An Overview of Hypermobile Connective Tissue Disorders

Epidemiology, Overview of Comorbidities, Interview, Diagnosis, Treatment

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2/11/25

Disclosures

Sonia Sosa has no disclosures

Alena Guggenheim has no disclosures

In the news…

Sia:

“Hey, I'm suffering with chronic pain, a neurological disease, ehlers danlos and I just wanted to say to those of you suffering from pain, whether physical or emotional, I love you, keep going. Life is (bleeping) hard. Pain is demoralizing, and you're not alone.”

What the headlines said:

“Sia announces that she has a neurologic condition called Ehlers Danlos”

Call to Action

> “They (those with EDS) are questioned, judged not to be ill but suffering from an imaginary illness, and given a psychiatric diagnosis (‘it’s all in your head’). Moreover, they have been ignored, belittled and blamed for their condition. The gaps and uncertainties in health-care professionals’ medical knowledge concerning EDS symptoms cause their patients to struggle for their credibility and dignity.”

–Berglund, B., et al. (2010) Dignity not fully upheld when seeking health care: experiences expressed by individuals suffering from Ehlers-Danlos Syndrome. Disability and Rehabilitation 32:1-7.

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Clinician-associated traumatization from difficult medical encounters: Results from a qualitative interview study on the Ehlers-Danlos Syndromes

Colin M.E. Halverson [a,b,c,d,*], Heather L. Penwell [a], Clair A. Francomano [e]

"We found that the cumulative effects of numerous negative encounters lead patients to lose trust in their healthcare providers and the healthcare system, and to develop acute anxiety about returning to clinic to seek further care. We describe this as clinician associated traumatization. Ultimately, our interviewees described the result of this traumatization as worse – but preventable – health outcomes."

Learning objectives

- Discuss the prevalence of hypermobility and Ehlers-Danlos Syndrome (EDS) and the implications of delayed diagnosis
- Define hypermobile EDS and explain how this differs from generalized hypermobility and also the other EDS subtypes.
- Apply diagnostic criteria to suspected hypermobile connective tissue disorders
- Review the conditions which are most commonly associated with a diagnosis of hypermobile EDS.
- Describe some treatment options for patients with hypermobile EDS.

EDS Myths

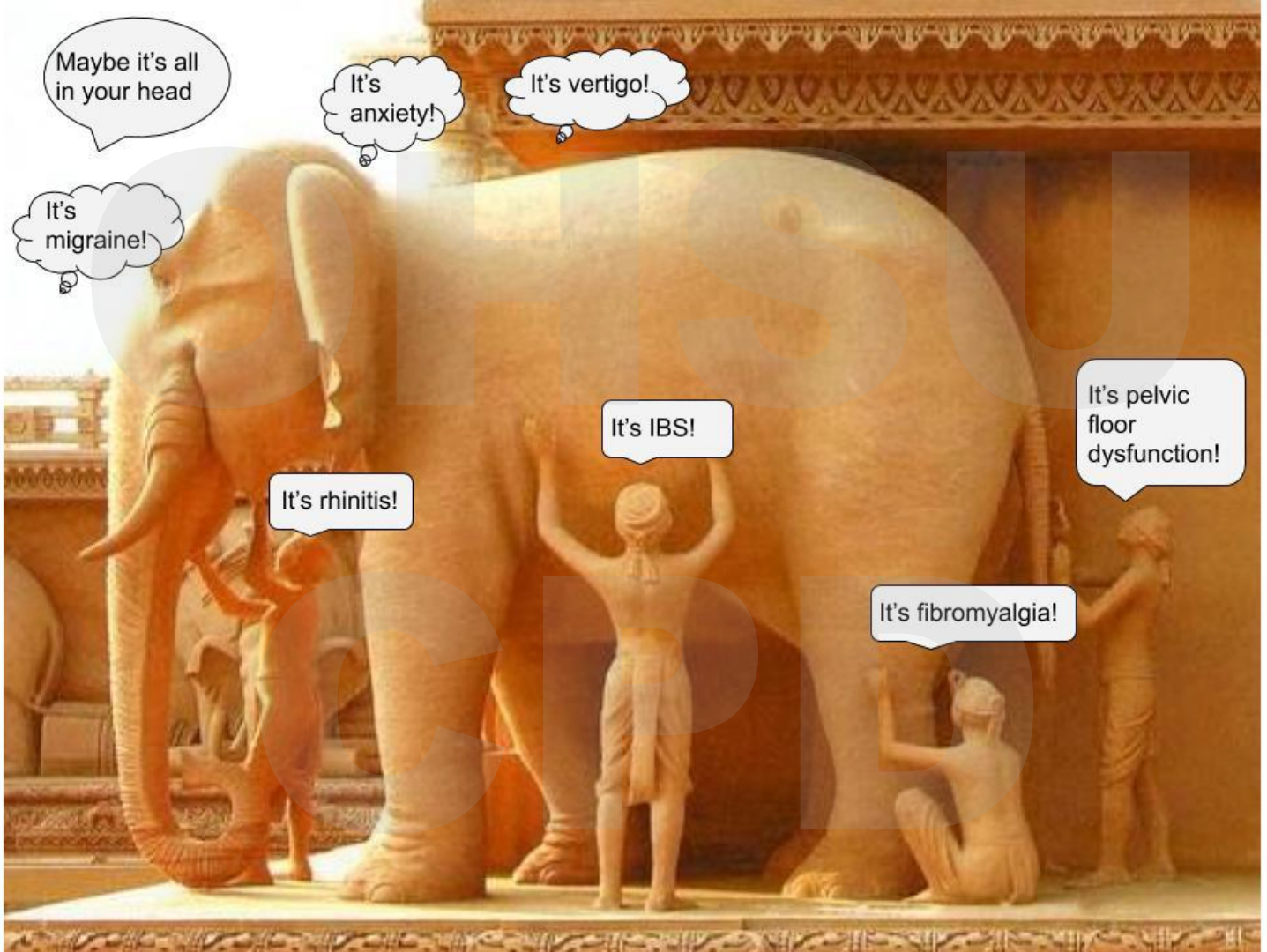
There is no point in diagnosing because it does not change management

