RhAPP

RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

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Don’t Be Scared:
Your Next Patient Has EDS

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Faculty Disclosure

- Speakers Bureau: GSK, AstraZeneca, Sanofi, Pfizer

Objectives

- Explore the diagnosis and clinical manifestations of Ehlers-Danlos syndrome (EDS) and hypermobility spectrum disorders (HSD).
- Consider the pharmacologic and non-pharmacologic management of EDS and HSD.
- Share clinical pearls and tools to help care for patients with EDS and HSD.

Most Common Types

- Classical EDS (Types I and II) – cEDS
- Hypermobile EDS (Type III) – hEDS
- Vascular EDS (Type IV) – vEDS
- Kyphoscoliosis EDS (Type VI) – kEDS

International Classification of EDS (2017)

- **Classical – cEDS (Type I, II)**
- Classical-like – EDSCLL1, EDSCLL2
- Cardiac-valvular – cvEDS
- **Hypermobile – hEDS (Type III)**
- **Vascular – vEDS (Type IV)**
- Kyphoscoliotic – kEDS (Type VI)
- Arthrochalasia – aEDS (Type VIIA, VIIB)
- Dermatosparaxis – dEDS (Type VIIC)
- Brittle cornea syndrome – BCS
- Spondylodysplastic – spEDS
- Musculocontractural – mcEDS
- Myopathic EDS – mEDS
- Periodontal – pEDS (Type IX)

Epidemiology

- Overall frequency is 1 in 5000
  - hEDS is the most common
- hEDS is likely genetically heterogeneous, but many types of distinct genetic identities
- In most types, the underlying pathophysiology involves inherited alternations in genes affecting synthesis and processing of different forms of collagen.
  - We know that collagen is important in the structure of skin, tendons, ligaments, vasculature, skeleton and eyes.
  - Classic, vascular and most hEDS types are autosomal dominant pattern.
  - About 50% of patient with cEDS have mutations that are de novo and neither parent is affected.
  - kEDS is autosomal recessive pattern, as well as many of the rare forms of EDS.

Differential Diagnosis

- Joint hypermobility syndrome
  - Musculoskeletal pain and joint hypermobility
- Marfan syndrome
- Cutis laxa
- Loey-Dietz syndrome
- Osteogenesis imperfecta
- Larsen syndrome
- Strickler syndrome
- Arterial tortuosity syndrome

Clinical Manifestations

- Common:
  - Joint dislocations or subluxations
  - Joint/musculoskeletal pain
  - Premature degenerative arthritis
- Other
  - Pes planus and pectus excavatum, high arched palate (can be present in all forms)
  - Myopia and sometimes retinal detachment

Joint Hypermobility/Laxity

- Hallmark feature
- Can be proximal and distal joints
- Beighton hypermobility scale
  - Score of at least 5/9 is diagnostic

