EDS TODAY

and

TOMORROW
• NO financial disclosures

• Currently at Cincinnati Children’s Hospital
• As of 9/1/12, will be at Lutheran General Hospital in Chicago

• Also serve on the Board of Directors of the Ehlers-Danlos National Foundation (all Directors are volunteers)
What is EDS?

- Ehlers-Danlos syndrome(s)
- A group of inherited (genetic) disorders of connective tissue
- Named after Edvard Ehlers of Denmark and Henri-Alexandre Danlos of France
## Ehlers-Danlos Syndrome Classifications

<table>
<thead>
<tr>
<th>Villefranche 1997</th>
<th>Berlin 1988</th>
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<tbody>
<tr>
<td><strong>Classical Type</strong></td>
<td>Gravis (Type I)</td>
</tr>
<tr>
<td></td>
<td>Mitis (Type II)</td>
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<tr>
<td><strong>Hypermobile Type</strong></td>
<td>Hypermobile (Type III)</td>
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<td><strong>Vascular Type</strong></td>
<td>Arterial-ecchymotic (Type IV)</td>
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<td><strong>Kyphoscoliosis Type</strong></td>
<td>Ocular-Scoliotic (Type VI)</td>
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<td><strong>Arthrochalasia Type</strong></td>
<td>Arthrochalasia (Type VIIA, B)</td>
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<tr>
<td><strong>Dermatosporaxis Type</strong></td>
<td>Dermatosporaxis (Type VIIC)</td>
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</tbody>
</table>
2012?
Other Variants

- X-Linked EDS (EDS Type V)
- Periodontitis type (EDS Type VIII)
- Familial Hypermobility Syndrome (EDS Type XI)
  - Benign Joint Hypermobility Syndrome
  - Hypermobility Syndrome
- Progeroid EDS
- Marfanoid habitus with joint laxity
- Unspecified Forms
• Brittle cornea syndrome
  • PRDM5
  • ZNF469

• Spondylocheiro dysplastic

• Musculocontractural/adducted thumb clubfoot/Kosho
  • D4ST1 deficient EDS

• Tenascin-X deficiency
# Ehlers-Danlos Syndromes -- Etiology

<table>
<thead>
<tr>
<th>EDS Type</th>
<th>Genetic Defect</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical</td>
<td>Type V collagen (60%) Other?</td>
<td>Dominant</td>
</tr>
<tr>
<td>Hypermobile</td>
<td>Largely unknown</td>
<td>Dominant</td>
</tr>
<tr>
<td>Vascular</td>
<td>Type III collagen</td>
<td>Dominant</td>
</tr>
<tr>
<td>Kyphoscoliosis</td>
<td>Lysyl hydroxylase (PLOD1)</td>
<td>Recessive</td>
</tr>
<tr>
<td>Arthrochalasia</td>
<td>Type I collagen</td>
<td>Dominant</td>
</tr>
<tr>
<td>Dermatosporaxis</td>
<td>ADAMTS2</td>
<td>Recessive</td>
</tr>
</tbody>
</table>
Joint Hypermobility
Beighton’s Criteria for Generalized Joint Hypermobility

1. Passive dorsiflexion of 5th digit to or beyond 90°
2. Passive flexion of thumbs to the forearm
3. Hyperextension of the elbows beyond 10°
   1. >10° in females
   2. >0° in males
4. Hyperextension of the knees beyond 10°
   1. Some knee laxity is normal
   2. Sometimes difficult to understand posture-forward flexion of the hips usually helps
5. Forward flexion of the trunk with knees fully extended, palms resting on floor
   1. May be negative in those with flat feet and tight hamstrings

Age-adjusted
Race/ethnic-adjusted

1 point for each side
A score of at least 5 defines hypermobility
Throughout the world, how people do the examination varies

The cut-off value can vary

Should it vary by age, gender, or race?

These and more are being questioned with more to come as well
Clinical Features: Classical EDS

Major Diagnostic Criteria

- Skin hyperextensibility
- Widened atrophic scars
- Generalized joint hypermobility

Inheritance: Autosomal dominant

Incidence: 1 in 10,000--15,000
Atrophic Scarring

- Often pre-tibial
- Develops in early childhood from the “bumps and bruises”
- Fragile or friable skin
- “cigarette paper”
“Mild” classic EDS may not have atrophic scars initially until injury or surgery!!!!