You can only have EDS if you have dislocations

hEDS requires a genetic test for diagnosis

EDS doesn’t cause pain

EDS causes broken bones


Maybe it's all in your head
It's anxiety!
It's vertigo!
It's migraine!
It's IBS!
It's pelvic floor dysfunction!
It's rhinitis!
It's fibromyalgia!

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)

Most common previous diagnoses

- Chronic fatigue syndrome
- Fibromyalgia
- Chronic pain syndromes
- IBS and functional dyspepsia
- Anxiety
- Amplified pain disorder
- Medically unexplained symptoms

Types of EDS

- **Hypermobile: Covered below**
- Classical: Velvety, stretchy, fragile skin, spontaneous ecchymosis. (more common)
- Classical-like: hypermobility, soft/fragile skin
- Vascular: Possible arterial/organ rupture (most serious)
- 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

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: discovered April 2018: joint laxity, hyperextensible skin, abnormal scars, osteoporosis

Evolving terminology

- Generalized joint hypermobility/laxity (**GJH**) & benign joint hypermobility (BJH)
  - Does not specify presence of pain
- Joint hypermobility syndrome (**JHS**) & hypermobility syndrome (**HMS**)
- Ehlers-Danlos Syndrome – hypermobility type (**EDS – HT** or **type III**) old terminology
- **Newly proposed terminology: hypermobile Ehlers-Danlos Syndrome (hEDS) and Hypermobility Spectrum Disorder (HSD)**
- **Available ICD10 codes: Hypermobility syndrome M35.7, hypermobile EDS Q79.62**

Prevalence of HSD/EDS

Prevalence of HSD

- 1/5000 (0.0002%) Steinmann 2002
- 7.5/1000-20/1000 (0.75-2%) HSD (Hakim 2006)
- 30.4/1000 (3.4%) HSD (Mulvey 2013)
- 1/500 (0.2%) in recent Wales population study (Demmler 2019)
- **80-90% of all EDS is hEDS, affects ~10 million people in the U.S. (Tinkle 2017)**
- **True prevalence is unknown due to lack of provider education and recognition**

The Patient Visit

Approach to history

- Start in early childhood and work towards present
- General health timeline with major medical events, symptoms, diagnoses, work-up, trauma, medication trials & trauma
- Nutritional, environmental, and infectious history
- Ask about sleep, stressors, support systems
- Family history

Remember!

- These patients often normalize their own experiences
- Often have a family member that experienced the same and reinforced normality or that dismiss(ed) their symptoms
- Have often been dismissed by many physicians as anxious or having somatic complaints

Diagnostic criteria for hypermobile Ehlers-Danlos syndrome (hEDS)

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

Distributed 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

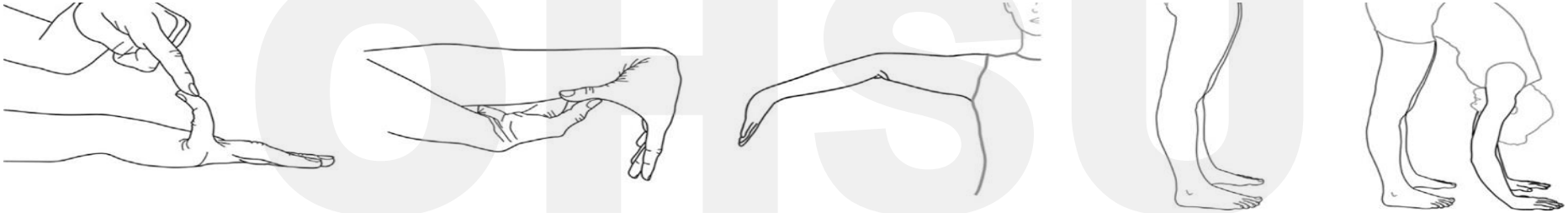
2017 hEDS Diagnostic Criteria

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

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:

