoliosis
- Joint dislocations
- Hitchhiker thumb
- Short thick bones
- Clubfoot
- Ossification of pinna and laryngeal cartilages
Achondrogenesis Ib
Atelosteogenesis II
Diastrophic Dysplasia
Pseudoachondroplasia

• COMP gene family
• Allelic to:
Multiple Epiphyseal Dysplasia
MED Variance

- Some of MED is due to a defect of DDST gene
- Clue was miniepiphyses with joint dislocation and double layered patella
Conclusion

• If a definite specific diagnosis can be made….then do so
• If not, then try to identify the correct family of abnormality and be happy