



Ehlers-Danlos Syndrome Rare Types

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On behalf of Fransiska Malfait, MD and the
Rare Disease Committee

Ehlers-Danlos Society Global Learning Conference

July 14-16, 2016 | Hilton Baltimore Hotel, Baltimore, MD

Revised EDS Classification

Defects in collagen primary structure and processing			
EDS classical	<i>COL5A1/COL5A2</i>	Type V collagen	AD
EDS vascular	<i>COL3A1</i>	Type III collagen	AD
EDS cardiac-valvular	<i>COL1A2</i>	Type I collagen (total absence of $\alpha 2$ chain)	AR
EDS classical with vascular fragility	<i>COL1A1</i>	Type I collagen (R-to-Cys substitutions)	
EDS arthrochalasia	<i>COL1A1/COL1A2</i>	Type I collagen (N-propeptide processing)	AD
EDS dermatosparaxis	<i>ADAMTS2</i>	ADAMTS2	AR
Defects in collagen folding and crosslinking			
EDS kyphoscoliosis	<i>PLOD1</i>	Lysylhydroxylase 1	AR
EDS FKBP22	<i>FKBP14</i>	FKBP22	AR
Defects in structure and function of the myomatrix, the interface between muscle and ECM			
EDS Tenascin-X	<i>TNXB</i>	Tenascin-X	AR
EDS/Myopathy overlap	<i>COL12A1</i>	Collagen XII	AR/AD
Defects in glycosaminoglycan biosynthesis			
Dermatan 4-sulfotransferase 1-deficient EDS	<i>CHST14</i>	Dermatan 4-sulfotransferase 1	AR
Dermatan sulfate epimerase 1-deficient EDS	<i>DSE1</i>	Dermatan sulfate epimerase 1	AR
$\beta 4$ GalT7 -deficient EDS	<i>B4GALT7</i>	$\beta 4$ GalT7 (Galactosyltransferase I)	AR
$\beta 3$ GalT6 -deficient EDS	<i>B3GALT6</i>	$\beta 3$ GalT6 (Galactosyltransferase II)	AR

Revised EDS Classification

(cont'd)

<i>Defects in intracellular processes</i>			
EDS spondylocheirodysplastic	SLC39A13	ZIP13	AR
Brittle Cornea syndrome	ZNF469 PRDM5	ZNF469 PRDM5	AR
<i>Unresolved forms of EDS</i>			
Poly-articular EDS	?	?	AD
Periodontal EDS	?	?	AD
<i>Defects in myomatrix, the interface between muscle and extracellular matrix</i>			
EDS Tenascin-X	TNXB	Tenascin-X	AR
EDS/Myopathy overlap	COL12A1	Collagen XII	AR/AD
<i>Conditions not included in EDS spectrum anymore</i>			
Occipital horn syndrome (EDS IX)	ATP7	ATP7	X-L
Fibronectin-deficient (EDS X)	-	-	AD
Familial articular hypermobility (EDS XI)	-	-	AD
X-linked EDS with muscle hematoma (EDS V)	-	-	X-L
<i>Open for discussion</i>			
Filamin A related EDS	FLNA	Filamin A	X-L



Vascular Ehlers-Danlos Syndrome Road Map to Diagnosis

Peter H. Byers, MD

University of Washington

EDS Education Meeting, July 14, 2016

Ehlers-Danlos Society Global Learning Conference

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Implications for testing

Testing in families is for specific mutation found previously

Testing in new person must sequence the entire gene

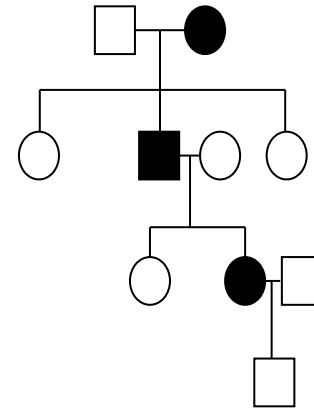
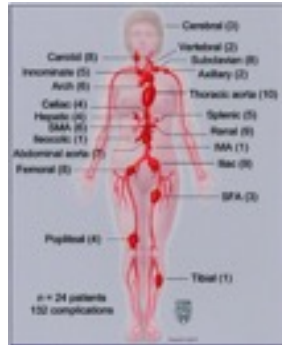
Rare examples of whole gene (one copy) deletion will be missed by sequencing

