Inheritable Connective Tissue Diseases: Or It’s Probably Not Marfan’s

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This pretty much sums it up.
Inheritable Connective tissues diseases

- A homogenous collection of varied syndromes with a similar phenotype; HYPERMOBILITY
- Typically caused by a defect in the genes required for structural proteins i.e. elastin or collagen
- I suspect that they are wildly under diagnosed at large.
List of stuff

- Ehlers-Danlos Syndrome
  - Hypermobility type, vascular, classic and mixed
- Loeys-Dietz Syndrome
- Peyrionie’s Disease (giggle)
- Stickler Syndrome
- Congenital Contractural Arachnodactyly (Beel’s)
- Bicuspid aortic valve (?)
- Benign Familial Hypermobility
- Marfan’s Syndrome
Why do cardiologists care about connective tissue diseases

- Because the heart and vessels are made of connective tissues too!
- There can be significant cardiac manifestations
  - Valve dysfunction
  - Cardiac Dysfunction
  - Arrhythmia
  - ...And of course aortic dissection
What is aortic dissection?

<table>
<thead>
<tr>
<th>De Bakey Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stanford Type A</td>
<td>Type B</td>
<td>Type C</td>
</tr>
<tr>
<td>Type III</td>
<td></td>
<td>Originalising aorta, propagated beyond it distally regardless of the ascending aorta</td>
</tr>
<tr>
<td>Stanford Type A</td>
<td>All dissections involving the ascending aorta, regardless of the Stanford Type B</td>
<td></td>
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<tr>
<td>Stanford Type B</td>
<td>All dissections not involving the ascending aorta</td>
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- De Bakey Type I: Originalising aorta, propagated beyond it distally regardless of the Stanford Type B.
- Stanford Type A: All dissections involving the ascending aorta, regardless of the Stanford Type B.
- Stanford Type B: All dissections not involving the ascending aorta.
Okay sure, but how bad is it?

Really it’s pretty bad

Guess which type of aortic dissection our connective tissue disease patients are at risk for?

At baseline...

- Aortic dissections occur at roughly 5-30 million people a year.
- Untreated Marfan’s patients carry a risk of roughly 0.8%/year of acute dissection.
- When we replace the roots ahead of time we can expect < 2% mortality on the 30 day prospectus.
- We really want to catch these patients before they have problems.
Fibrillin-1

- Extracellular matrix protein
- The core building block of microfibrils that are used with elastin fibers
- Elastin is the stringy aspect of our tissues.

Kinsey et al. 2008
This is the offending gene in Marfans

- Our understanding of this gene accounts for the
  - Hypermobility
  - Marfan Phenotype
- Doesn’t really explain
  - Muscle abnormalities
  - Long bone overgrowth
  - Abnormal subcutaneous fat
TGF-B

- Normally important
  - Regulates cell cycle
  - Regulates apoptosis
  - Causes cell differentiation
  - Plays a critical role in extracellular structure
Some cool physiology

- Fibrillin grabs TNF-B
- Defective fibrillin doesn’t
- Mice who received TGF-B blocking antibodies didn’t develop the stigmata of mitral valve disease or aortic root dilation.
Which brings us to...

- Marfans
  - Arachnodactyly
  - Tall and thin
  - Scoliosis
  - Pectus excavatum/carianatum
  - Hypermobility
  - Pes Planus
  - Poor tooth alignment
  - Stretch marks
Are just those things diagnostic?

NO
More specific findings

- Aortic dilation
- Ectopia Lentis
- FBN1 Deletions
- Wrist and thumb sign
- Hindfoot deformity
- Plain flat foot
- Spontaneous Pneumothorax
- Dural Ectasia
- Protucio Acetabulae

- Scoliosis
- Reduced elbow extension
- Skin Striae
- Severe Myopia
- Mitral valve prolapse
- Increase wingspan/reduced upper segment ratio
Aortic Root dilation
Ectopia Lentis
Wrist and thumb sign
Hindfoot deformity
PES PLANUS
Spontaneous Pneumothorax
Dural Ectasia
Protrusio
Acetabuli
Scoliosis
Stretch marks
Mitral Valve prolapse
Wingspan
Ghent criteria