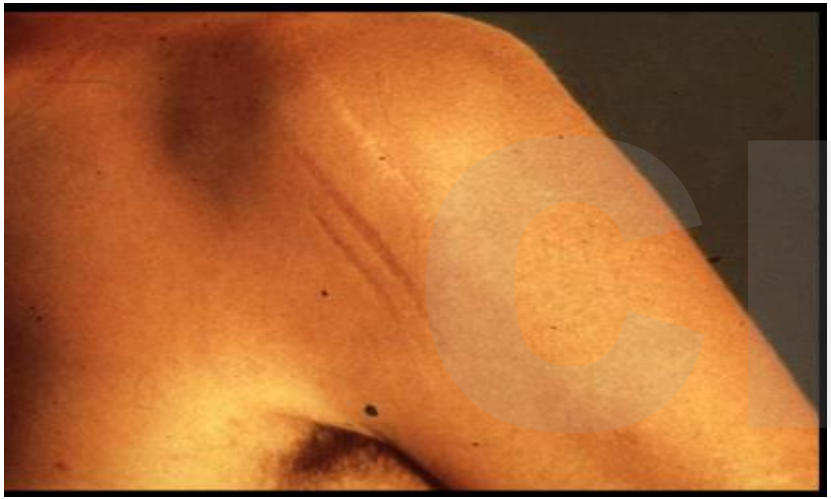
A. Systemic manifestations: 5 of 12 options positive
B. Family history
C. Musculoskeletal complications: 1 of 3 options positive

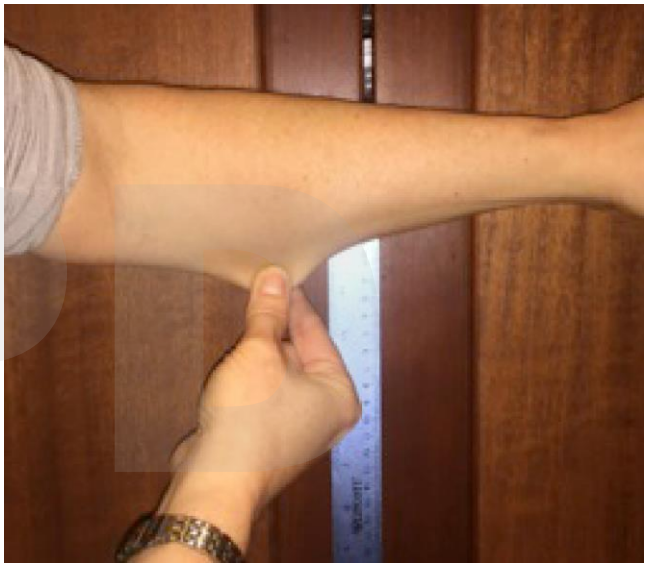
Criteria 2A: Systemic Manifestations

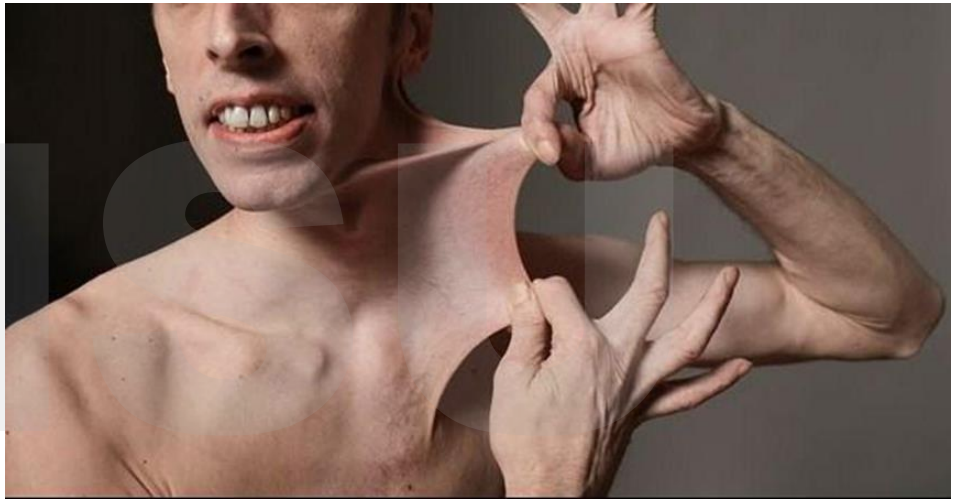
i. Unusually soft or velvety skin

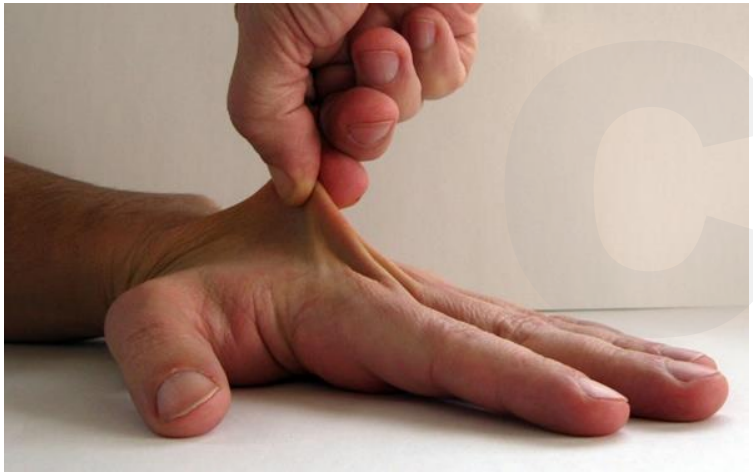
ii. Mild skin hyperextensibility (>1.5 cm on volar, non-dominant forearm)