Second step is to measure how many copies are present (Array)

Mutations in both copies of COL3A1 are very rare

Family history of vascular EDS with causative variant in *COL3A1*

Arterial rupture at a young age



Spontaneous sigmoid colon perforation

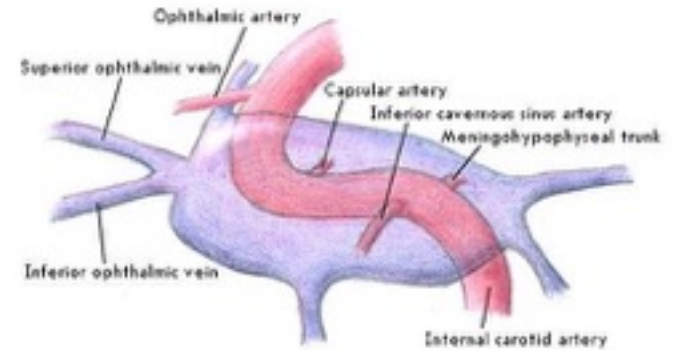
Uterine rupture during the third trimester in the absence of previous C-section

Severe peripartum perineum tears

Carotid-cavernous sinus fistula (CCSF)

Bruising unrelated to identified trauma; unusual sites such as cheeks and back

Thin, translucent skin with increased venous visibility.



Spontaneous pneumothorax

Characteristic facial appearance

Acrogeria

Talipes equinovarus (club foot)

Congenital hip dislocation

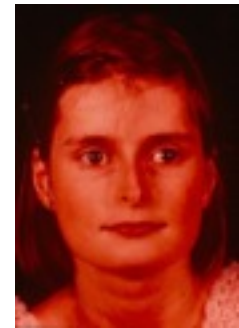
Hypermobility of small joints

Tendon and muscle rupture

Keratoconus (thin cornea)

Gingival recession and gingival fragility

Early-onset varicose veins (under age 30 and nulliparous if female)



Differential diagnosis

Loeys Dietz syndromes

Familial aneurysm syndromes

Fibromuscular dysplasia (FMD)

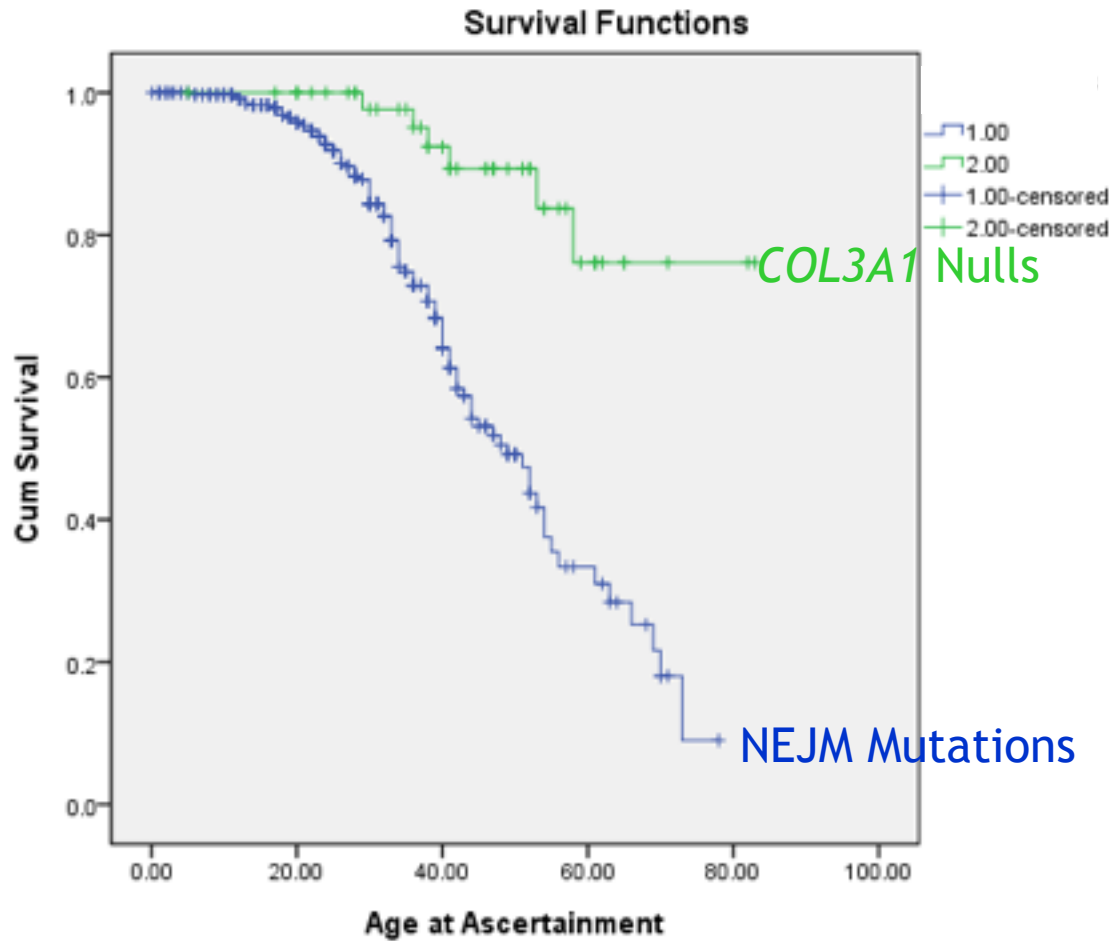
Hemophilia A, B and other clotting disorders