Beighton Hypermobility Scale

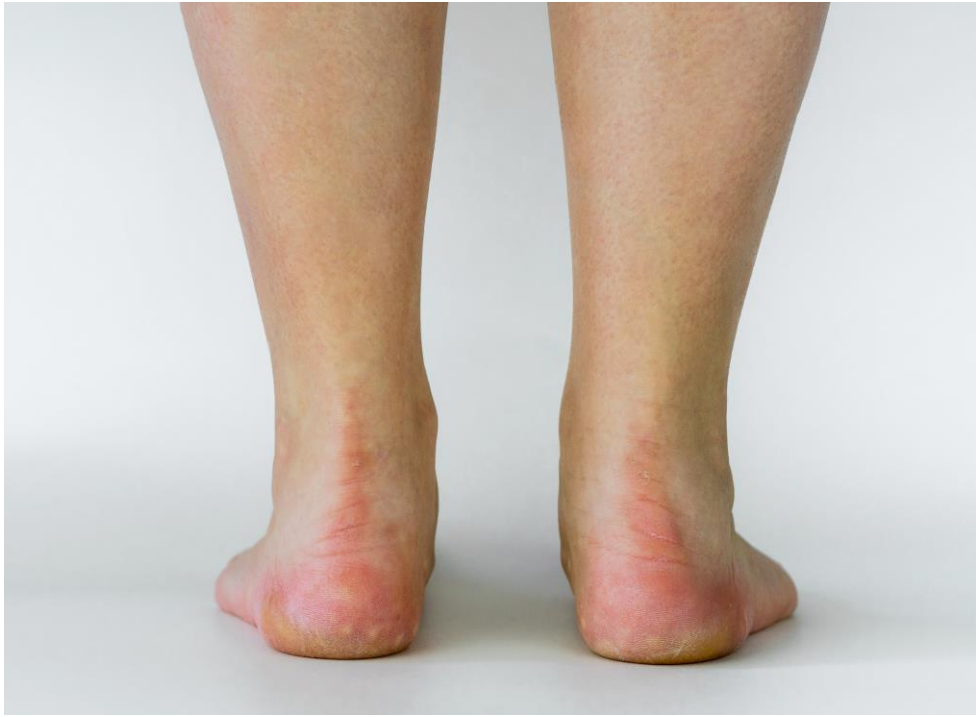
Other Features

- Skin hyperextensibility
  - Can stretch skin 4 cm or more from a neutral site until feeling resistance – common in cEDS
  - Soft skin
- Mitral valve prolapse

Classical EDS – cEDS

- Skin findings:
  - Velvety/soft, hyperextensible and fragile skin
  - Abnormal wound healing (atrophic papyraceous scars- cigarette paper-like)
  - Increased bruisability
  - Metenier sign- upper eyelid can be everted easily
  - Piezogenic papules
  - Molluscoid pseudotumors*
  - Subcutaneous spheroids
- Fatigue
- Development of hernias
- Cervical insufficiency
- Uterine prolapse
- Less common: aortic root dilation, mitral valve prolapse, spontaneous pneumothorax

Piezogenic Papules



Hypermobile EDS – hEDS

- Large, small-joint and spine hypermobility
- Joint dislocations/subluxations (shoulder, patella, TMJ common)
- Chronic joint pain (can mimic fibromyalgia)
- Premature osteoarthritis (OA)
- Soft and smooth skin (not as extensible as cEDS)
  - Wound healing is normal
  - Skin changes are not as significant than with cEDS
- Delayed gastric emptying (gastroparesis) and irritable bowel syndrome
- POTS/autonomic dysfunction
- Headaches (~1/3 of patients)
- Mild aortic root dilation, mitral valve prolapse

Diagnosis – hEDS

- Clinical!!
  - Generalized hypermobility (can decrease with age)
  - Two or more of A, B, or C
  - No evidence of skin fragility or other connective tissue disorder

A	B	C
1. Soft velvety skin 2. Mild skin hyperextensibility 3. Straie 4. Bilateral piezogenic heel papules 5. Abdominal hernias 6. Atrophic scarring 7. Prolapse of pelvic floor, rectum or uterus 8. Dental crowding and high palate 9. Arachnodactyly 10. Arm-span-to-height ratio >1.05 11. MVP or aortic root dilation	1. Positive family history in first degree relative	1. Daily musculoskeletal pain in two or more extremities (3+ months) 2. Chronic pain for 3+ months 3. Recurrent joint dislocations 4. Atraumatic joint instability

Vascular EDS – vEDS

- Could be life-threatening due to increased risk of spontaneous vascular or visceral rupture (80% have major event by age of 40)
- Absence of large-joint hyperextensibility
- Less common and not well studied (~1 in 100,000, 4% of cases overall)
- Maternal mortality during pregnancy is ~12% (not usually related to delivery)
- Skin is thin and may be look translucent (chest and abdomen), atrophic scars, increased brusiability and varicosities.
- Skin is not significantly hyperextensible
- Minor trauma leads to excessive bleeding
- Skeletal abnormalities: acrogeria, facial appearance with prominent eyes, thin face and nose and lobeless ears
- Gingival recession is common

Diagnosis of vEDS

- Major: arterial rupture (young), intestinal rupture, uterine rupture, carotid-cavernous sinus fistula and positive family history.
- Minor:
  - Increased bruising (atraumatic)
  - Thin, translucent skin
  - Characteristic facial features
  - Acrogeria
  - Hypermobility of small joints
  - Tendon and muscle rupture
  - Talipes squinovarus
  - Congenital hip dislocation
  - Early-onset varicosities
  - Spontaneous pneumothorax
  - Gingival recession
  - Keratoconus
- Genetic testing – COL3A1 gene has a high sensitivity

Management of hEDS and HSD

- Individualized
- Physical therapy (and consider occupational therapy as well)
  - Appropriate exercise, splinting, adaptive devices, etc.
- Support groups
  - Ehlers-Danlos Society, other national based charities/local organizations
  - Facebook groups, etc. (i.e. Ehlers-Danlos Colorado Support Group)
  - May is EDS awareness month

Management Cont.

