Making Sense of Hypermobility Syndromes:

MARCIA FRIEDMAN, MD
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Disclosures

I have no relevant disclosures
Objectives

1. Diagnosing hypermobility: the Beighton score
2. Joint hypermobility vs joint hypermobility syndrome (JHS)
3. JHS vs Ehlers Danlos-hypermobility type (EDS-HT)
4. DDx of hypermobility
5. Management: MSK and associated features
6. When and where to refer?
Case:

• 25 year old man with years of generalized pain.
• Reports dislocating his shoulder twice, has never been the same.
• Feet, knees, back hurt, can’t do a lot of exercise without being in pain.
• ROS: often feels lightheaded, constipation alternating with diarrhea, generally fatigued
FIG. 2. A drawing by a 25-year-old man with JHS/EDS-HT illustrating his musculoskeletal, craniofacial, and neurologic symptoms. The widespread and multisystemic derangement typical of this condition clearly emerges from this autonomously administrated, symptom evaluation procedure. Though not standardized, this method illustrates what the patient feels and thinks about his symptoms and offer an invaluable instrument to rapidly correlate symptoms with body parts. The various question marks scattered in the picture exemplify the major concerns the patient has about his symptoms. Annotations are in Italian.
Case con’t

• On exam:
  • Thin, tired, but otherwise healthy-appearing young man
  • Tender over the left knee, left shoulder, and low spine/paraspinal muscles.
  • No joint effusions, no synovitis, has flexible joints.
  • Few bruises, otherwise normal appearing skin
  • Remainder of his exam is normal

• Is he hypermobile? Can we be any more specific?

• Does he have an underlying heritable connective tissue disorder?

• Are his complaints connected? How can we help him?
Joint hypermobility = Beighton score ≥ 4/9

Give yourself 1 point for each of the manoeuvres you can do, up to a maximum of 9 points.

- Can you bend your thumb back onto the front of your forearm?
- Can you put your hands flat on the floor with your knees straight?
- Can you bend your knee backwards >10 degrees?
- Can you bend your elbow backwards >10 degrees?
- Can you bend your little finger up at 90° (right angles) to the back of your hand?
Hypermobility vs. Joint Hypermobility Syndrome (JHS)

• Hypermobility is relatively common, especially in young people, women, and Asian/African ancestry.

• Most hypermobile people are asymptomatic and do not have an underlying connective tissue disorder.

• Joint hypermobility syndrome: heritable connective tissue disorder with pain, dislocations, bursitis, tendonitis, fatigue, dysautonomia, and multi-system involvement.
Joint hypermobility syndrome (JHS): Brighton criteria

(...not to be confused with Beighton score)
Now that you’ve diagnosed JHS...

“I looked this up, and I’m pretty sure I have EDS!”

“Do you mind if I get a second opinion off the internet?”
Does this patient have EDS-hypermobility type (EDS-HT)...

**Must meet 1, 2, and 3:**

1. **Beighton score ≥ 4/9**

2. **Two or more of the following:**
   - Systemic manifestation of a connective tissue disorder with ≥ 5 of the following: unusually soft/velvety skin, mild skin hyper-extensibility, unexplained striae, bilateral piezogenic papules of the heel, atrophic scars, recurrent or multiple abdominal hernias, pelvic floor/rectal/uterine prolapse without clear cause, dental crowding or high/narrow palate, arachnodactyly, arm span to height ≥ 1.5, MVP, or aortic root dilatation
   - Positive family history with 1 or more 1º relatives affected
   - MSK complications ≥1 of the following: MSK pain in two or more limbs for at least 3 months, chronic widespread pain for ≥ 3 months, recurrent joint dislocations in the absence of trauma

3. **None of the following:**
   - Unusual skin fragility (consider other types of EDS)
   - Other heritable or acquired connective tissue disorder (if you do, must have both 2A and 2B)
   - Alternative diagnosis associated with hypermobility
Are JHS and EDS-HT the same condition?

- Clinically indistinguishable
- Neither has an objective diagnostic test, molecular cause, or known gene mutation
- JHS: Brighton criteria (from rheum literature)
- EDS-HT: Villefranche criteria (from peds/genetics literature)
- Is JHS a mild variant of EDS-HT? Are they the same condition?
- Increasingly these are thought of as interchangeable or at least part of the same spectrum.

What else could this be? Ddx..