Genetic disorders of platelet dysfunction

Von Willibrand Disease

Kaplan-Meier Survival Curve

Index Patients and Relatives



Summary of management recommendations

Identify causative variants in *COL3A1* prior to application of diagnosis; consider appropriate differential diagnosis when no mutation is found

Modulate life style to minimize injury

Identify and create care team

Provide individual identifiers with diagnosis and management plan

Centralize management at centers of excellence (experience) when feasible

Maintain blood pressure in the normal range and treat hypertension aggressively

Surveillance of vascular tree by CTA (low radiation alternatives) or MRA if feasible on a biannual basis

Initial evaluation of ocular and oral structures to determine if followup is necessary



Hypermobile EDS

Howard P. Levy, MD, PhD
Associate Professor,
Johns Hopkins University
July 15, 2016

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Considerations

- III
- Hypermobile
- Hypermobility
- Joint hypermobility syndrome (not EDS)
- Systemic
- Multisystemic
- Polyarticular
- Common
- Variable
- etc

Goals

- More descriptive
- Less confusing
- Concern re: changing name just when wider recognition is being achieved

Naming Consensus...

Not achieved

Discussion continues

DIAGNOSTIC CRITERIA

Back to Basics

EDS is a heritable connective tissue disorder

- Alteration of connective tissue (particularly collagen)
- Generalized joint hypermobility
- Skin involvement

Defining hEDS

- Heritable
 - Family history
- Connective tissue
 - Generalized joint hypermobility
 - Skin/other connective tissue involvement
- Disorder (functional consequence)
 - Joint dislocations
 - Pain
 - Stress injuries?

Proposed Diagnostic Criteria for hEDS

A. Generalized joint hypermobility

AND

B. Features of a heritable connective tissue disorder (must have at least 1)

AND

C. Functional criteria (must have at least 1)

AND

D. Absence of exclusion criteria

A. Generalized joint hypermobility

- Beighton score
 - Cut off of 5 as basic starting point
 - Adjustments for age and sex?
 - Higher for children
 - Lower for older adults
 - Lower for males
 - Adjustment for injury/trauma?
- Other joints (shoulder, hip, back)?