- In the absence of family history
  - 1. Aortic root dilation AND Ectopia Lentis
  - 2. Aortic root dilation AND an FBN1
  - 3. Aortic root dilation AND 7 pts on the the stigmata scale
  - 4. Ectopia Lentis AND an FBN1 mutation
With a family history

- Ectopia Lentis
- 7 points on the scale
- Aortic root dilation (degree depends on age)
So what about people who don’t meet criteria

- They probably have a different disease
Loeys-Dietz

- Positive for aortic root enlargement
- Skeletal stuff
- Dural Ectasia
What’s different

- Craniosynostosis
- Arterial Tortuosity
- Cleft palate
- Club foot
- Cervical Spine instability
- No ectopia lentis
- Hypertelorism
- Easy bruising
- Translucent skin
Aortic Root Size doesn’t matter for these kids!

- They dissect at pretty much any size root
Familial Thoracic Aortic Aneurysm and Dissection

- Like Marfans without the stretchy stuff
- Unique findings:
  - Iris Flocculi
  - No ectopia lentis
  - No dural ectasia
Shprintzen-Goldberg

- Has
  - Mitral Valve prolapse
  - Systemic Findings
  - Myopia
- Unique
  - Craniosynostosis
  - Hypertelorism
  - Significant cognitive delay
  - Aortic root involvement rare
  - C1-C2 malformations
Homocysteinuria

• In common with Marfans
  • Ectopia Lentis!
  • Mitral Valve prolapse
  • Skeletal findings

• Unique
  • Developmental delay
  • Seizures
  • Thrombosis
Beals Syndrome

**Commonalities:**
- Mitral Valve prolapse
- Aortic involvement
- General skeletal stuff

**Differences:**
- Finger contractures
- Crumpled ear
- Motor delay
- No dissection really
Stickler Syndrome

- Stickler Syndrome
  - Myopia, retinal detachment
  - Joint hypermobility
  - Scoliosis
  - Mitral Valve prolapse

- Differences:
  - Hearing involvement
  - Chorioretinal and vitreous degeneration
  - Orofacial involvement
  - Osteoarthritis as a prominent features
MASS Phenotype

- Mitral valve disease
- Aortic Root Involvement
- Skin findings
- Skeletal Findings
- Myopia

- Minimal risk of dissection
- No ectopia lentis
- No smoking gun genetically
Ehler’s Danlos Syndrome

- Four “main” categories
  - Vascular type
  - Hypermobility type
  - Kyphoscoliotic Type
  - Classic Type

- Genetic causes
  - Collagen defects
  - Or PLOD1
Vascular EDS

- Arterial, intestinal, uterine fragility
- Facial phenotype
- Translucent skins
- Easy bruising
- Dystropic scars

Hindawi et al 2011
Kyphoscoliotic EDS

• Presents at birth to first of life
• Scleral Fragility
• Severe hypotonia
• Friable hyperextensible
• Generalized joint laxity
Classic Type

- Skin fragility
- Atrophic Scars
- Joint laxity
- Aortic root dilation
- Dermatographia
Hypermobility type...or is it benign familial hypermobility syndrome?

- So EDS is a big ol’ mess of diagnoses of similar phenotypes (marfanoid + skin stuff) that covers a huge breadth of diseases with widely variable pathology.

