Brief Overview of hypermobility, Ehlers Danlose Syndrome and POTS

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NARA NW and OHSU
4/17/26

Why?

You will see patients with these conditions!

- Prevalance: 80-90% of all EDS is hEDS (1:3,100-500), affects ~10 million people in the U.S. (Tinkle 2017)
- On average there is a 10-12 year delay from symptom onset to diagnosis for hEDS
- Reducing time to diagnosis reduces medical trauma
- Since the start of the COVID pandemic there has been a five fold increase in Postural Orthostatic Tachycardia Syndrome (POTS) diagnoses

"Early diagnosis of Heritable Disorders of Connective Tissue's (HDCTs) is important to reduce physical injury, reduce psychological harm to the affected individual and family members, and prevent the risks associated with inappropriate or fragmented medical care." -National Academy of Sciences

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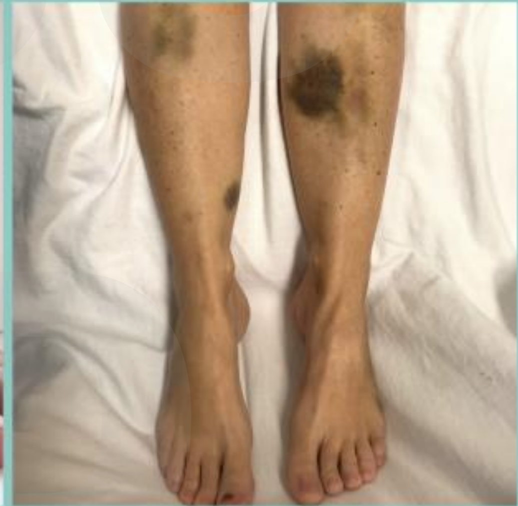
Ehlers Danlos Syndrome

EDS



Joint Hypermobility

Skin hyperelasticity

Tissue fragility

When to Suspect Hypermobile Joint Disorders

- Chronic joint instability
- Pain
- Fatigue
- Chronic abdominal symptoms
- Postural symptoms
- Allergy/atopy
- Autoimmunity
- Poor fine motor skills (such as handwriting)

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Types of EDS

- **Hypermobile: Joint hypermobility, soft, stretchy skin**
- Classical: Velvety, stretchy, fragile skin, spontaneous ecchymosis.
- Classical-like: hypermobility, soft/fragile skin
- Vascular: Possible arterial/organ rupture
- Kyphoscoliosis: Joint laxity, muscle hypotonia, developmental delay (severe functional loss over time)
- Arthrochalasia: Congenital hip dislocation, lax joints
- Dermatosparaxis: Severe skin fragility & bruising
- Cardiac-Valvular: mitral and aortic valve dysfunction, joint laxity, bruising
- Brittle Cornea: thin cornea, keratoconus/globus, blue sclera

Malfait, et al, 2017

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Types of EDS

- Spondylodysplastic: short stature, bowed limbs, muscle hypotonia
- Musculocontractural: congenital contractures, skin hyperextensibility
- Myopathic: muscle hypotonia, proximal joint contractures, hypermobility
- Periodontal: early onset severe periodontitis, lack of attached gingiva
- AEBP1 mutation: joint laxity, hyperextensible skin, abnormal scars, osteoporosis

All subtypes have a single, known genetic mutation except for hEDS

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Diagnostic criteria for hypermobile Ehlers-Danlos syndrome (hEDS)

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The International Consortium on Ehlers-Danlos Syndromes & Related Disorders

Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)

This diagnostic checklist is for doctors across all disciplines to be able to diagnose EDS

Coordinated by The Ehlers Danlos Society.

Patient name: ______________ DOB: __________ DOV: __________ Evaluator: ______________

The clinical diagnosis of hypermobile EDS needs the simultaneous presence of all criteria, 1 **and** 2 **and** 3.

CRITERION 1 – Generalized Joint Hypermobility

One of the following selected:

- ☐ ≥6 pre-pubertal children and adolescents
- ☐ ≥5 pubertal men and woman to age 50
- ☐ ≥4 men and women over the age of 50

Beighton Score: ____/9

If Beighton Score is one point below age- and sex-specific cut off, two or more of the following must also be selected to meet criterion:

- ☐ Can you now (or could you ever) place your hands flat on the floor without bending your knees?
- ☐ Can you now (or could you ever) bend your thumb to touch your forearm?
- ☐ As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
- ☐ As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
- ☐ Do you consider yourself "double jointed"?