B. Features of a heritable connective tissue disorder (must have at least 1)

1. Skin/fascia (must have 2 or more)

2. Marfanoid features (must have 2 or more)

3. Family history

B. Features of a heritable connective tissue disorder (must have at least 1)

1. Skin/fascia (must have 2 or more)

- Unusually soft or velvety skin
- Mild skin hyperextensibility
- Unexplained striae
- Recurrent or multiple abdominal hernia(s)
- Atrophic scarring involving at least two sites
- Bilateral piezogenic papules of the heel
- Pelvic floor, rectal, and/or uterine prolapse
- Hypoplastic or absent lingual frenulum

B. Features of a heritable connective tissue disorder (must have at least 1)

1. Skin/fascia (must have 2 or more)

2. Marfanoid features (must have 2 or more)

- Dental crowding AND high or narrow palate
- Arm span/height ≥ 1.05 OR upper/lower segment ratio < 0.89
- Arachnodactyly (positive wrist AND thumb sign on at least 1 side)
- Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria?
- Aortic root dilatation with Z-score > 2

B. Features of a heritable connective tissue disorder (must have at least 1)

1. Skin/fascia (must have 2 or more)

2. Marfanoid features (must have 2 or more)

3. Family history

- First degree relative independently meets diagnostic criteria

C. Functional criteria (must have at least 1)

1. Joint dislocations/instability, without trauma
2. Musculoskeletal pain
3. Stress injuries (recurrent events of ≥ 2 types)?

C. Functional criteria (must have at least 1)

1. Joint dislocations/instability, without trauma
 - ≥ 3 dislocations in the same joint or ≥ 2 dislocations in two different joints occurring at different times
 - Independent medical confirmation of joint instability at two or more sites, not related to trauma

C. Functional criteria (must have at least 1)

1. Joint dislocations/instability, without trauma

2. Musculoskeletal pain

- ≥ 2 limbs, recurring daily for at least 3 months
- Chronic, widespread pain for ≥ 3 months

C. Functional criteria (must have at least 1)

1. Joint dislocations/instability, without trauma

2. Musculoskeletal pain

3. Stress injuries (recurrent events of ≥ 2 types)? *

- Peripheral neuropathy

- Plantar fasciitis

- Bursitis

- Epicondylitis

- Tenosynovitis

*Consider evaluation for inflammatory arthritis

D. Absence of exclusion criteria

1. Other heritable & acquired connective tissue disorders, including autoimmune rheumatologic conditions
2. Neuromuscular disorders, which may cause joint hypermobility by means of hypotonia and/or connective tissue laxity
3. Unusual skin fragility, which should prompt consideration of other types of EDS

Features too non-specific or insufficiently studied to include as diagnostic criteria:

- Sleep disturbance & fatigue
- Postural orthostatic tachycardia
- Functional gastrointestinal disorders
- Dysautonomia
- Anxiety & depression
- Chiari & tethered cord
- Mast cell dysfunction