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







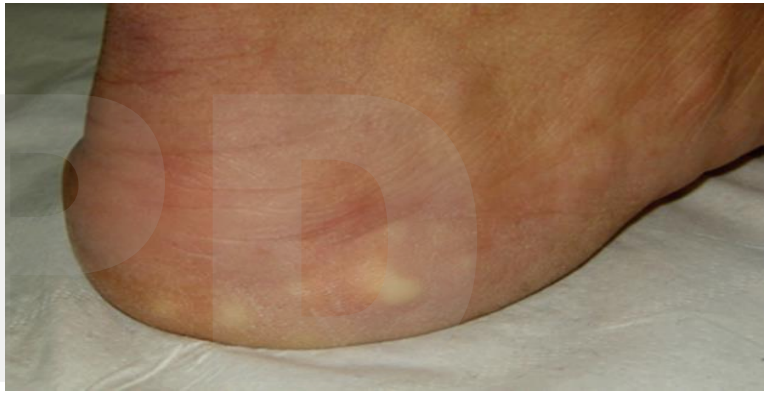


VS

Criteria 2A: Systemic Manifestations

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

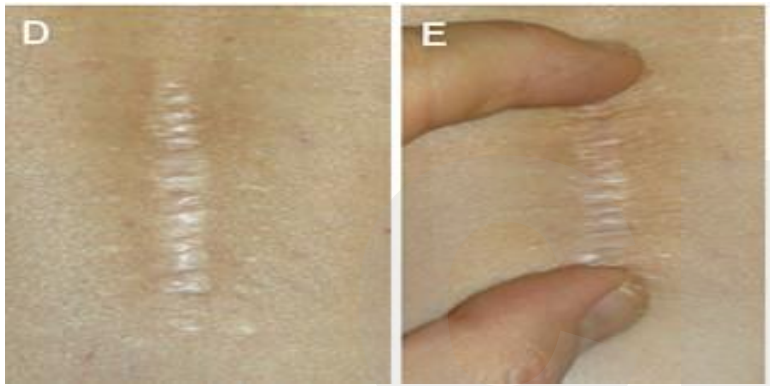
Subcutaneous fat herniations through the fascia, may appear only with **weight bearing*