CRITERION 2 – Two or more of the following features (A, B, or C) must be present

Feature A (five must be present)

- ☐ Unusually soft or velvety skin
- ☐ Mild skin hyperextensibility
- ☐ Unexplained striae distensae or rubae at the back, groins, thighs, breasts and/or abdomen in adolescents, men or pre-pubertal women without a history of significant gain or loss of body fat or weight
- ☐ Bilateral piezogenic papules of the heel
- ☐ Recurrent or multiple abdominal hernia(s)
- ☐ Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or hemosideric scars as seen in classical EDS
- ☐ Pelvic floor, rectal, and/or uterine prolapse in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition
- ☐ Dental crowding and high or narrow palate
- ☐ Arachnodactyly, as defined in one or more of the following: (i) positive wrist sign (Walker sign) on both sides, (ii) positive thumb sign (Steinberg sign) on both sides
- ☐ Arm span-to-height ratio ≥1.05
- ☐ Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
- ☐ Aortic root dilatation with Z-score >+2

Feature A total: ____/12

Feature B

- ☐ Positive family history; one or more first-degree relatives independently meeting the current criteria for hEDS

Feature C (must have at least one)

- ☐ Musculoskeletal pain in two or more limbs, recurring daily for at least 3 months
- ☐ Chronic, widespread pain for ≥3 months
- ☐ Recurrent joint dislocations or frank joint instability, in the absence of trauma

CRITERION 3 – All of the follow prerequisites MUST be met

1. Absence of unusual skin fragility, which should prompt consideration of other types of EDS
2. Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. In patients with an acquired CTD (e.g. Lupus, Rheumatoid Arthritis, etc.), additional diagnosis of hEDS requires meeting both Features A and B of Criterion 2. Feature C of Criterion 2 (chronic pain and/or instability) cannot be counted toward a diagnosis of hEDS in this situation.
3. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (e.g. Bethlem myopathy), other hereditary disorders of the connective tissue (e.g. other types of EDS, Loeys-Dietz syndrome, Marfan syndrome), and skeletal dysplasias (e.g. osteogenesis imperfecta). Exclusion of these considerations may be based upon history, physical examination, and/or molecular genetic testing, as indicated.

Diagnosis: ______________________________

https://ehlers-danlos.com/wp-content/uploads/hEDS-Dx-Criteria-checklist-1.pdf

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2017 hEDS Diagnostic Criteria

Must meet all 3 criteria:

1. Generalized joint hypermobility (Beighton)
2. Features of heritable connective tissue disorder, meet ≥2 of 3 categories, A-C
3. Absence of exclusion criteria

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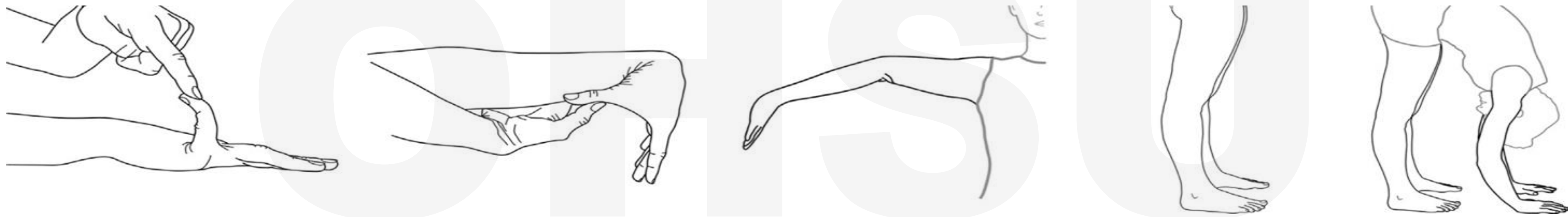
Criteria 1: Generalized Joint Hypermobility

Malfait, et al, 2017; diagram Juul-Kristensen



Beighton Score ≥5/9

(Over 50 ≥4/9, Prepubescent ≥ 6/9)

- 2: Bend 5th finger back >90°
- 2: Touch thumb to forearm
- 2: Elbow hyperextension >10°
- 2: Knee hyperextension >10°
- 1: Palms to floor, knees straight

Add a point for ≥2/5 on the 5-Item Questionnaire:

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself “double-jointed”?