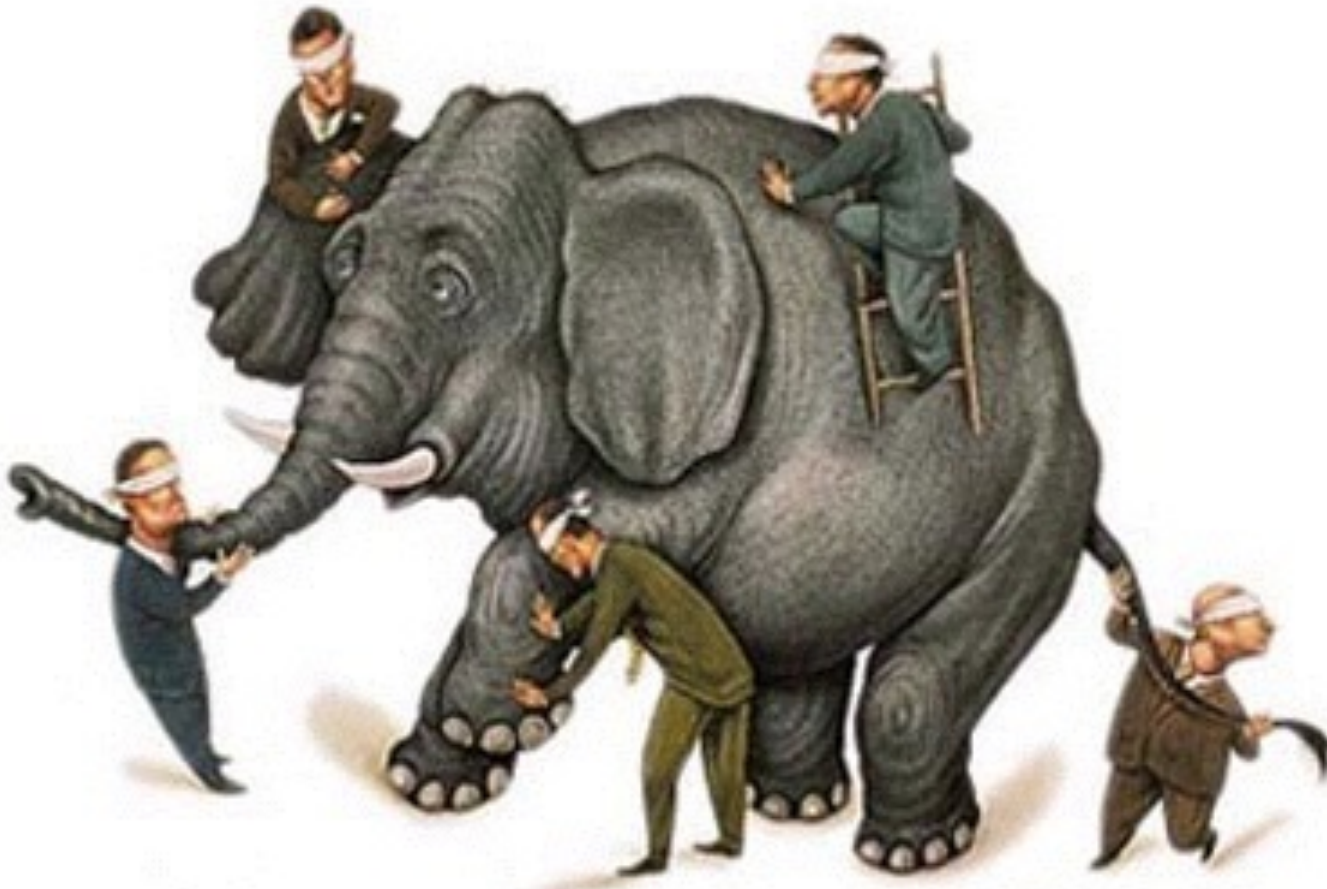
hEDS v. JHS/HMS

- hEDS defined by Villefranche criteria
 - Pediatric and genetic biases
- JHS/HMS defined by the Brighton criteria
 - Adult and rheumatologic biases
- Both include generalized joint hypermobility, joint instability and pain
- Both require exclusion of other conditions
- Neither has an objective diagnostic algorithm or test

hEDS v. JHS/HMS

- Lack of clear distinction between the two
- Families in which both diagnoses are made in different relatives

hEDS v. JHS/HMS



Blind men and the elephant

hEDS COMMITTEE:

**“IT IS OUR OPINION THAT
hEDS AND JHS ARE ALLELIC
AND INDISTINGUISHABLE.”**

hEDS v. JHS/HMS

Broader consortium response mixed

- What about people with joint laxity who are clearly not “normal” but don’t meet hEDS criteria?
 - Need a diagnostic term
 - Need to avoid “over-medicalizing”
 - Risk (further) loss of credibility if criteria are too lax

hEDS & JHS:

New working group formed to further elaborate

2016 EDS Conference Update

EDS Diagnostic Criterion

Notes from lecture by Claire Francomano, MD Ehlers-Danlos Society National conference
July 2016. Contents to be published March 2017

CLASSICAL TYPE EDS (cEDS)

- Types I Gravis - extreme skin laxity
and II Mitis - more mild skin involvement
- Villefranche 1997 I and II became Classical
- COL5A1 is the gene
- NOW cEDS = CLASSICAL

Criterion

- 1st Major criteria of (1) skin hyperextensibility AND atrophic scarring
- **plus** either - 2nd major Criteria (2) Joint hypermobility
- or 3 minor criteria