1. Other forms of EDS:
   - Many other forms, but most are extremely rare and have severe phenotypes from a young age.
   - Classic EDS: skin is a significant finding
   - Vascular EDS: arterial ruptures/dissections

2. Marfan Syndrome:
   - Tall stature, family history of Marfan or aortic dissection, pectus deformities, arachnodactyly, myopia, lens dislocations

3. Loey’s Dietz:
   - Widely spaced eyes, cleft palate/bifid uvula, severe arterial tortuosity. Arterial aneurysms/dissections

4. Osteogenesis Imperfect:
   - Fragile bones, frequent fractures, blue sclera
Skin Hyper-extensibility: Classic EDS

Test at a neutral site, such as volar surface of the forearm or neck.
Pull skin up until resistance is felt.
Ability to stretch the skin 4cm or more
Difficult in children due to subcutaneous fat

http://www.forgottendiseases.org/assets/EhlersDanlos_Classic_Type1_Type2.html

Tissue Fragility: Classic EDS

Presence of easy bruising and dystrophic scars

Scars are mostly on pressure points: knee, elbow, forehead, chin and have a thin papyraceous appearance.

Scars are frequently wide and discolored, wound healing is impaired
A. Post-traumatic, atrophic and widened scar

B. Skin stretching between examiner’s fingers shows mild atrophy of the underlying dermis

C. Atrophic and widened scar due to wound healing delay after nevus excision

D. Papyraceous and hemosideric scar after repetitive wound opening with molluscoid psuedotumor

E. Papyraceous scar and cutis laxa

F. Subcutaneous spheroid

G. Huge molluscoid psuedotumor
**Classic EDS**

**Genetics**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
<th>Mode of Inheritance</th>
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<tbody>
<tr>
<td>COL5A1/COL5A2</td>
<td>1/20,000</td>
<td>Autosomal dominant</td>
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</table>

**Classification criteria**

**Major:**
1. Skin hyper-extensibility and wide atrophic scars
2. Joint hypermobility

**Minor:**
1. Easy bruising
2. Soft, doughy skin
3. Skin fragility (traumatic tearing)
4. Molluscoid pseudotumors
5. Subcutaneous spheroids
6. Hernias
7. Epicanthal folds
8. Complications of joint hypermobility

Positive family hx

**Criteria to prompt confirmatory testing:**
- Both major criteria OR
- Skin hyper-extensibility and atrophic scars + ≥ 3 minor

**Genetic testing:** COL5A1/5A2

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### Vascular EDS

#### Genetics

| COL3A1 | 1/100,000 | Autosomal dominant |

#### Classification criteria

**Major criteria:**
1. Family history of vascular EDS
2. **Arterial rupture** at a young age
3. Spontaneous *sigmoid colon perforation*
4. **Uterine rupture** during 3rd trimester
5. **Carotid-cavernous sinus fistula**

**Minor criteria:**
1. Excessive bruising without trauma
2. Thin, translucent skin with venous visibility
3. Characteristic facial features
4. Spontaneous pneumothorax
5. **Acrogeria**
6. Hypermobility of small joints
7. Club foot
8. Congenital hip dislocation
9. Small joint hypermobility
10. Tendon/muscle rupture
11. Keratoconus
12. Gingival recession
13. Early onset varicose veins (<age 30)

**Diagnostic testing:** COL3A1 gene

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[More information available online](http://www.forgottendiseases.org/assets/EhlersDanlos_Vascular_Type4.html)
DDx of hypermobility

1. **Other forms of EDS:**
   - Classic EDS: skin is a significant finding
   - Vascular EDS: arterial ruptures/dissections
   - Many other forms, but most are extremely rare and have severe phenotypes from a young age.

2. **Marfan Syndrome:**
   - Tall stature, family history of Marfan or aortic dissection, pectus deformities, arachnodactyly, myopia, lens dislocations

3. **Loey’s Dietz:**
   - Widely spaced eyes, cleft palate/bifid uvula, severe arterial tortuosity. Arterial aneurysms/dissections

4. **Osteogenesis Imperfecta:**
   - Fragile bones, frequent fractures, blue sclera
Back to EDS-HT / JHS:

- **Prevalence:**
  - EDS literature estimates 1:5,000
  - JHS estimates up to 3% of the population (self reported questionnaire)

- Patients with self-reported hypermobility are 40% more likely to have chronic widespread pain.

- Multi-system involvement
Systemic manifestations of EDS-HT/JHS

- Fatigue: >80%
- Dysautonomia: 75%
  - Orthostatic intolerance, PoTS, pre-syncope/syncope, dizziness, palpitations
- Headaches: 75% of female patients suffer from migraines
- Abdominal pain: >80%
  - Partially related to dysautonomia
  - Constipation, diarrhea, hernias, pelvic prolapse, nausea/vomiting, bloating
- Structural cardiac disease: Mitral valve prolapse in 6%
- Psychiatric: increased anxiety, depression, kinesiophobia
Management: general principles

• MSK symptoms: search for underlying cause
• Musculoskeletal pain management centers on physical therapy and lifestyle modification: strengthening, proprioception, limited stretching
• Recognize signs of autonomic dysfunction (PoTS) and functional GI disorders
• Cognitive behavior therapy to help learn to cope and live with chronic condition
MSK complications