Malfait 2017

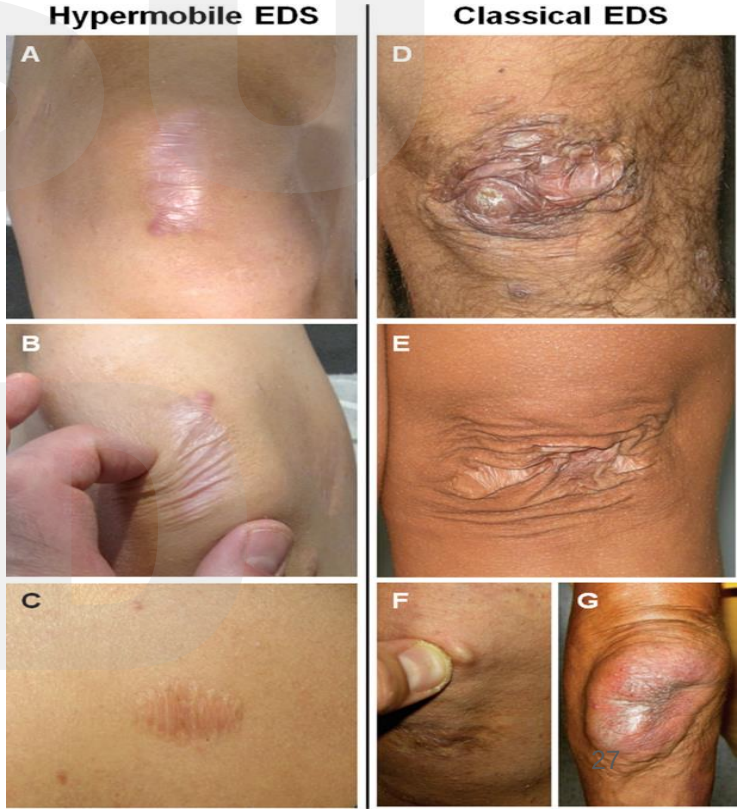
Criteria 2A: Systemic Manifestations

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



Castori, et al, 2015

Malfait, et al, 2017

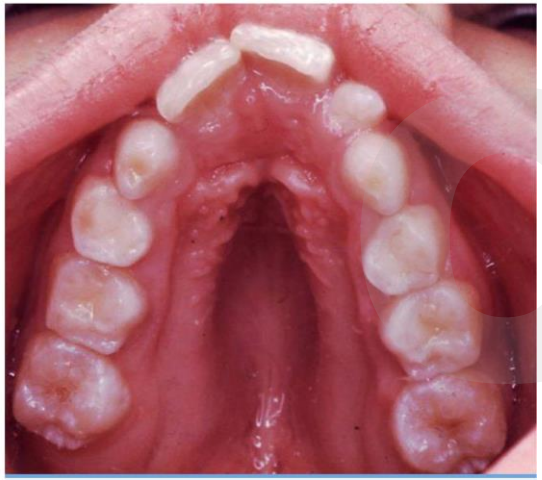


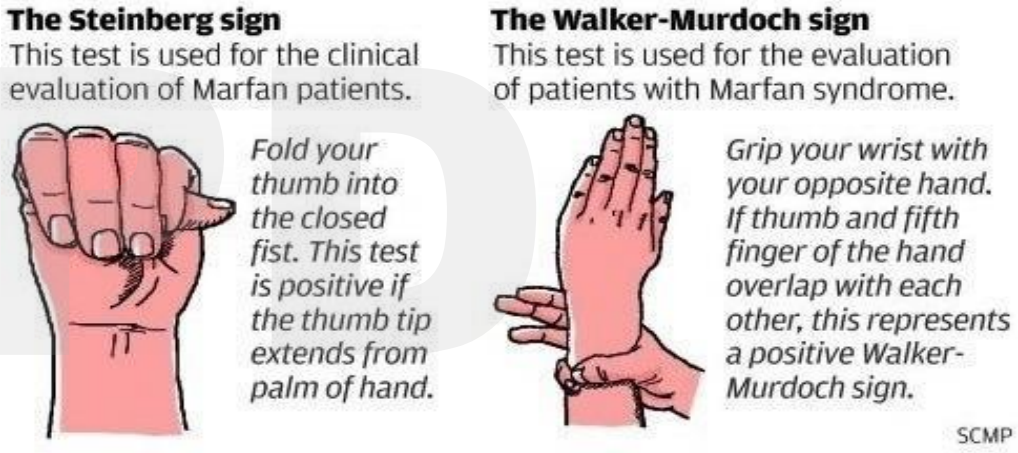
Criteria 2A: Systemic Manifestations

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



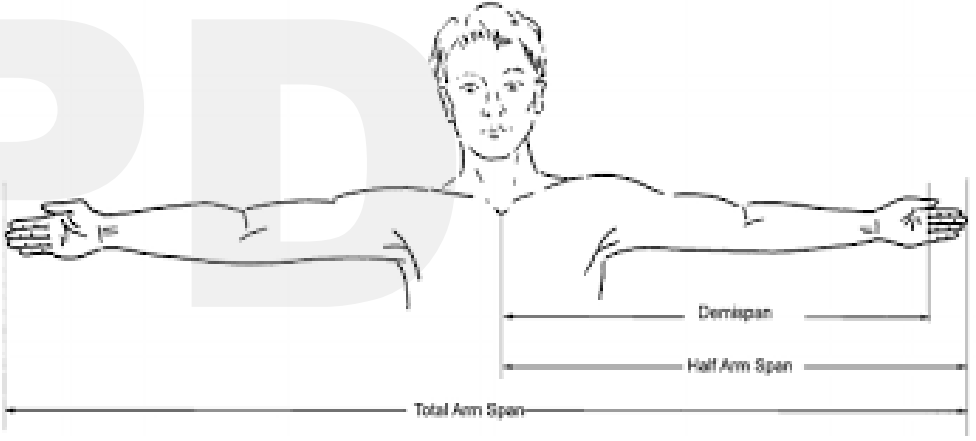


2A: Systemic Manifestations

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

xi. Mitral valve prolapse, mild

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



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

2B: Family History

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

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

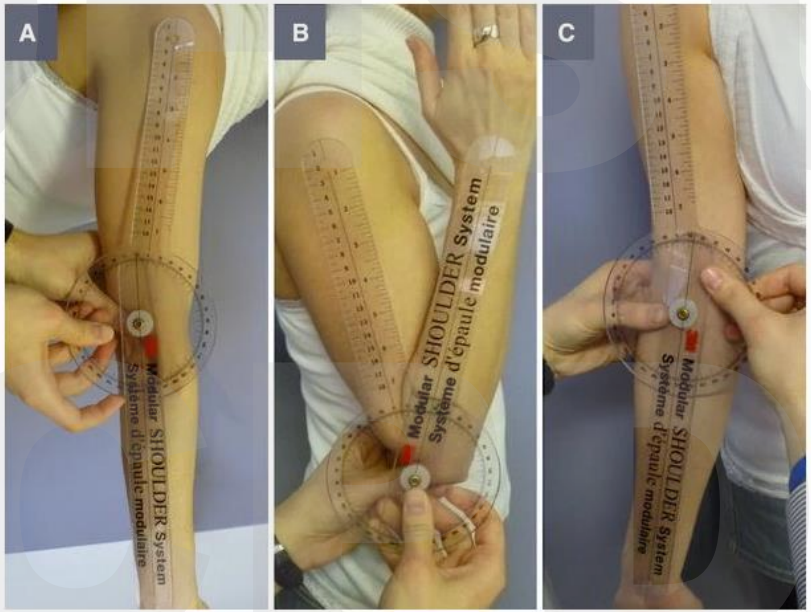
If yes to ≥ 1 item, then positive for musculoskeletal complications

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.)

Goniometric Measures: Cheap and Inaccurate



The landmarks for (**A**) extension and (**B**) flexion are the lateral epicondyle, tip of the acromion, and midline of the wrist. (**C**) The instrument was centered on the crossline of the biceps tendon and the interepicondyle axis for the carrying angle measurement.