Criteria 2: Features of Heritable Connective Tissue Disorder

Must have ≥ 2 of the following 3 categories:

A. Systemic manifestations: 5 of 12 options positive
B. Family history
C. Musculoskeletal complications: 1 of 3 options positive

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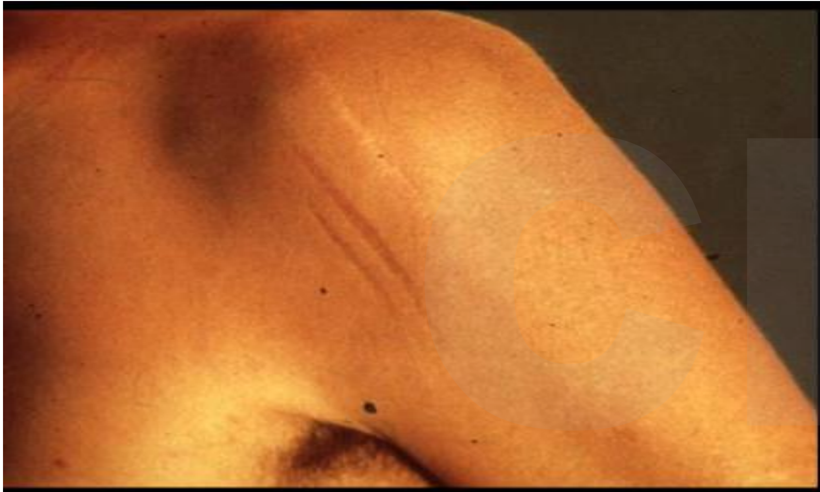
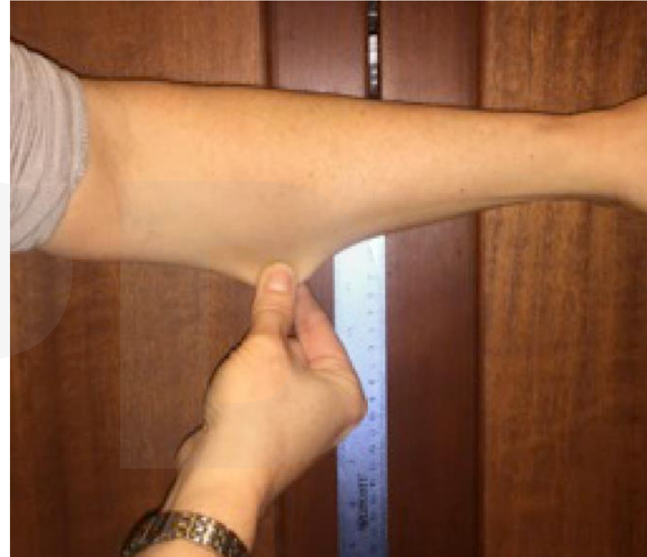
Criteria 2A: Systemic Manifestations

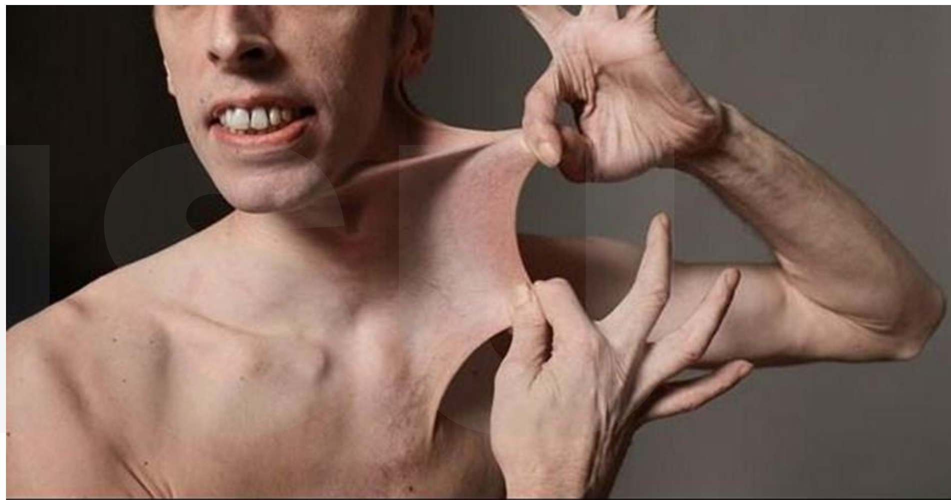
i. Unusually soft or velvety skin

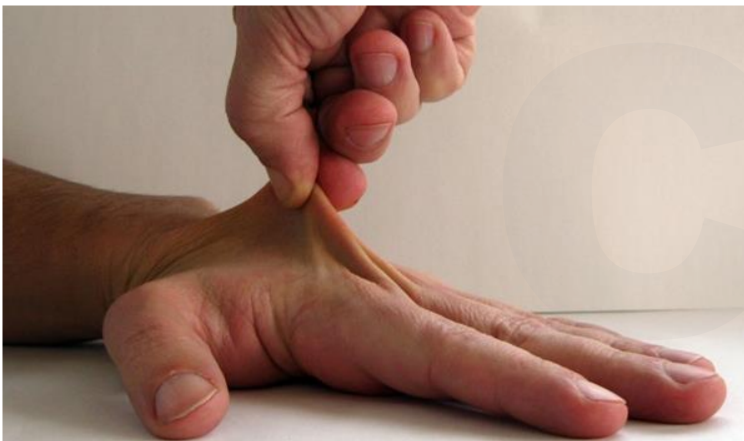
ii. Mild skin hyperextensibility (>1.5 cm on volar, non-dominant forearm)

iii. Unexplained striae/stretch marks in any ♂ or prepubertal ♀ w/o significant weight change









