How to approach a patient with an unknown Skeletal Dysplasia.

Basics and Mnemotechnique

5th European Course in Clinical Dysmorphology

Rome, Nov 2013

Jürgen Spranger
Skeletal Dysplasias are numerous

> 400 listed in the "Nosology and Classification of Genetic Skeletal Disorders"

but individually rare.

Achondroplasia: 0.5-0.8/10,000
Osteogenesis imperfecta: 0.4-0.7/10,000

They are

Orphan Diseases

(<1:10,000)
Patient with an Orphan Disease

The Challenge:

A) Diagnosis
B) Management
### Why establish a diagnosis?

<table>
<thead>
<tr>
<th>Area of impact</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<td>Labeling</td>
<td><strong>A diagnosis</strong>….. - puts parents to rest - stops unnecessary procedures</td>
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<td>allows for….. - primary prevention (genetic counseling) - secondary prevention (prenatal diagnosis, fetocide) - removes guilt</td>
<td>- may create guilt - involves genetic manipulation - may, in its consequences, reduce the number of handicapped persons</td>
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<td>- may remove hope incl. reduced life expectancy (‘cannot take more’)</td>
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How to make a diagnosis

1) THE 'HUNCH‘ APPROACH

Shooting from the hip
1) The hunch approach

- Proportionate dwarfism
  (normal head circumference)
- Triangular face
- Birth weight 2.500g (40wk gest)

Russel-Silver Dwarfism

Hypomethylation 11p15 negative (≈30% +)
UPD7 negative (≈10% +)
• Proportionate dwarfism
  (normal head circumference)
• Triangular face
• Birth weight 2.500g (40wk gest)

Examination: Thoracic deformity

History: Nuchal edema in utero

2nd hunch: Noonan Syndrome

Confirmatory test: PTPN11 +
The hunch approach is likely to fail if you rely on single signs or symptoms.

In Skeletal Disorders:

Never make a diagnosis from a single film

Recognize and memorize patterns, i.e. samples of abnormalities of form and/or structure of bone(s)

Achondroplasia

...but even the pattern may not be specific...!
The 'hunch' approach never works in a case like this.

5 years' history, short stature, global developmental delay, choanal stenosis, sleep apnoeas, myopia, hypothyreosis, short left leg, skoliosis, dilatative cardiomyopathy, anemia, osteoporosis.

Osteochondrodysplasia
Johannsen-Blizzard-Syndrome
Binder Syndrome
Chondrodysplasia punctata
Pseudohypoparathyreoidism

Acrodysostosis
How to make a diagnosis

2) THE ‘PANNING‘ APPROACH

Basic rule 1 1

Before you see the patient
Prepare yourself …
Obtain data from history and examination

Reduce
complex findings
into

Core complaints
Core signs
= a Pattern

Core complaints
Core signs
= a Pattern
Parents may be more knowledgeable than you think

Get an Idea ...

Enter Relevant data = core findings
Good diagnostic sign
Yes          No

Poor diagnostic sign
More         Less

are always abnormal

may be normal

[Graph showing normal distribution with 95% and 99.7% confidence intervals]
Scientific consensus: A phenomenon or event that occurs with a frequency of less than $1:100 (= <1\text{\%ile})$ is rare enough to build a hypothesis, namely that it is nonaccidental, i.e. caused by an 'accident'.

...but in an individual case you never know if it is a variant or an anomaly.
A 15 year old boy with repeated fractures and other abnormalities

Multiple fractures

Osteogenesis imperfecta

Molecular analysis

COL 1 negative

hunch
- Iris coloboma,
- Hexadactyly
- Ureteral stenosis
- Hypospadias
- Clavicular pseudarthrosis
A 15 year old boy with repeated fractures and other abnormalities.

- Iris coloboma,
- Polydactyly
- Ureteral stenosis
- Hypospadias
- Clavicular psseudarthrosis

**Examination**

- 1st fracture at age 11, 2nd and 3rd after immobilisation
- Short stature (158 cm)
- Microphthalmia
- Preaxial
- Absent anthelix
- Deviated nasal septum
- Delayed eruption of lower incisors, microdontia
A 15 year old boy with repeated fractures and other abnormalities

Files

History → Multiple fractures + Coloboma

First idea

Osteogenesis imperfecta

Second idea

Osteoporosis-Pseudoglioma Syndrome?
Osteoporosis Pseudoglioma syndrome?