<table>
<thead>
<tr>
<th>Name of EDS Subtype</th>
<th>IP†</th>
<th>Genomic Basis</th>
<th>Protein Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classical EDS (sEDS)</td>
<td>AD</td>
<td>Major: COL5A1, COL5A2</td>
<td>Type V collagen</td>
</tr>
<tr>
<td>Classical-like EDS (nEDS)</td>
<td>AR</td>
<td>Rare: COL5A1 c.3040+7, p.(His1013fs)</td>
<td>Type I collagen</td>
</tr>
<tr>
<td>Cardio-vascular EDS (cEDS)</td>
<td>AR</td>
<td>COL5A2 splicing mutations that lead to COL5A2 NMD and absence of pro (A)I collagen chains</td>
<td>Type I collagen</td>
</tr>
<tr>
<td>Vascular EDS (vEDS)</td>
<td>AD</td>
<td>Major: COL5A1 c.3040+7, p.(His1013fs) c.12720+T, p.(Arg2740fs) c.32720+T, p.(Arg1090fs)</td>
<td>Type I collagen</td>
</tr>
<tr>
<td>Hypermobile EDS (hEDS)</td>
<td>AD</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Asthenosclerotic EDS (aEDS)</td>
<td>AD</td>
<td>COL1A1, COL1A2</td>
<td>Type I collagen</td>
</tr>
<tr>
<td>Dermalosarcoma EDS (dEDS)</td>
<td>AR</td>
<td>ADAMTS2</td>
<td>ADAMTS2</td>
</tr>
<tr>
<td>Kyphoscoliotic EDS (kEDS)</td>
<td>AR</td>
<td>PLOD1</td>
<td>L1H</td>
</tr>
<tr>
<td>Brittle cornea syndrome (BCS)</td>
<td>AR</td>
<td>ZNF469</td>
<td>ZNF469</td>
</tr>
<tr>
<td>Spinal hypotonic dystrophy (SHD)</td>
<td>AR</td>
<td>B4GALT7</td>
<td>B4GALT7</td>
</tr>
<tr>
<td>Spondylocostal dysostosis (sCOSD)</td>
<td>AR</td>
<td>SLC26A15</td>
<td>SLC26A15</td>
</tr>
<tr>
<td>Musculoskeletal EDS (mEDS)</td>
<td>AR</td>
<td>GHST1</td>
<td>GHST1</td>
</tr>
<tr>
<td>Hypertrophic EDS (hEDS)</td>
<td>AD or AR</td>
<td>COL1A2</td>
<td>Type XII collagen</td>
</tr>
<tr>
<td>Periosteal EDS (pEDS)</td>
<td>AD</td>
<td>CHR</td>
<td>Chr</td>
</tr>
</tbody>
</table>
Where to start

- Beighton
  - It’s a screening tool
  - It’s not diagnostic

Pull little finger back beyond 90°
(one point for each side)

Pull thumb back to touch forearm
(one point for each side)

Bend elbow backwards beyond 10°
(one point for each side)

Bend knee backwards beyond 10°
(one point for each side)

Lie hands flat on floor while keeping knees straight and bending forward at waist
Even this test is kind of a mess

- >4 is suggestive of Benign Joint Hypermobility syndrome
- >5 in adults or 6 in kids is concerning for EDS...

- I have no idea why 1 point on this test carries so much weight.
- Generally I look to systemic involvement to lean more towards connective tissue disease vs benign phenomena
Next step

- In the presence of skin fragility I think that the genetic testing is appropriate.
- If the aortic root is appreciably enlarged then I also recommend genetic testing.
- Otherwise I bump them into a “screening pool” with the diagnosis of hypermobility type with annual or every other year screening.
Chasing a meaningful diagnosis.

- Diagnostic criteria:
  - Must have a positive Beighton
  - Two of the following
    - Systemic manifestations of generalized connective tissue disease
    - Family history of a relative who meets criteria
    - Musculoskeletal complications

- Can’t have any of the other diseases that we’ve discussed

- Big rule outs:
  - Skin fragility
  - On going autoimmune disease
Systemic manifestations

- Soft velvety skin
- Skin hyperextensibility
- Striae
- Piezogenic papules of the heel
- Recurrent hernias
- Atrophic Scarring, but not as bad as classic EDS
- Rectal prolapse
- Dental crowding
- Arachnodactyly
- Wingspan >1.05
- Aortic Root z>2
- Mitral Valve prolapse

- Have to have 5 of these
Musculoskeletal Complications

- Pain in two or more limbs of 3 months
- Chronic widespread pain for 3 months
- Recurrent joint dislocation
- Have to have one.
These kids have all the complaints
The internet has kind of ruined this diagnosis, which is why stringent application of the diagnostic criteria is so important.
So this is it

- We care about connective tissue disease because there is real risk of morbidity if it goes undetected
- We also care because it can account for a lot of non-specific complaints

- When to refer?
  - A positive beighton
  - Multiple stigma present, but failing to meet diagnostic criteria
Thanks!