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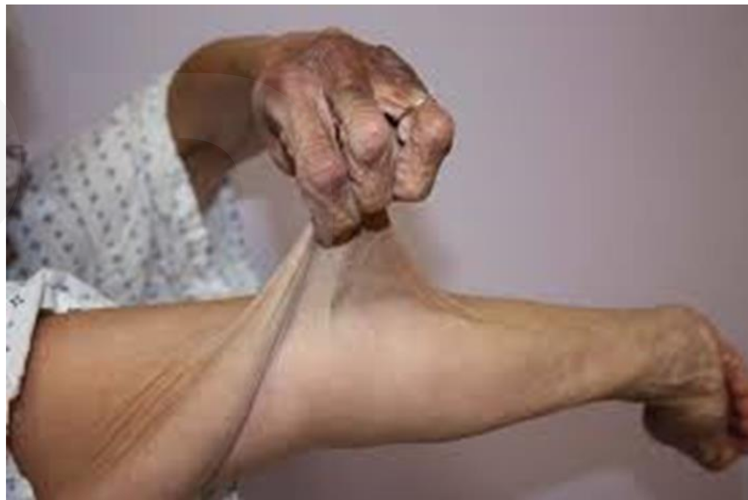
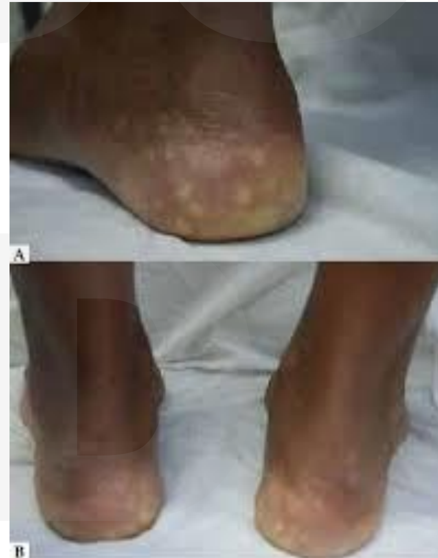


Criteria 2A: Systemic Manifestations

iv. Bilateral piezogenic papules of heel *
v. Recurrent or multiple abdominal hernias (umbilical, inguinal, crural; not hiatal hernia)

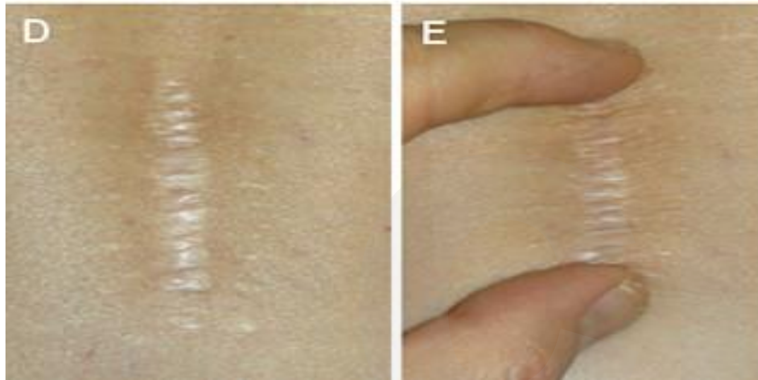
Subcutaneous fat herniations through the fascia, may appear only with **weight bearing*



Malfait 2017

Criteria 2A: Systemic Manifestations

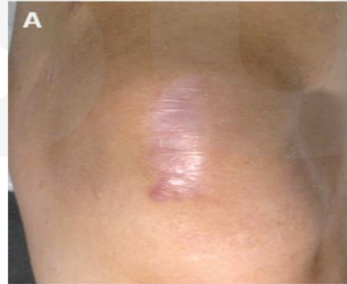
vi. Atrophic scarring involving at least 2 sites (not like classical EDS)