- **POTS/autonomic dysfunction**
  - Cardiology, neurology
- **GI symptoms (dysmotility, prolapse, etc.)**
  - Gastroenterology, nutrition support
- **Bruising/bleeding**
  - Hematology- ? Underlying disorder vs EDS
- **Spinal instability**
  - Upright MRI with flexion extension views
  - Orthopedic evaluation
- **Mast cell activation syndrome**
  - Allergy/Immunology

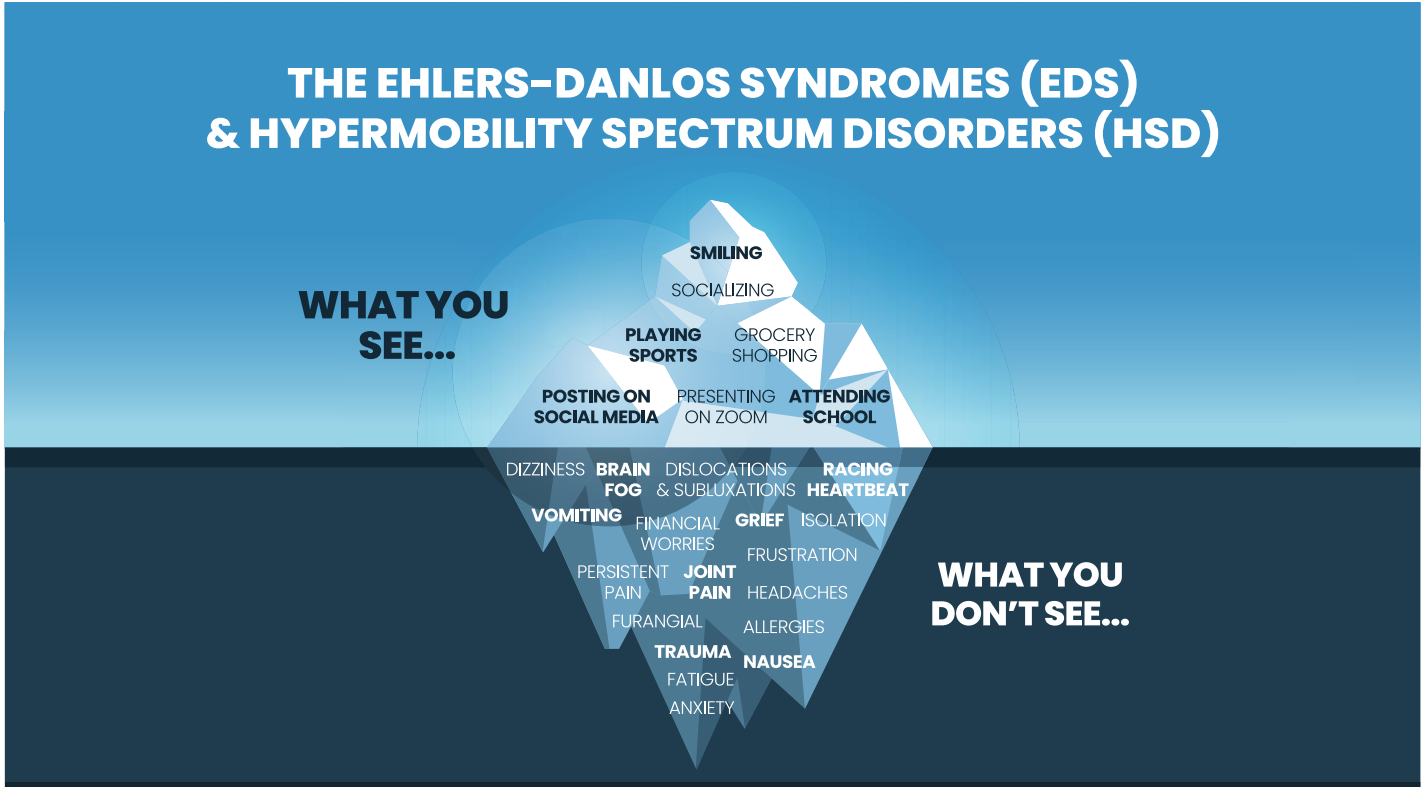
Pharmacologic Considerations

- Chronic widespread pain:
  - NSAIDs
  - Gabapentin/Lyrica
  - Duloxetine
  - Muscle relaxants

Clinical Pearls

- Validate and LISTEN!
- Hydroxychloroquine
- Doxycycline?
  - Matrix Metalloproteinases Inhibition by Doxycycline Rescues Extracellular Matrix Organization and Partly Reverts Myofibroblast Differentiation in Hypermobile Ehlers-Danlos Syndrome Dermal Fibroblasts: A Potential Therapeutic Target? (https://pubmed.ncbi.nlm.nih.gov/34831458/)
- Hip pain/shoulder pain
  - Labral tears are common

Food for Thought…



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