- Hexadactyly
- Dental Anomalies
- Hypospadias

Not consistent with diagnosis
Ideas

Osteogenesis imperfecta
Osteoporosis Pseudoglioma Syndrome

not sustained

Add physico-chemical data;
e.g. Skeletal Radiographs
Skeletal Dysplasia X-ray Survey

- Hand
- Pelvis
- Lateral Spine
- Knee
- General
Slender bones

Patient

Primordial dwarfism

Kenny-Caffey Syndrome

Intrauterine hypomobility

Osteocraniostenosis
These differential diagnoses

(Primordial dwarfism
Kenny-Caffey Syndrome
Intrauterine hypomobility)

could explain

- Slender bones
- Fractures
- Short stature (158 cm)

but not

- Iris coloboma, microphthalmia
- Preaxial polydactyly
- Ureteral stenosis
- Absent anthelix
- Deviated nasal septum
- Delayed eruption of lower incisors, microdontia
- Hypospadias
Go to database again
Remember Selection Criteria

good

poor

rare

frequent

dis-continuous

continuous

primary

secondary
1st fracture at age 11, Iris coloboma, microphthalmia
• Preaxial polydactyly
• Ureteral stenosis
• Absent anthelix
• Hypospadias

2nd and 3rd fractures after immobilisation
• Short stature (158 cm)
• Deviated nasal septum
• Delayed eruption of lower incisors, microdontia
<table>
<thead>
<tr>
<th>Pivotal findings</th>
<th>O.i.</th>
<th>Ostp</th>
<th>Ocular</th>
<th>Goltz-Gorlin Syndrome</th>
</tr>
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<tbody>
<tr>
<td>Slender bones (fractures)</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Short stature</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Coloboma, microphthalmia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Preaxial polydactyly</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
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<tr>
<td>Ureteral stenosis</td>
<td>+</td>
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<td>Absent anthelix</td>
<td>+</td>
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<td>Delayed dentition</td>
<td>+</td>
<td></td>
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<td>Hypospadias</td>
<td>+</td>
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<td></td>
<td></td>
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<td>Clavicular pseudarthrosis</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
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</table>
Clinical Diagnosis: Lenz Microphthalmia Syndrome

Confirm clinical diagnosis with special test, e.g. molecular analysis

BCOR mutation
Clinical Diagnosis: 

? 

Confirm clinical diagnosis with special test, e.g. molecular analysis 

Not confirmed 

Retinitis pigmentosa Nephropathy Hypertension 

17 years 

Time 

18 mo 

17 years 

Craniofacial conodysplasia ? 

NGS 

≈ 25%
## Why establish a diagnosis?

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-stops unnecessary procedures | **A diagnosis**  
- stereotypes the child,  
puts them into a box‘ |
| Etiology       | allows for…..  
-primary prevention (genetic counseling)  
-secondary prevention (prenatal diagnosis, fetocide)  
-removes guilt | -may create guilt  
-involves genetic manipulation  
-may, in its consequences, reduce the number of handicapped persons |
| Prognosis      | allows for…..  
-tertiary prevention (incl. raised life expectancy)  
-formulation of realistic expectations and goals | -may remove hope  
-incl. reduced life expectancy (‘cannot take more)‘ |

- it will make you proud
- it is fun to learn
The task: Diagnosis

5 years, short stature, global developmental delay, choanal stenosis, sleep apnoeas, myopia, hypothyreosis, short left leg, skoliosis, dilatative cardiomyopathy, anemia, osteoporosis.

Acrodysostosis

Osteochondrodysplasia
Johannsen-Blizzard-Syndrome
Binder Syndrome
Chondrodysplasia punctata
Pseudohypoparathyreoidism
G-Protein

Parathyroid hormone

PTH-Receptor

Pseudohypoparathyreoidism

IA  IB  PPH

PDE4D

PDE4D

Inactive PKA Active PKA

PRKAR1

GNAS

Acrodysostosis 1

Acrodysostosis 2

AMP

PDE4D

cAMP

ATP

Protein - P

Protein - P

+ +

++

Adenylate cyclase

AMP
---but finally, with or without a diagnosis, you have filed the data. You will classify, name and store them. You will bring order to chaos by classifying.

Classifying is a memorizing technique.