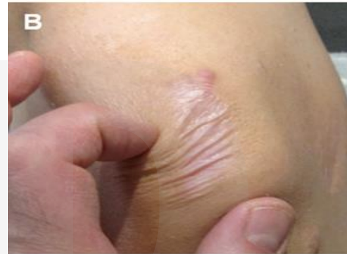


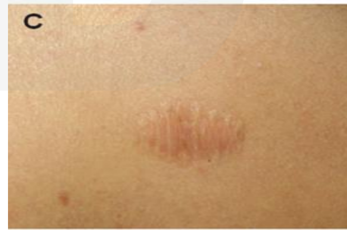
Castori, et al, 2015

Malfait, et al, 2017

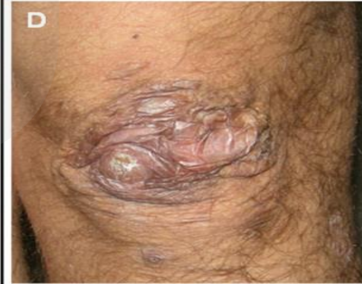
Hypermobile EDS

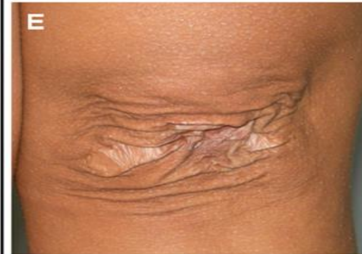


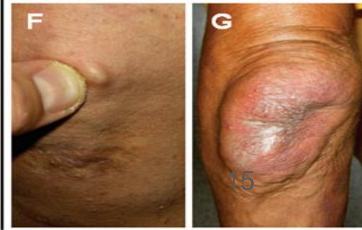




Classical EDS





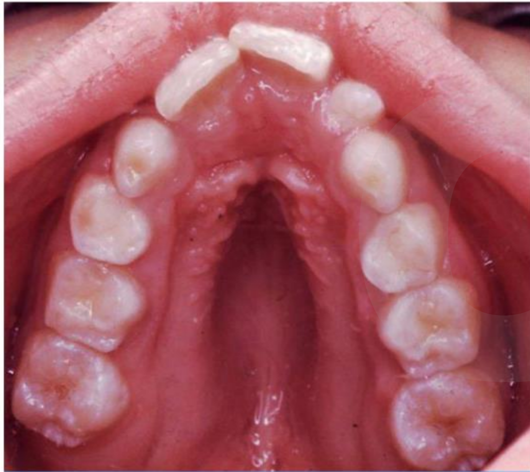


Criteria 2A: Systemic Manifestations

vii. Pelvic floor, rectal, and/or uterine prolapse in children, ♂, nulliparous ♀ w/o obesity

viii. Dental crowding and high or narrow palate

ix. Bilateral arachnodactyly with Steinberg or Walker signs



The Steinberg sign
This test is used for the clinical evaluation of Marfan patients.

Fold your thumb into the closed fist. This test is positive if the thumb tip extends from palm of hand.

The Walker-Murdoch sign
This test is used for the evaluation of patients with Marfan syndrome.

Grip your wrist with your opposite hand. If thumb and fifth finger of the hand overlap with each other, this represents a positive Walker-Murdoch sign.

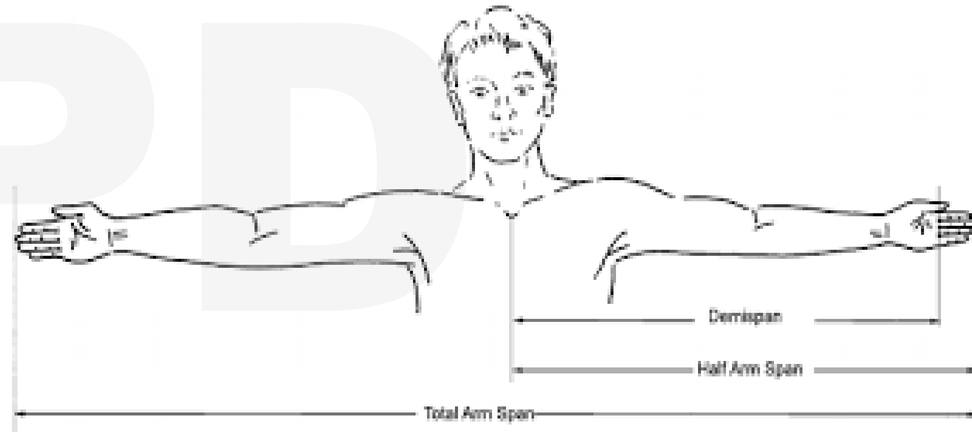
SCMP

2A: Systemic Manifestations

x. Arm span/height ≥ 1.05, measured between 3rd finger tips

xi. Mitral valve prolapse, mild

xii. Aortic root dilation, z-score >+2



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Summary of Criteria 2A: Systemic Manifestations

i. Unusually soft/velvety skin
ii. Mild skin hyperextensibility (forearm)
iii. Unexplained striae/stretch marks
iv. Bilateral papules of heel
v. Recurrent/multiple abdominal hernias
vi. Atrophic scarring in ≥ 2 sites
vii. Pelvic floor, rectal, uterine prolapse
viii. Dental crowding or high, narrow palate
ix. Arachnodactyly bilateral Steinberg or Walker sign
x. Arm span/height ≥ 1.05
xi. Mitral valve prolapse mild or greater
xii. Aortic root dilation