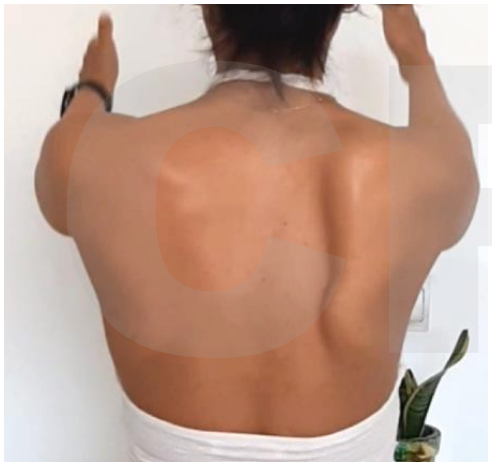
Chapleau 2011

Genetic Connective Tissue Physical Exam MSK

Chest wall deformity

Scoliosis

Pes Planus/hindfoot deformity

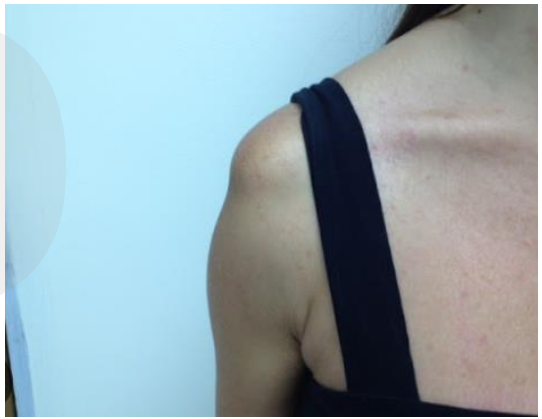


Wingspan

Scapular winging

Arachnodactyly

Sulcus sign



Genetic Connective Tissue Physical Exam Skin

Stretch marks

Soft, velvety skin

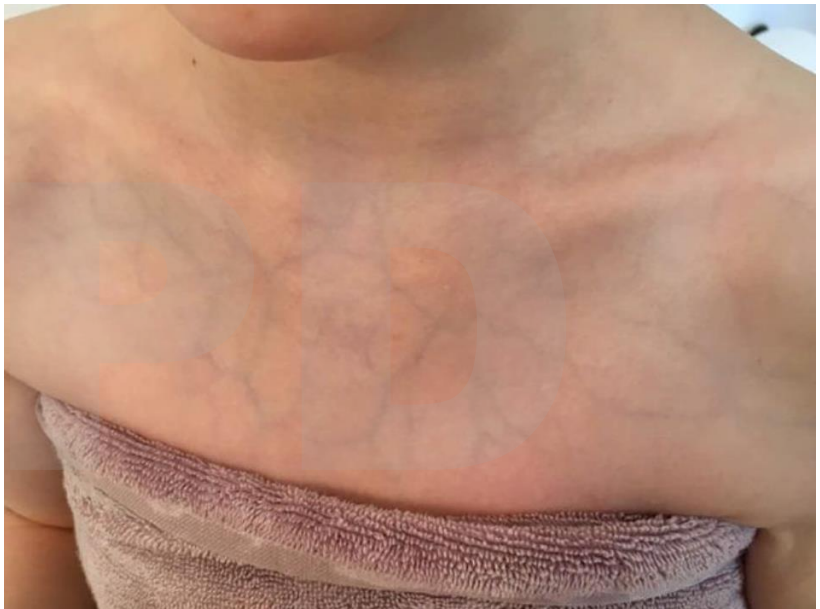
Translucent skin

Skin elasticity

Skin feel

Scar atrophy

Piezogenic papules- heels



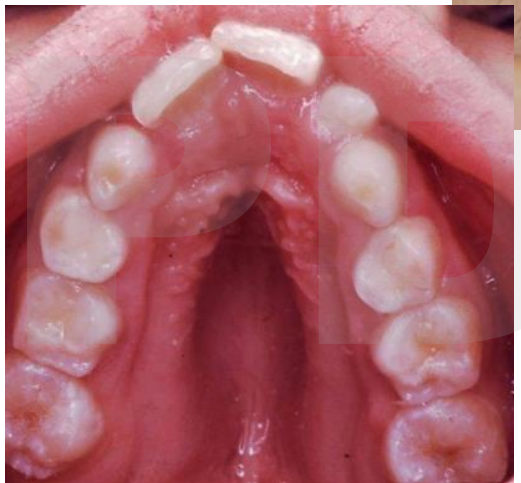
Genetic Connective Tissue Physical Exam Orofacial

Blue sclera

Mallampati score

Dentition crowded

High arched palate/palate expander



Effects of hEDS on the body systems

Musculoskeletal

Hypermobility
Subluxations
Dislocations
Recurrent sprains
Muscle spasm
Pes Planus
Arthralgia
Myalgia
Kyphosis/Scoliosis
Early osteoarthritis
Labral tears
Tendon/ligament tears

Tinkle 2017, Stern 2017

Hypermobility and Pain

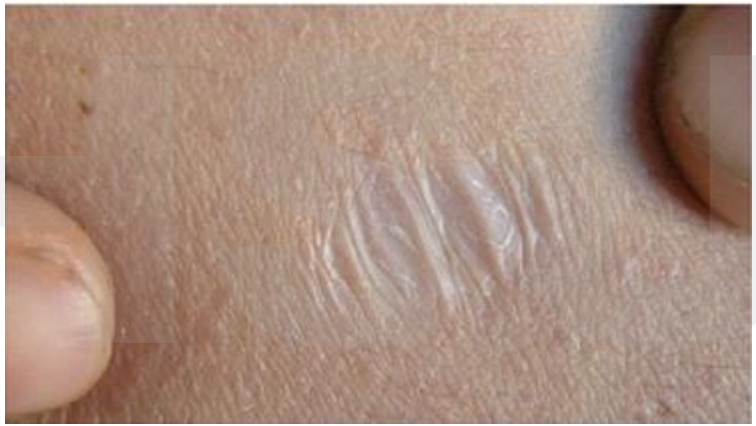
Molander et al evaluated 40,518 patients in a pain registry comparing PROMS in different pain diagnoses including HSD, spinal pain, whiplash injury, fibromyalgia.