Historical perspective on developmental concepts and terminology
John M. Opitz1,*, Giovanni Neri2
Journal of Medical Genetics Part A
Special Issue: Special Issue: The Giovanni Neri Festschrift
Volume 161, Issue 11, pages 2711–2725, November 2013

Classis 1. Mammalia
Classis 2. Aves
Classis 3. Amphibia
Classis 4. Pisces
Classis 5. Insecta.
Classis 6. Vermes
Classification of Bone Dysplasias
Development, growth, homeostasis, degeneration of bone are highly complex involving a myriad of causative mechanisms, all of which can fail and result in too many diseases to remember. The human brain handles this by grouping, categorizing, classifying individualized disorders.

Proteins
- COMP
- Matrilin
- Perlecan
- Filamin
- Microfibrils

Lysosomal enzymes
- Alkaline phosphatase

N-Ac-glucosamine-P-transferase
- Sialic acid transporter

PAPS Synthetase

Sulfate transporter SLC25A2
- Carbohydrate sulfotransferases

Signal Transduction Hormones
- FGFR3

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Signal Transduction Hormones
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Transcription factors
- DNA/RNA Processing
  - SOX 9 (SRY-related HMG Box gene 9)
  - SHOX (Short stature homeobox gene)
  - RMRP (RNA-processing endoribonuclease)
  - SMARCAL 1 (chromatin regulator)

Cytoskeleton Organelles
- Actin filaments
- Filamins
- Golgi apparatus
- Microtubules
Nosology and Classification of Genetic Skeletal Disorders: 2010 Revision

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Martine LeMerrer,1 Geert Mortier,1 Stefan Mundlos,6 Gen Nishimura,6 David L. Rimoin,4
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Genetic disorders involving the skeletal system arise through disturbances in the complex processes of skeletal development, growth and homeostasis and remain a diagnostic challenge because of their variety. The Nosology and Classification of Genetic Skeletal Disorders provides an overview of recognized diagnostic entities and groups thereby clinical and radiographic features and molecular pathogenesis. The aim is to provide the Genetics, Pediatrics and Radiology community with a list of recognized genetic skeletal disorders that can be of help in the diagnosis of individual cases, in the delineation of novel disorders, and in building bridges between clinicians and scientists interested in skeletal biology. In the 2010 revision, 496 conditions were included and placed in 48 groups defined by molecular, biochemical, and/or radiographic criteria. Of these conditions, 344 were associated with mutations in one or more of 220 different genes ranging from common, recurrent mutations to “private” found in single families or individuals. Thus, the Nosology is a hybrid between a list of clinically defined...
### Morphologic („Folk“) Classification

(Folk taxonomy)

Classification according to shared physical characteristics

e.g. Color, Size, Form, Structure, Function

<table>
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<tr>
<th>Bent bones dysplasias</th>
<th>Inheritance</th>
<th>MIM</th>
<th>Chromosomal Location</th>
<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campomelic dysplasia (CD)</td>
<td>AD</td>
<td>114290</td>
<td>17q24.3-25.1</td>
<td>SOX9</td>
<td>SRY-box 9</td>
</tr>
<tr>
<td>Stüve-Wiedemann dysplasia</td>
<td>AR</td>
<td>601559</td>
<td>5p13.1</td>
<td>LIFR</td>
<td>Leukemia Inhibitory Factor Receptor</td>
</tr>
<tr>
<td>Kyphomelic dysplasia, several forms</td>
<td>?</td>
<td>211350</td>
<td>heterogeneous</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

### Scientific Classification

(ScientificTaxonomy)

Classification based on common descent (Darwin)

a. Pathogenetic
b. Etiopathogenetic

### File Unclassified bent bone

(better would be ‘Kyphomelia’ to indicate ‘Symptom’ rather than ‘Disease’)

![X-ray image of bent bones]
Mnemotechniques

• Morphological Classification
Morphologic classification of Skeletal Dysplasias
[according to size, form, structure of bone(s)]

A. Dysplastic tubular bones with or without spine involvement
B. Localized dysplasias
B. Abnormal Bone Density
C. Signs of anarchic bone development
D. Osteolyses
A- Dysplasia of tubular bones with/without spinal dysplasia
B. Localized Bone Dysplasias

Spinal  Rhizomelic  Mesomelic  Acral
C. Anarchic bone development

e.g. Exostoses
e.g. Enchondromata
e.g. Dysplasia epiphysealis hemimelica
D. Abnormal Bone Density