Meets Systemic Manifestations if YES to ≥ 5 items

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2B: Family History

1st degree relative meets diagnostic criteria for hEDS as determined by a knowledgeable physician

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Criteria 2C: Musculoskeletal Complications

1. Pain ≥ 2 limbs, recurring daily for at least 3 months
2. Chronic widespread pain for ≥ 3 months
3. Recurrent joint dislocations or frank joint instability in absence of trauma (a *or* b)
   a. 3+ atraumatic dislocations of same joint OR 2+ dislocations of 2 different joints at different times
   b. Medical confirmation of joint instability at 2+ joints not related to trauma

If yes to ≥ 1 item, then positive for musculoskeletal complications

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Criteria 3: Absence of Exclusion Criteria

To meet this Criterion, **all 3 of the following must be ABSENT:**

1. Unusual skin fragility (should prompt consideration of other types of EDS)
2. Other heritable or acquired connective tissue disorder (lupus or RA) cannot use Criteria 2C (i.e., must have a first degree relative that meets criteria)
3. Neuromuscular disorders that may cause joint hypermobility by means of hypotonia or connective tissue laxity (e.g., Marfan, other EDS, OI, CMT etc.)

***If not yet done I will check ESR, CRP at minimum

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Variability in Expression

- Biologic sex/hormones
- Age: hypermobility>pain>stiffness
- Physical characteristics: build, strength, muscle tone, general health
- Psychological characteristics
- Sports/work activities
- Dietary habits
- **Traumas**/surgeries/periods of **immobility**

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Biological Sex

Assigned female at birth>assigned male at birth

Generally more inherent joint stability in presence of testosterone

Hormonal influences:

- *–Testosterone > muscle bulk around joints which creates more stability*
- *–Progesterone> joint instability*

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Major Comorbidities

Mast Cell Activation Syndrome: systemic inflammation, aberrant tissue growth, allergy

Autoimmunity: celiac disease, inflammatory bowel disease, psoriasis, ankylosing spondylitis, rheumatoid arthritis*

Gastrointestinal disorders: gastroesophageal reflux disease , irritable bowel syndrome, malabsorption syndrome, small intestinal bacterial overgrowth

Dysautonomia: postural orthostatic tachycardia syndrome, orthostatic hypotension, thermoregulation, GI motility dysfunction, pelvic floor dysfunction

Vascular/nerve compression syndromes: median arcuate ligament syndrome (2.5%), thoracic outlet syndrome, carpal tunnel, Nutcracker syndrome

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Obstetrics

Worsening musculoskeletal laxity: pelvic girdle pain, spine pain

Vascular issues: varicose veins in pelvis and legs

POTS - can get better or worse, perhaps due to increased blood volume

Increase risk of miscarriage - data is mixed

Premature rupture of membranes- 6-50%

Cervical insufficiency

Placenta previa

vEDS - significant events like uterine rupture, arterial rupture, increased risk during pregnancy, labor and postpartum.

Makatsariya 2020, Hurst 2014, Castori 2012, Karthikeyan 2018, Spiegel 2020

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Obstetrics- in labor

Abnormal fetal presentation: transverse, breech

Rapid 2nd stage of labor

Increased risk of bleeding/postpartum hemorrhage

Requirement for more anesthesia

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Referral to genetics

“Super” stretchy skin: >1-2 inch spread

Extensive scarring

Hemosideristic or “super” atrophic scars

Family or personal history of vascular or organ rupture

Kyphoscoliosis

Spontaneous pneumothorax

Severe gum disease

***Consider ordering genetic testing yourself: GeneDX Panel J555 or Invitae Connective Tissue Disorders panel

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Building a team

Primary Care

Physical Therapy

Occupational Therapy

Pain Psychology

Manuel Therapists: osteopathic manipulation, acupuncture, Rolfing, massage, chiropractic (no high velocity adjustments)

Therapeutic movement modalities: water based, Pilates, Gyrotonics, Feldenkrais, yoga?