Major Criteria

1. skin hyperextensibility AND atrophic scarring

- 1.5 cm for distal forearm and back of hand, 3cm at elbow/knee
- scarring - hemosiderotic - deposition of hemosiderin which gives dark appearance
- look at the shins, forehead/chin
- minority of Classical type have mild scarring

2. Joint hypermobility

- use Beighton score with cut off of 5 or more which is open to some discussion (some consider it 4 or more)

Minor Criteria:

1. Easy bruising - can occur anywhere on the body including unusual sites, shins stained with hemosiderin from previous bruises
2. soft doughy skin - skin texture is a subjective assessment
3. skin fragility
4. molloscoid pseudotumours - over pressure points - elbow, knees, fingers (swelling)
5. subcutaneous spheroids - small hard bodies frequently mobile and palpable on forearms and shins. May be calcified and detectable on x-ray
6. hernia or history
7. epicathal folds in eyes - often seen in childhood and may see in adulthood - fold in nasal part of eye
8. family hx of 1st deg relative who meets clinical criteria

WHAT TO DO:

- do confirmatory analysis if meet criteria. 90% + with COL5A1 and 2
- or look at electron microscopy of skin and see collagen flowers on skin biopsy

Research article: by Symoens et al : Comprehensive Molecular Analysis demonstrates Type V collagen mutations in over 90% of patients with classic EDS and allows to refine diagnostic Criteria 2012

- TYPE 1 only in this group now

ORGAN SYSTEM REVIEW:

expert opinion mostly because not many articles for classical

- musculoskeletal - mild muscle hypotonia
- skeletal morphology alterations - pectus, increased growth of arm/leg long bones, osteopenia osteoporosis
- skin - stretch, soft, severe atrophic scarring in most, easy bruising and scars dark
- cardiovascular- can be aortic root dilation but rarely progresses (often they grow into their aortic root), mitral valve prolapse, (Cardiac valvular type are more of a concern)
- GI -dysphagia, dyspepsia, reflux, hernia, IBS, abdominal pain, Constipation, diarrhea, rectocele
- Neuro - pain, dysautonomia, headache, frequency of Chiari1, C0-1 instability, tethered cord as yet undefined

OTHER findings:

- Prolonged bleeding time - its a problem with the way the platelets sit on the collagen (technically have normal platelets)
- chronic fatigue syndrome
- MCAD
- giant bladder diverticuli

TREATMENT:

no clinical trials on these yet

- Ascorbic acid 2 gm/day
- closure of wounds by plastic surgeon
- DDAVP may normalize bleeding time
- avoid excessive sun exposure
- avoid trauma prn
- PT to strengthen mm and increase muscle tone
- avoid high impact activities
- avoid excessive demonstration of hypermobility
- multidisciplinary team
- ring splints an bracing/orthotics

PAIN MANAGEMENT:

- neuro assessment to r/o neuropathic pain/compression neuropathy
- regular light non-weight bearing exercise
- PT for muscle relaxation and MFR trigger point release
- relaxation techniques esp mindfulness stress reduction and biofeedback
- counseling support Cognitive Behavioral Therapy
- anti-inflammatory drugs and pain meds - this is a last option
- opiates are not the answer in most cases.

CARDIAC MANAGEMENT:

- echo to look for aortic root and mitral valve prolapse but usually of little clinical significance
Research: Atzinger2011 - Echo 1x in adulthood and if normal then stop doing them or only every 3-5yrs
- Specific mutation: consider vascular imaging/aggressive blood pressure control if glycine substitution near the C terminal end of the triple helix or family history of arterial aneurysm

GI:

- upper endoscopy or 24 hr pHmetry to eval reflux disease and proton pump inhibitor if needed (if reduce acid you reduce absorption of nutrients) try to avoid PP inhibitors prn
- Colonoscopy with care due to increased risk of bleeding
- treatment is limited - no tailored strategy currently, pt. education diet, nutritional advice most effective, some have bad reaction to meds

PREGNANCY:

- f/u t/o warranted
- prematurity more often when fetus is affected and due to premature rupture of membranes
- breech presentation more common if baby affected due to hypotonia

DIFFERENTIAL DX:

