Ehlers-Danlos Syndrome and the Overlap with Orthostatic Intolerance

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PRESENTATION

Summary:
- Ehlers-Danlos Syndrome (EDS) is a heterogeneous disorder of connective tissue characterized by varying degrees of skin hyperextensibility, joint hypermobility, and cutaneous fragility.
- Most forms of EDS result from mutations in genes encoding fibrillar collagens or the collagen-modifying enzymes.

Presenter Disclosure Information

Peter C. Rowe, MD
• No relationships to disclose

EDS, JH, and Orthostatic Intolerance

Overview of Ehlers-Danlos Syndrome
Illustrative case
Orthostatic intolerance in EDS and JH
Challenges

Classification of EDS

Classification of EDS:
- Classical (formerly EDS I and II)
- Hypermobility (formerly EDS III)
- Vascular (formerly EDS IV)
- Kyphoscoliosis
- Arthrochalasia
- Dermatosparaxis


Presentation Slide:
- Image of 3 generations with Classical EDS.
- Note: hemosiderin deposition in knees and shins, varicose vein stripping on R.
### Updated EDS Classification

<table>
<thead>
<tr>
<th>EDS subtype</th>
<th>Inheritance pattern</th>
<th>Protein</th>
<th>Gene</th>
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</thead>
<tbody>
<tr>
<td>Classic</td>
<td>AR</td>
<td>Collagen Type V</td>
<td>COL5A1, COL5A2</td>
</tr>
<tr>
<td>Marfan-like</td>
<td>AR</td>
<td>Tropomodulin</td>
<td>TPM3</td>
</tr>
<tr>
<td>Beighton</td>
<td>AR</td>
<td>Procollagen</td>
<td>COL1A1, COL1A2</td>
</tr>
<tr>
<td>Vascular</td>
<td>AR</td>
<td>Procollagen</td>
<td>COL1A1, COL1A2</td>
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<td>Kyphoscoliosis</td>
<td>AR</td>
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<td>COL1A1, COL1A2</td>
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<td>X-linked</td>
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<td>Behringer</td>
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<td>COL1A1, COL1A2</td>
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<td>Arthrosclerotic</td>
<td>AR</td>
<td>Procollagen</td>
<td>COL1A1, COL1A2</td>
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<tr>
<td>ELS/Arthritis</td>
<td>AR</td>
<td>Procollagen</td>
<td>COL1A1, COL1A2</td>
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<tr>
<td>Dermatosclerotic</td>
<td>AR</td>
<td>Procollagen</td>
<td>COL1A1, COL1A2</td>
</tr>
</tbody>
</table>

### Presentations suggestive of EDS

- **Joints:** Hypermobility, Dislocations, Pain
- **Skin:** Bruising, Hyperextensibility, Atrophic scars, Striae
- **Vessels/hollow organs:** Rupture, Sudden death
- **Other features:** GI dysmotility, Kyphoscoliosis, Chiari, Pneumothorax, Organ ptosis or prolapse

*Sobey G. Clinical Medicine 2016;14:432, Castori M. ISRN Dermatology 2012*
Beighton score (possible scores 0-9):
On each side, 1 point for > 90° hyperextensibility of 5th finger, 1 point for thumb to forearm, and 1 for > 10° hyperextensibility at elbow.

Gender and EDS

“The striking preponderance of affected women vs. men in EDS-HT is presently unexplained.”


Gender and joint hypermobility

<table>
<thead>
<tr>
<th>Country</th>
<th>Ages</th>
<th>Males</th>
<th>Females</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA (1987) N=260</td>
<td>5-17</td>
<td>7%</td>
<td>18%</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Israel (1991) N=429</td>
<td>6-14</td>
<td>8%</td>
<td>18%</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>USA (1997) N=264 athletes</td>
<td>12-19</td>
<td>6%</td>
<td>22%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Iceland (1999) N=267</td>
<td>12</td>
<td>13%</td>
<td>41%</td>
<td>&lt;.001</td>
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</tbody>
</table>

On each side, 1 point for >10° hyperextensibility at knees, 1 point for palms to floor.