Therefore may be difficult to distinguish from hypermobile type
• Symoens et al., 2012
  • Using all of the major criteria, >90% of cEDS patients had mutations in the type V collagen genes (COL5A1/COL5A2)

• Proposed: cEDS only defined with these criteria making those with milder features that overlap with type III (hypermobility) likely grouped together
EDS-Hypermobility Type

Major Diagnostic Criteria

• Mild skin hyperextensibility with velvety texture *subjective*
• Normal or near-normal scarring
• Generalized joint hypermobility

Inheritance: Autosomal Dominant
Genetic causation: Unknown
Incidence: ≥ 1 in 5,000???????????????
Minor Diagnostic Criteria

• Recurring joint dislocations
• Chronic joint/limb pain
• Positive family history
Hypermobile Syndrome
The 1998 Revised Brighton Criteria

Major criteria
• Beighton score of 4 (either currently or historically)
• Arthralgia for 3 months in 4 joints

Minor criteria
• Beighton score of 1, 2, or 3 (0-3 if age 50 years or older)
• Arthralgia (3 months) in 1-3 joints or back pain (3 months),
• Spondylosis, spondylolisthesis
• Dislocation/subluxation in 1 joint, or in 1 joint on 1 occasion
• Soft tissue rheumatism 3 lesions (e.g., epicondylitis, tensosynovitis, bursitis)
• Marfanoid habitus (tall, slim, span:height ratio 1.03, upper: lower segment 0.89, arachnodactyly)
• Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring
• Eye signs: drooping eyelids or myopia or antimongoloid slant
• Varicose veins or hernia or uterine/rectal prolapse

* The diagnosis of benign joint hypermobility syndrome (BJHS) requires the presence of 2 major criteria, or 1 major + 2 minor criteria, or 4 minor criteria, or 2 minor criteria and an unequivocally affected first-degree relative. BJHS is excluded by the presence of Marfan’s syndrome or Ehlers-Danlos syndrome (EDS), other than hypermobility-type EDS.
Vascular EDS

Major Diagnostic Criteria

• Thin translucent skin
• Extensive bruising
• Characteristic facial appearance
• Organ rupture

Inheritance: Autosomal dominant
Genetic cause: COL3A1 (type III collagen)
Incidence: 1 in 15,000--20,000
Vascular EDS Clinical presentation

- Purpura
- Massive internal bleeding
- Spontaneous bowel rupture
- Peripartum uterine hemorrhage
Vascular EDS

Associated Features

• Acrogeria
• Hypermobility of small joints
• Tendon and muscle rupture
• Talipes equinovarus (clubfoot)
• Early-onset varicose veins
• Arterio-venous fistula
Major Criteria

• Generalized joint laxity
• Severe muscle hypotonia
• Kyphoscoliosis, usually early onset
• Scleral fragility

Inheritance: Autosomal recessive
Genetic cause: PLOD1
Kyphoscoliosis Types

Type VIA
• Two mutations in PLOD1 (lysyl hydroxylase gene)

Type VIB
• No mutation in PLOD1
• Some feel that this is Brittle Cornea Syndrome
• Also known as:
  • Musculocontractural
  • Adducted thumb clubfoot
  • Kosho type
• D4ST1 deficient EDS
• Will it remain VIB or another form altogether? Is it a type of EDS?
Arthrochalasia Type (VIIA/B)

Major Criteria

• Severe joint laxity with recurrent dislocations in many joints
• Congenital, bilateral hip dislocation

Inheritance

Autosomal dominant
Arthrochalasia Type

Etiology

Mutations in either COL1A1 or COL1A2 that interfere with amino-terminal propeptide cleavage of proα1(I) or proα2(I) chains respectively.
Dermatospororaxis Type (VIIC)

Major Criteria

• Severe skin fragility
• Sagging, redundant skin (not hyperextensible)

Inheritance

Autosomal recessive
Dermatospororaxis Type

Etiology

Homozygous mutations in Type I collagen amino-peptidase and deficiency of the enzyme.
Then the hard part.....
Defining the various aspects of each type

The even harder part is improving the health of all affected