Orthopedics

Orthotist

Nutritionist

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Sample Treatment Plan

1) Appropriate referrals
2) Movement: progressive resisted exercise, water based, supine, strength training
3) Judicious use of splinting/compression
4) Herbs and Supplements: magnesium (muscle relaxer), alpha lipoic acid and acetyl L-carnitine (decrease neuropathic pain), turmeric (pain and inflammation), nettles, california poppy (pain)
5) Medications: tylenol, NSAIDs, topical pain relief (diclofenac, capsaicin, epsom, lidocaine), gabapentin/pregabalin, duloxetine, memantine, low dose naltrexone (LDN)
6) If not yet done ECHO- ask for eval of the mitral valve and aorta

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Resources

Local PTs:

- Hey Doc
- Good Health PT
- Evolution Healthcare
- OHSU- Bill Rubine, Noriko Yamaguchi, Ryan Bourdo
- Amy Werner- for dancers

Online:

- EDS Society: Home - The Ehlers Danlos Society

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Low Dose Naltrexone

Benefits of LDN:

LDN increases the secretion of naturally occurring Endorphins (“feel good, runner’s high”). Endorphins relieve pain, give a happy feeling and reduce inflammation.

LDN increases the release of Opioid Growth Factor which works powerfully to reduce inflammation, auto-immune responses and tumor cell growth.

LDN reduces inflammatory immune cell signaling (Toll like Receptor-4). When these immune “look out cells” get excited, they signal the immune system to get overly busy, which can cause or worsen auto-immune and inflammatory responses. These “look out cells” are located all over the body, including the gut and the brain.

LDN calms glial cells in the nervous system. Glial cells make up over 70% of the immune system and can either protect nerve pathways or cause inflammation of nerves. We want our glial cells to remain in a calm and protective mode!

LDN increases dopamine levels. Dopamine is a neurotransmitter that makes us feel happy and rewarded, gives us energy and helps our brain solve problems. When dopamine is low, we feel depressed.

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Low-dose naltrexone instructions:

1. Dissolve one 50 mg naltrexone tablet in 50 mL of distilled water (1mg/ml solution). Shake well. Keep this solution in a closed container in a dark cabinet.

2. Take 1 mL of the solution nightly for approximately 2 weeks.

3. Increase by 1 mL approximately every 2 weeks to a maximum dose of 4.5 mL.

4. You will make a new solution weekly even though you will have leftover solution.

5. If you are having significant side effects at a dose remain there and do not increase at the 2-week mark.

Or pay to have it compounded- Community Compounding is the most affordable around here

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Postural Orthostatic Tachycardia Syndrome

Definition of POTS

- Heart rate increase of >30 beats per minute (or exceeding 120bpm without orthostatic hypotension) within 10 minutes of moving from lying to standing (>40bpm in adolescents less than 20)
- Tachycardia lasts at least 30 seconds
- Symptoms worsen with standing and improve with recumbency
- Symptoms last >6 months
- Absence of other overt causes of orthostatic symptoms or tachycardia

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Symptoms

- Cardiac symptoms: tachycardia, palpitations, chest discomfort, dyspnea
- Presyncope
- Fatigue
- Brain fog
- Nausea
- Exercise intolerance
- Headache/migraine
- Blurry/tunnel vision
- Dependent acrocyanosis
- Poor sleep
- Daytime somnolence
- Abnormal sudomotor regulation
- *Symptoms are often positional

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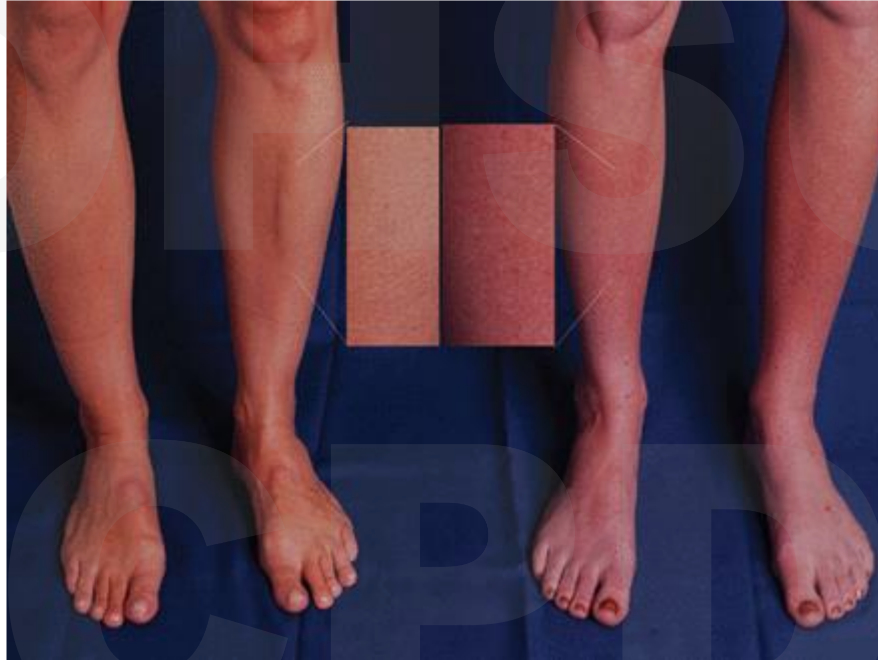
Acrocyanosis