Decreased

Increased
### E. Osteolyses

<table>
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<tr>
<th>Type</th>
<th>Localisation</th>
<th>Inheritance</th>
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<tr>
<td>Torg-Winchester syndrome</td>
<td>carpo-tarsal</td>
<td>AR</td>
</tr>
<tr>
<td>Multicentric-carpo-tarsal osteolysis</td>
<td>carpo-tarsal</td>
<td>AD</td>
</tr>
<tr>
<td>Hajdu-Cheney syndrome</td>
<td>distal phalanges</td>
<td>AD</td>
</tr>
<tr>
<td>Mandibuloacral dysplasia A</td>
<td>distal phalanges</td>
<td>AR</td>
</tr>
<tr>
<td>Mandibuloacral dysplasia B</td>
<td>distal phalanges</td>
<td>AR</td>
</tr>
<tr>
<td>Familial expansile osteolysis</td>
<td>diffuse</td>
<td>AD</td>
</tr>
<tr>
<td>Gorham syndrome</td>
<td>diffuse</td>
<td>unknown</td>
</tr>
</tbody>
</table>
Mnemotechniques

- Morphological Classification
- Preliminary Causal Classification
Preliminary Pathogenetic Classification

Normal variant

Malformation  Disruption  Dysplasia  Deformation

Diagram showing the progression from normal variant to malformation, disruption, dysplasia, and deformation.
a gene -acting in blastogenesis producing a malformation
-acting in organogenesis producing a metaphyseal dysplasia
**Early-onset gene expression**
- Persistent
- Dysostosis - Dysplasia

**Temporally limited gene expression**
- Dysostosis

**Late embryonic gene expression**
- Congenitally manifest Dysplasia

**Postnatal gene expression**
- Postnatally manifest Dysplasia

**Embryogenesis**

**Birth**

**Ellis van Creveld**
Mnemotechniques

- Morphological Classification
- Preliminary Cause-related Classification
  Grouping in developmental families
- Final Cause-related Classification
  Grouping in etiologic and pathogenetic Families
Similar phenotypes are often causally related. They represent 

Etiologic (molecular) or Pathogenetic Families
Disease or Entity

Sydenham 1624-1689

Hippokrates 460-370 BC

---

Cause

Etiology
The primary causes
a) Disruptive factors
b) Genome

Pathogenesis
The cascade of secondary changes
Proteome

Phenotype
The sum of morphologic and functional changes

Allelic mutations
Non-allelic mutations

Natural course
Families

a) a common etiology (allelic mutations)
b) a common pathogenesis (e.g. pathways/affected structures)

results in

Similar Phenotypes

Disease or Entity

- Etiology
  - The primary causes
    - Genome

- Pathogenesis
  - The cascade of secondary changes
    - Proteome

- Phenotype
  - The sum of morphologic and functional changes

Allelic mutations

Non-allelic mutations

Natural course
A. Etiologic family  (Allelic heterogeneity)
Mucopolysaccharidosis III-B

Mucopolysaccharidosis II

Mucopolysaccharidosis I

Mucopolysaccharidosis III-A

Mucopolysaccharidosis III-C

Mucopolysaccharidosis III-B

Mucopolysaccharidosis III-D

Heparan sulfate

B. Pathogenetic Family

(non-allelic heterogeneity)
The pattern of

Dysostosis multiplex

MPS II

ML II

MPS III

MPS I

MPS IV
Short rib (- polydactyly ) family

Ellis-van Creveld syndrome

Asphyxiating thorax dysplasia

SRP Verma-Naumoff
Ciliary basal body structure participating in hedgehog signal transduction

Anterograde transport protein \textit{IFT 80}

Retrograde transport protein \textit{DYNC2H1}

Ziliopathies

ATD

SRP Saldino-Noonan

SRP Verma-Naumoff

SRP Langer-Beemer
Diastrophic Dysplasia Family

SO₄

mutation

Adenosine-5-Phospho-SO₄

3-P-Adenosine-5-P-SO₄

Undersulfated Proteoglykan

SO₄

Diastrophic dysplasia

Autos. recessive MED

Achondrogenesis 1B

Atelosteogenesis II (de la Chapelle)
TRPV4
transient receptor potential cation channel

Bracholmia, AD
Spondylometaphyseal d. Kozlowski
Metatropic dysplasia
Mnemotechniques
Summary

The present classification system uses
Morphologic Criteria (‘bent bones‘)

Pathogenetic criteria
  a. Gross: Developmental (Dysplasia Malformation)
  b. Fine: Pathogenetic families (‘MPSoses‘,’Ciliopathies‘)

Etiologic criteria (Molecular families (‘FGFR3‘)
The greatest gift to parents of a child with an orphan disease which we cannot heal is
to know a place where they can go and
find a person who cares