TABLE I. The 1998 Beighton Criteria for a Diagnosis of Benign Joint Hypermobility Syndrome (Grahame et al., 2000)

Major criteria
1. Beighton score of ≥4/9
2. Articularia for > 3 months in >4 joints

Minor criteria
1. Beighton score of ≥1–3
2. Articularia in 1–3 joints
3. History of joint dislocation
4. Soft tissue lesions > 3
5. Marfan-like habitus
6. Skin striae, hyperextensibility, or scarring
7. Eye signs, Ike Henby
8. History of varicose veins, hernia, visceral prelapse

For a diagnosis to be made either
- Both of the major criteria must be present
- OR one major and two minor
- OR four minor
- And other disorders of connective tissue need be excluded
Ehlers-Danlos Syndrome
Illustrative case
Orthostatic intolerance in EDS and JH
Challenges

24 yr old with fatigue, LH, warmth

No syncope, but vision goes black, hearing distant
Brings knees to chest when seated; studies lying down; stays in motion when standing
Hands and feet often appear purple
Sensation of warmth or heat when upright for long periods

24 yr old with fatigue, LH, warmth

Worried about having to stand for long periods of time for clinical rotations in PA school
Energy fairly good
Shoulders sublux easily
HR 60 supine in early AM, 90s during day
Normal mood; laid-back disposition

24 yr old with fatigue, LH, warmth

O/E: Tall, thin young woman
Wt 62 kg; ht 180.2 cm (>97th); BMI 19.1
Easy eversion of lids; + Gorlin’s sign; can touch tongue to elbow, place leg behind head
BS = 7/9; no arachnodactyly
Lordotic posture
Cardiac exam normal
Echo and labs normal

The Lack of Clinical Distinction Between the Hypermobility Type of Ehlers–Danlos Syndrome and the Joint Hypermobility Syndrome (a.k.a. Hypermobility Syndrome)

It is our collective opinion that BHS/HMS and EDS hypermobility-type represent the same phenotypic group of patients that can be differentiated from other HCTDs but not distinguished from each other. Clinically, we serve this population better by uniting the two diagnostic labels.
Course

“The atenolol at 12.5 mg seems to be working well. My upright HR has remained lower, ranging from 60-95. Hot flashes are significantly less frequent, no headaches, much easier time with exercising as well. My resting HR has usually been in the high 50s. No side effects. BP 105/70. Should I stay at 12.5 mg or is it OK to go to 25mg?”

Possible treatments

• Midodrine
• Methylphenidate
• Beta blocker
• Mestinon
• Resume oral contraceptives
• Desmopressin acetate
• ARB/ACE inhibitor

Course

• Increased LH and fatigue as temperatures rise in the late spring
• Adds midodrine, with benefit for energy.
• Tries dexedrine as an alternative (sib on this)
• On dexedrine with atenolol, feels 100%.
• Appetite suppression on dexedrine; now uses it only on days when upright longer, taking midodrine on other days

What we tried:

• Midodrine
• Methylphenidate
• Beta blocker
• Mestinon
• Resume oral contraceptives (stopping them associated with ↑symptoms)
• Desmopressin acetate
• ARB/ACE inhibitor

EDS, JH, and Orthostatic Intolerance

Overview of Ehlers-Danlos Syndrome
Illustrative case
Orthostatic intolerance in EDS and JH
Challenges
**Is neurally mediated hypotension an unrecognised cause of chronic fatigue?**

Peter C Rowe, Issam Bou-Hailagah, Jean S Kan, Hugh Cahkins


**The Relationship Between Neurally Mediated Hypotension and the Chronic Fatigue Syndrome**

Issam Bou-Hailagah, MD; Peter C. Rowe, MD; Jean Kan, MD; Hugh Cahkins, MD

*JAMA* 1995;274:961-7

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**Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome**

Peter C. Rowe, MD; Donna F. Marston, MD; Hugh Cahkins, MD; Irene H. Movassess, MD; Patrick Y. Tang, MD, PhD; and Michael T. Cauthen, MD, MPH

Of 100 adolescents seen in the CFS clinic at JHH over a 1 year period, we identified 12 subjects with EDS (P < .01, binomial test)