Patients with HSD were younger, more often female, and suffered from pain for the longest time and of similar severity compared with patients who had localized/regional pain conditions.

Chronic pain is found in up to 90% of patients with hypermobile EDS.

Molander 2020
Voermans 2010

Integumentary



Soft skin

Stretchy skin

Easy bruising

Atrophic scarring

Poor wound healing

Telangiectasias

Translucent skin

Beckers et al 2016; Castori et al, 2011; Castori 2015 Columbi et al, 2015; Fickree 2017; Tinkle et al, 2017

Cardiovascular

Mitral valve prolapse

Aortic root dilation

Varicose veins

Pelvic congestion syndrome

Dysautonomia with tachycardia, hyper/hypotension*

*not cardiovascular in origin

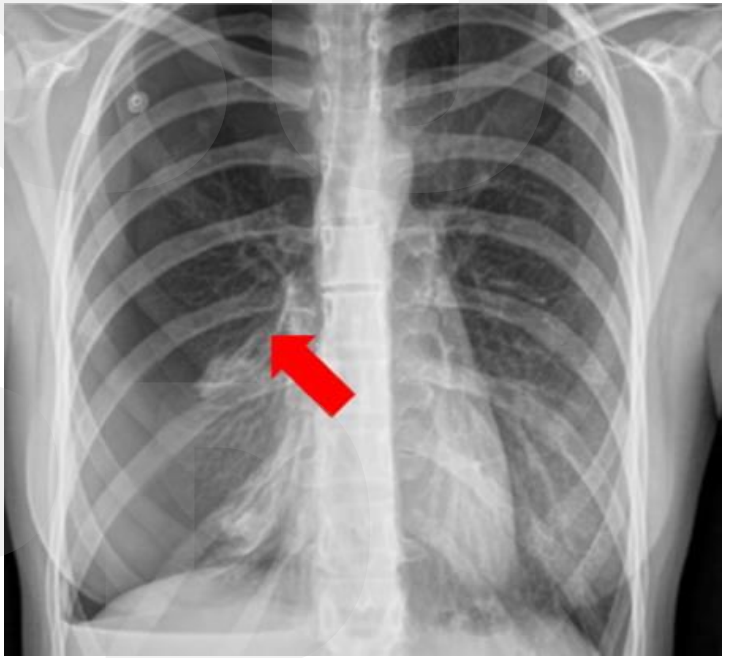
Beckers et al 2016; Castori et al, 2011; Castori 2015 Columbi et al, 2015; Fickree 2017; Tinkle et al, 2017

Pulmonary

Spontaneous pneumothorax

Reactive airway disease

Dyspnea



Gastrointestinal

Gastritis
Irritable bowel syndrome
Rectal prolapse
GERD
Esophageal spasms
Low pressure dysphagia
Dysmotility
Small intestinal bacterial overgrowth

Hemorrhoids
Vascular compression syndromes
Hernias
Diverticula
Inflammatory bowel disease
Celiac

Fikree 2017, Inayet 2018, Alomari 2020, Nelson 2015

Gynecology

Gynecological issues are more common in hEDS compared to other genetic subtypes

Menorrhagia 76%

Dysmenorrhea 72%

Dyspareunia 43%

Vulvodynia

Pelvic organ prolapse

Gilliam 2019, Hugon-Rudin 2016, Glayzer 2021

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

Obstetrics- in labor

Abnormal fetal presentation: transverse, breech

Rapid 2nd stage of labor

Increased risk of bleeding/postpartum hemorrhage

Requirement for more anesthesia

Urinary

Incontinence
Enuresis
Vesicoureteral reflux
Renal cysts
Bladder diverticula
Interstitial cystitis/painful bladder syndrome
Chronic UTI