- cardiac valvular type EDS
- Tenascin X deficient EDS
- Spondylocheirodysplastic type
- Loeys Dietz - tortuous vessels
- OI/EDS overlap syndrome - looks like classical clinically

REPRODUCTIVE:

- Pelvic floor is at risk due to ligament laxity with classical or hypermobility type - prolapse is a common issue
- intercourse pain related to skin sensitivity
- pelvic PT for strengthening important

MUSCULOSKELETAL:

- muscle hypotonia more present in classical
- early arthritis - assoc with increased joint mobility causing an inflammatory response (wear and tear causes inflammation)

BRAIN FOG:

can come with classical too: CAUSES

- CSF flow
- venous insufficiency
- dysautonomia
- MCAD
- most common cause is poor sleep

DIET:

- Heidi Collins, MD
- basically eliminate processed foods, artificial or real sweeteners, eliminate gluten and dairy in some people really helps, probiotics

BLADDER ISSUES:

- look into tethered cord

SLEEP STUDIES:

- disordered sleep architecture with less stage 3 and REM sleep which may be dysautonomia

FOUR CRITERIA TO MEET HEDS (A-D)

A. Generalized joint hypermobility

Beighton score cut off of 5 as basic starting point

- does have good reproducibility, have some standards but not as objective as it needs to be, do we need to use a goniometer or just eyeball?
- adjustments for age and sex - higher for children, lower for older adults, lower for males
- adjustment for injury/trauma
- other joints (shoulder, hip back) - past history of laxity there

B. Features of Heritable Connective Tissue Disorder (must have 1)

1. Skin/fascia (must have 2 or more)

- unusually soft or velvety skin
- mild skin hyperextensibility
- unexplained striae (stretch marks)
- recurrent or multiple abdominal hernias - not talking about hiatal hernia
- atrophic scarring involving at least 2 sites
- bilateral piezogenic papules of heel
- pelvic floor, rectal, and/or uterine prolapse
- hypoplastic or absent lingual frenulum

2. Marfanoid features (must have 2 or more)

- dental crowding and high or narrow palate
- arm span/height \geq or equal 1.05 OR upper/lower segment ratio \geq .89
- long fingers - arachnodactyly + wrist AND thumb sign on at least 1 side (thumb sticks out of fist)
- mitral valve prolapse mild or greater based on strict echo criteria
- aortic root dilation

3. Family history

- 1st degree relative independently meets diagnostic criteria

C. Functional Criteria (must have 1)

1. joint instability without trauma (need one)

- 3 or more dislocations of same joint OR
- 2 or more dislocations of 2 different joints at diff times
- independent exam says non injury related laxity

2. musculoskeletal pain (need one)

- pain in > or equal to 2 limbs, recurring daily for at least 3 months
- chronic widespread pain for > or equal to 3 months

3. stress injuries (recurrent events of > 2 types)

- peripheral neuropathy, plantar fasciitis, bursitis, epicondylitis, tenosynovitis
- (consider eval for inflammatory arthritis)

D. Absence of exclusion criteria

(don't have something else)

- other heritable or acquired connective tissue disorder (lupus or RA)
- neuromuscular disorders, which may cause joint hypermobility by means of hypotonia or connective tissue laxity (ex: mitochondrial disorder causing hypotonia)
- unusual skin fragility which should prompt consideration of other types of EDS

FEATURES TOO NONSPECIFIC OR INSUFFICIENTLY STUDIED TO INCLUDE AS DX CRITERIA:

- sleep disturbance and fatigue
- POTS
- Functional GI disorders
- Dysautonomia
- MCAD
- anxiety and depression
- chiari and tethered cord

HEDS and JHS

Are they the same? THEY ARE THE SAME!!!

- hEDS defined by Villefranche criteria - pediatric and genetic biases
- JHS/HMS defined by Brighton criteria work with Adults and rheumatological biases
- both have generalized joint hypermobility

IF YOU just have loose joints but no other issues then DON'T get the label – must meet criterion

MITOCHONDRIAL DISORDER

- is it inherited or is it acquired by environmental exposure?
- typically low tone t/o body and all organ systems affected