- 6 classical-type
- 6 hypermobile-type EDS

11 females, 1 male


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**EDS features in 12 patients with CFS**

- Median Beighton score = 7 (range 5-9)
- Joint dislocations in 12/12
- Joint surgery in 3/12
- Acrocyanosis in 12/12
- Localized skin hyperextensibility (most commonly eyelid) in 12/12
- Papyraceous scars in 6/12
EDS in CFS Patients With Orthostatic Intolerance

5 had at least 3 episodes of syncope
7 had lightheadedness, but no syncope
NMH in 9/12, POTS in 10/12

Beighton Joint Hypermobility Scores in 58 Adolescents With CFS And 58 Healthy Controls

Dysautonomia in Adult JHS

• Subjects:
  – 48 consecutive patients with joint hypermobility syndrome
  – 30 healthy controls
• Methods
  – Questionnaire of symptoms
  – Autonomic testing in a subset

Dysautonomia in JHS: Results

• OI symptoms more common in JHS patients
  – LH, syncope, palpitations, fatigue, impaired concentration, dyspnea, tremulousness, nocturia
• OI more common
  – 78% of JHS vs. 10% of controls had OI
  • Mix of OH, POTS and uncategorized OI
  – Standing time: 14.5 (6) vs. 19 (3.5) min

Joint hypermobility is more common in children with chronic fatigue syndrome than in healthy controls

Study question: do children with CFS have a higher prevalence of joint hypermobility?
Beighton scores obtained in 58 new & 58 established CFS patients, and in 58 controls
Median Beighton scores higher in CFS (4 vs. 1)
Beighton score ≥ 4 higher in CFS (60% vs. 24%)

Young adult with EDS (patellar dislocations, pneumothoraces, CFS, recurrent syncope)
Dysautonomia in JHS

Dose to increase HR 15 bpm

Dose to increase SBP 15 mm Hg

Differences between POTS+JH vs POTS alone

<table>
<thead>
<tr>
<th>Feature</th>
<th>POTS+JH N=26</th>
<th>POTS alone N=39</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>30±13</td>
<td>40±11</td>
<td>.01</td>
</tr>
<tr>
<td>Female gender</td>
<td>100%</td>
<td>90%</td>
<td>.07</td>
</tr>
<tr>
<td>Migraine</td>
<td>73%</td>
<td>28%</td>
<td>.001</td>
</tr>
<tr>
<td>Syncope</td>
<td>62%</td>
<td>30%</td>
<td>.04</td>
</tr>
<tr>
<td>Viral onset</td>
<td>0%</td>
<td>15%</td>
<td>.07</td>
</tr>
</tbody>
</table>


Differences between POTS+JH vs POTS alone

Response to tilt

Proposed mechanisms for the association of JH/EDS and OI syndromes

1. Connective tissue laxity in blood vessels allows increased vascular compliance, promotes excessive pooling during upright posture, leading to diminished blood return to the heart, and thus to OI symptoms. (Rowe PC, et al. J Pediatr 1999;135:494-9)

2. Physical inactivity as a result of joint dislocations and pain “may be disabling due to associated anxiety, depression, and a somatosensory amplification state; this may lead to secondary hyperadrenergic responses triggered by fear of pain on standing.” (Benarroch EE. Mayo Clin Proc 2012;87:1214-25)


4. Could the excessive mobility of the cervical cord lead to transient, dynamic compression and autonomic symptoms? (Nehrir AZ. Fibromyalgia Research 2012)

5. Other shared factor
What about prognosis in EDS with POTS?

- 16 yr old who had been a healthy dancer and swimmer, develops LH at 12.
- HR 78 to 125, SBP 104 to 84 with presyncope at 7 min of HT
- Beighton score=7/9
- Blue sclerae, Gorlin sign, snapping scapula.
- Wellness score in 2010=40/100

Conclusions

- Females have a higher prevalence of JH and EDS-hypermobile type than males
- CFS patients with OI have an increased prevalence of EDS and JH
- Dysautonomia and OI are more common in those with EDS/JH
- Subjects with POTS + JH present earlier
- The mechanisms for the association between JH/EDS and OI syndromes are not known
- Improvement is common and recovery can occur

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