ENT

Dysphagia

Temporomandibular joint dysfunction

Obstructive Sleep Apnea

Upper airway resistance disorder

Dental crowding

Stöberl 2019, Sedky 2019, Mitakides 2017, Mitakides 2018

Ocular

Xeropthalmia
Myopia
Accomodation defects
Astigmatism

Beighton 1970, Pemberton 1966, Gharbiya 2012

Neurological

Dysautonomia

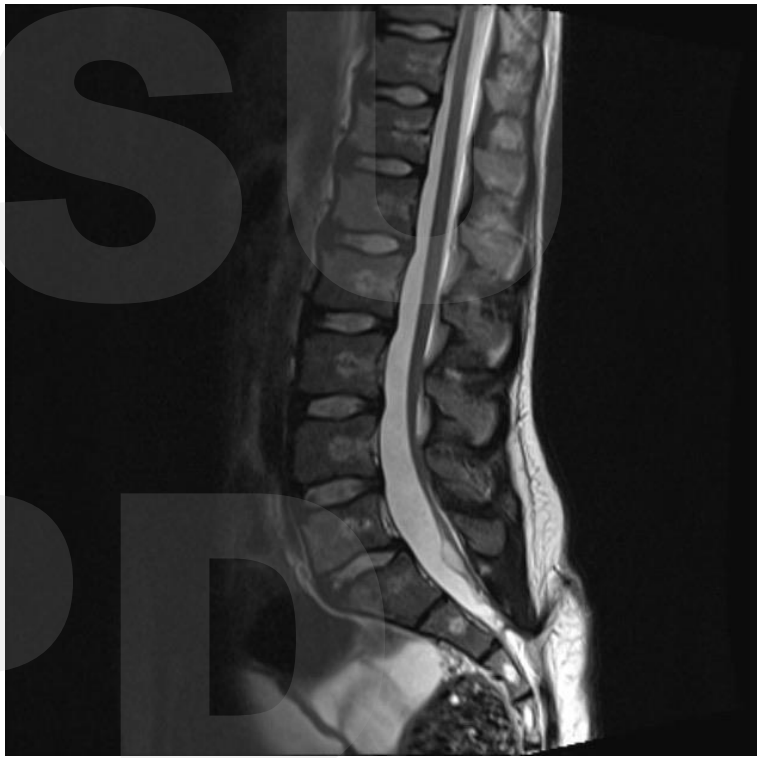
Migraine/ Chronic headache

Tethered cord

Chiari malformation

Spontaneous CSF leaks

Craniocervical instability



Klinge 2022, 2024, Henderson 2017, Reinstein 2013

Psychological

Anxiety

OCD

PTSD

Neurodiversity

ADHD

Depression

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**

Through the lifespan

Hypermobility phase (childhood):

Distribution equal between males and females

Sprains and dislocations

“Growing pains”

Pain with repetitive tasks such as handwriting

Easy fatigability

Developmental dyspraxia (clumsiness) with mild hypotonia

Pain phase (20-40s)

Generalized and chronic pain; often diagnosed with fibromyalgia
Headaches
Fatigue
Functional GI disorders
Autonomic dysfunction

Stiffness phase

Seen significantly more in females than males
Disabling pain and fatigue
Reduced muscle mass and weakness
Diminished proprioception
Early osteoarthritis, tendonitis, tendonosis

Biological Sex

Assigned female at birth>assigned male at birth

Generally more inherent joint stability in presence of testosterone

Hormonal influences:

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

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

Scheper 2017, Tinkle 2017, Rogers 2017, Bonamichi-Santos 2018, Skeik 2019

Dysautonomia/POTS

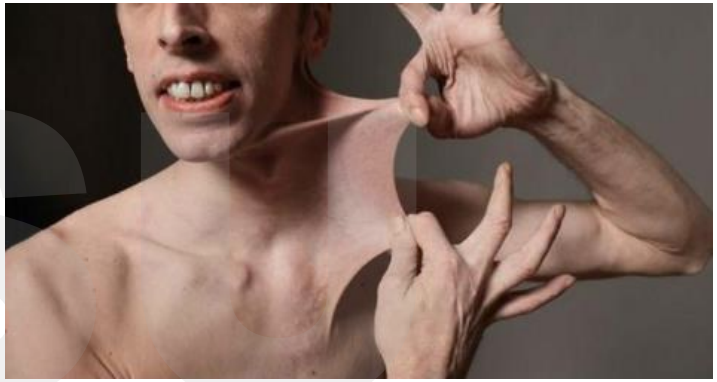
Diagnosis: Sustained heart rate increase of at least 30 beats/min (for adults) or at least 40 beats/min (for patients aged 12–19 yr) within 10 minutes of standing, in the absence of orthostatic hypotension and dehydration

- In office orthostatics (NASA lean)
- Autonomic reflex testing (available to order in EPIC)

Initial POTS treatment

- Boluses of water: aim for 80-100 ounces of water per day
- Salt: aim for 8-12 grams (2 teaspoons per day)
  - LMNT or Trioral have the highest amount of sodium
- Compression: the more coverage the better
- Elevate head of bed
- CHOPS exercise protocol/recumbent exercise program
- 1L IV saline or LR for acute tachycardia
- Medications: fludrocortisone, midodrine, pyridostigmine, ivabradine, beta blockers…

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

Genetics panel available to order by PCPs (may not covered by insurance): Invitae Connective Tissue Panel, order as lab other

Shalhub 2019

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

Sample Initial Treatment

1) Physical therapy with a PT that specializes in hypermobility

2) Occupational therapy- hand therapy, bracing…

3) Movement: progressive resisted exercise, water based, supine, strength training

4) Judicious use of splinting/compression

5) Body Work- massage, manipulation, craniosacral, acupuncture, chiropractic

6) Mental health: mindfulness, CBT, breath work

7) Herbs and Supplements: magnesium, NAC and acetyl L-carnitine, turmeric, nettles, california poppy

8) Medications: tylenol, NSAIDs, topical pain relief (diclofenac, capsaicin, epsom, lidocaine), gabapentin/pregabalin, duloxetine, memantine, **low dose naltrexone (LDN)**

9) Evaluate for and treat comorbidities such as POTS and MCAS

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.

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


Q & A

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