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Diagnosis

- Orthostatic vitals (NASA lean protocol)
  - Lying BP and HR- have patient lie for 5 min prior
  - Sit- check BP and HR immediately
  - Stand- check BP and HR, lean shoulder blades against the wall, feet 6-12 inches in front of wall
  - Continue standing and repeat HR and BP at 2, 5 min and 10 min
- Autonomic reflex testing (done through OHSU neurology, don't need to see a neurologist)
  - Quantitative sudomotor axon reflex test (QSART)- tests postganglionic sudomotor function
  - Heart rate response to deep breathing to assess cardiovagal function
  - Valsalva maneuver to assess cardiovascular adrenergic and cardiovagal function
  - Head up tilt to assess cardiovascular adrenergic function

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Non-pharmacologic treatment

- Boluses of water: 8-10 cups of water per day; 100 ounces
- Bolus of 1(2?)L of IVF over 1 hour for acute reduction of tachycardia; risks of long term use are significant
- Increase salt intake: goal 2 teaspoons (8-12 grams) per day
- Compression: stockings, thigh highs, high waisted tights, abdominal compression (30-40mmHg)
- Elevated head of bed
- CHOPS exercise protocol (aka Levine Protocol)/recumbent exercise program

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Electrolyte options

- Salt tabs/salt stick
- Electrolyte mixes/tablets: Liquid IV (500mg of sodium), Nuun (300mg of sodium), LMNT (1000mg of sodium, sweetened with stevia), Trioral (1695mg sodium, sweetened with stevia)…
- DIY electrolyte recipe:
  - 1.5-2 cups water
  - Juice of ½ lemon
  - ¼ teaspoon sea salt
  - 2 tsp raw honey

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Medications

- ***Fludrocortisone:*** expands plasma volume through sodium retention
  - SE: hypokalemia, worsening headaches, acne, fluid retention with edema
  - Dose: 0.05-0.3mg once daily
- ***Midodrine:*** α-1 agonist, vasoconstrictor
  - SE: positional hypertension, goose bumps, scalp tingling, headaches
  - Dose: 2.5-10mg PO q4 hrs 3 times per day with last dose 4 hours prior to lying down
- ***Pyridostigmine:*** increase levels of synaptic acetylcholine, increase parasympathetic nervous system, decreasing HR
  - SE: Gastrointestinal, diarrhea
  - Dose: 30-60mg QD-TID, start low and increase

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- ***Beta blockers:*** reduce heart rate
  - SE- fatigue, brain fog, exercise intolerance, hypotension
  - Dose: start with 10mg propranolol, increase to BID; may increase further as tolerated
- ***Clonidine:*** decrease sympathetic nervous system outflow
  - SE- hypotension, drowsiness, fatigue
  - Dose: 0.1-0.2 mg BID to TID
- ***Ivabradine:*** blocks the funny channel, decreases heart rate; consider early for long COVID if possible (usually requires cardiology referral for coverage)
  - SE: blurred vision, chest pain, irregular heartbeat, fatigue
  - Dose: 5-7.5mg BID

- ***DDAVP:*** expands plasma volume; only used as PRN, generally less than weekly use
    - SE: hyponatremia, edema, headache
    - Dose: 0.2mg per dose
- ***Methyldopa*:** false neurotransmitter, lowers HR and sometimes BP
    - SE: drowsiness, fatigue
    - Dose: 125-250mg BID
- **Droxidropa:** amino acid precursor of norepinephrine, helps with dizziness and fatigue
    - SE: headache, hypertension
    - Dose: 100mg PO TID; max 600mg TID
- ***Modafanil:*** stimulant which may help with brain fog without worsening tachycardia
    - SE: confusion, hypertension, GI symptoms
    - Dose: 50-200mg PO BID

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- ***Octreotide*: vasoconstrictor**
  - SE: supine hypertension
  - Dose: 12.5-50mcg SQ BID
- ***Erythropoetin*: increase blood volume**
  - SE: MI, stroke
  - Dose: 50U/kg, 3 times/week for 6-12 weeks

Meds that may worsen POTS

- Drosperinone: Yaz, Yasmin, Slynd
- Serotonin norepinephrine reuptake inhibitors
- Tricyclic antidepressants
- Angiotensin-converting enzyme inhibitors
- Calcium channel blockers
- Diuretics
- Monoamine oxidase inhibitors

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