• MSK symptoms—search for an underlying cause:
  • Recurrent and chronic joint injuries, dislocations, soft tissue injuries
  • Neuropathic pain: compressive neuropathies, axonal neuropathies (spine hypermobility, disk herniation)

• Headaches: c-spine hypermobility, migraine headaches, occipito-atlantoaxial instability, Chiari 1 malformations

• Avoid opiate pain medications—often ineffective and may worsen GI complications

• Chiropractic manipulation: general avoided due to intrinsic connective tissue laxity
Management: MSK

• **Physical Therapy:**
  - Exercise: specific, isolated, low-level, stabilization training.
  - Building deconditioned muscles, focus on **postural muscles**
  - **Proprioception exercises** improve joint stability—weight bearing, closed kinetic chain exercises:
    - Standing on one leg, mini squats, single knee bend, heel walking, walking backward, walking with eyes closed, slowly sitting/standing
    - Rocker-bottom wood, board-balance wood, foam rollers, etc

• **Joint protection/avoiding injury:**
  - Avoid excessive splinting/bracing—prefer muscle strengthening, however splints/braces can be used for stabilization or acute injury

• **Education:** avoid harm, don’t overstretch

**Taping:** can help with pain, mechanical stability, joint laxity, and proprioception

**Sports:** Aquatic exercises, T’ai Chi, Pilates/yoga/dance (but avoid excessive stretching).
GI/GU complications

• Anatomic complications:
  • Higher rates of abdominal hernias
  • Rectal and uterine prolapse/pelvic floor dysfunction are more common

• Functional complications:
  • Pathogenesis is poorly understood
  • Nausea, vomiting, bloating, constipation, IBS-symptoms and diarrhea are common

• Treat functional complications symptomatically

• Dysautonomia may contribute to GI complications?
PoTS: symptoms and diagnosis

• Symptoms: palpitations, dizziness, pre-syncope/syncope, fatigue, headaches
• Worsened by: heat, eating, exertion
• Diagnosis:
  • Head-up tilt-table test:
  • Tilt to 60° for 10 minutes → sustained 30bpm rise in BP, or max HR of ≥120bpm during the first ten minutes.
  • There is usually NO orthostatic hypotension

### PoTS: non-pharmacologic management

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<th>Avoid</th>
<th>Encourage</th>
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<tbody>
<tr>
<td>Sudden head-up postural changes</td>
<td>Head-up tilt at night</td>
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<td>Excessive exertion</td>
<td>Regular gradual exercise (swimming)</td>
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<td>Large meals (especially simple carbs)</td>
<td>Small, infrequent meals</td>
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<td>EtOH</td>
<td>High salt intake (if no HTN)</td>
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<td>Hot temperatures</td>
<td>Water repletion</td>
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<td>Vasodilator or vasodepressors (nitrates, Ca channel blockers, diuretics)</td>
<td>Elastic stockings/compression</td>
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<thead>
<tr>
<th>PoTS: Pharmacological Management</th>
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<td><strong>Third line: Low BP</strong></td>
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<td><strong>Third line: High/normal BP:</strong></td>
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<td><strong>Post-prandial tachycardia</strong></td>
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<td><strong>Other</strong></td>
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**References:**
Management: structural heart disease

Mitral valve prolapse: 6.4% of EDS-HT; 4.7% of JHS
  ◦ Generally mild

Aortic root dilatation: 1.6% of EDS-HT/JHS patients
  ◦ Rarely requires surgical repair.

Routine screening echo?
  ◦ Used to be routinely recommended but increasingly echo is only advised if symptoms warrant.
When/where to refer:

• Medical genetics:
  • There is no genetic testing for hypermobility EDS—these patients do not need to be referred to medical genetics
  • If you suspect other forms of EDS, Marfan syndrome, etc. → refer to medical genetics for detailed assessment, genetic testing, & family planning advice

• Cardiology:
  • Marfan’s syndrome, vascular EDS, Loey’s Dietz

• Rheumatology:
  • If an inflammatory connective tissue disease is suspected → refer to rheumatology to evaluate.
Take home points

• Beighton score to dx hypermobility: 60 second exam!
• JHS and EDS-HT are probably interchangeable.
• DDx: examine skin, stature, ask about vascular disease & family history
  • Other types of EDS, Marfan, Loey’s Dietz
• Management—recognizing that this is a multi-organ system disease:
  • Consider dysautonomia & PoTS—can make a big difference in symptoms
  • MSK: Think about the cause: entrapment neuropathies, spinal disease, dislocations/enthesitis/bursitis/tendonitis
  • Physical therapy & lifestyle modifications are the mainstay of treatment
• Referral to genetics is not necessary for EDS-HT, but can be useful for other forms of EDS, or other heritable connective tissue disorders.