Inherited Connective Tissue Disorders

Staci Kallish, DO
Hospital of the University of Pennsylvania
Perelman School of Medicine
Department of Medicine
Division of Translational Medicine and Human Genetics

Objectives

- Understand spectrum of inherited CT disorders
- Understand common signs suggestive of an inherited CT disorder
- Be able to recognize more common heritable CT disorders
- Understand when referral to Clinical Genetics is warranted
More than Marfan syndrome

- More than 35 distinct heritable disorders of connective tissue identified
- These conditions have overlapping features
- Some have significant risk of complications

The connective tissue problem

- Connective tissue varies from tissue to tissue
  - Contains a number of cellular types – collagen, elastin, fibrillin, others
  - Modified by a number of proteins – metalloproteinases, lysyl hydroxylase 3, homocysteine
  - Some proteins glycosylated
- Genetic defects in a single component of connective tissue may affect many organs (pleiotropy)
  - Overlapping, multi-systemic disorders
Marfan syndrome

- Clinical diagnosis based on characteristic findings, family history
- Prevalence ~1:5,000-1:10,000
- 25% de novo, 75% inherited
  - Autosomal dominant
- Molecular analysis useful in confirming diagnosis in proband, in testing family members before signs appear
Multi-system Disease in MFS

- **Eye**: myopia, ectopia lentis (~60%), retinal detachment
- **Skeleton**: excessive linear growth of long bones, pectus, scoliosis, joint laxity
  - Facial: long face, deep-set eyes, downslanted palpebral fissures, malar hypoplasia, micrognathia, narrow palate
- **Cardiac**: aortic dilatation
  - Progressive with predisposition to dissection, MVP
- **Dural ectasia**
- **Skin**: striae, hernias
- **Pulmonary**: bullae, predisposition to spontaneous pneumothorax
Ghent criteria

- **Without family history:**
  - Aortic z-score ≥2 + ectopia lentis
  - Aortic z-score ≥2 + *FBN1* mutation
  - Aortic z-score ≥2 + systemic score ≥7
  - Ectopia lentis + *FBN1* mutation + enlarged aorta and/or dissection

- **With family history:**
  - Ectopia lentis
  - Systemic score ≥7
  - Enlarged aorta (Z ≥2 or 3 depending on age)

Marfan Calculator

Marfan.org.
Pathogenesis of MFS

- Pathogenesis is complex
- Dominant negative effect of mutant fibrillin-1
  - Abnormal fibrillin-1 monomers interfere with function of normal fibrillin-1
- Fibrillin is a major building block of microfibrils
  - Serve as substrates for elastin in the aorta and other connective tissues
  - Constitute the structural components of the suspensory ligament of the lens
- Incorporation of mutant fibrillin-1 into microfibrils disrupts structure, stability, and function
- Fibrillins ultimately interact with TGF-B signaling pathway

Management of MFS

- ARB or B-blocker to reduce hemodynamic stress on aorta
  - ARB likely also impacts FBN/TGFBR pathway to prevent enlargement of aorta
- Moderate aerobic exercise is acceptable
  - Limit to 50% aerobic maximum
- Avoid strenuous static or isometric exercise
  - Increases peripheral blood pressure and proximal aortic wall stress
- Supportive care for skeletal, ophthalmologic features (surgical correction of severe scoliosis or pectus, eye examinations)
**Atenolol in MFS**

![Graph showing the rate of change in aortic ratio for Atenolol and Control groups.](image1)

- Figure 2. Empirical Distribution Functions of the Rate of Change in the Aortic Ratio, According to Study Group. The height of each curve at any point shows the proportion of patients with values at or below the value given on the x axis. There is little overlap between the two groups.

**Atenolol vs Losartan in MFS**

![Graph showing the change in aortic root z score and aortic root diameter according to treatment group.](image2)

- Figure 3. Change in Aortic Root z Score and Aortic Root Diameter, According to Treatment Group. The aortic-root z score is the z score for the maximum diameter of the aortic root, indexed to body-surface area. Panel A shows the baseline-adjusted rate of change in the aortic-root z score over the 3-year period (solid lines), with 95% confidence intervals (dashed lines) for the pairwise comparison. Panel B shows the baseline-adjusted rate of change in the maximum diameter of the aortic root over the 3-year period (solid lines), with 95% confidence intervals (dashed lines) for the pairwise comparison.
Atenolol vs Losartan in MFS

![Graph showing the comparison between Atenolol and Losartan in MFS](image)

**Figure 1.** Freedom from Adverse Clinical Outcomes, According to Treatment Group. The graph shows the estimated probability of freedom from aortic dissection, aortic root surgery, and death (solid lines), according to treatment assignment, with 95% confidence intervals (dashed lines) for the post hoc comparison. A total of 543 participants completed the 3-year follow-up visit (mean follow-up, 3.0±0.1 years). The inset shows the same data on an enlarged y-axis.

Allelic disorders

- **Ghent criteria distinguished MFS from:**
  - MASS phenotype
    - Myopia (but no ectopia lentis)
    - MVP
    - Borderline and non-progressive **A**ortic enlargement (Z<2)
    - Non-specific **S**kin and **S**keletal findings (systemic score ≥5)
  - Ectopia lentis syndrome – ectopia lentis ± systemic score + **FBN1** mutation not associated with aortic involvement or without **FBN1** mutation
  - Mitral valve prolapse syndrome – MVP + enlarged aorta (Z <2) + systemic score (<5) without ectopia lentis
<table>
<thead>
<tr>
<th>Loeys Dietz syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Clinical diagnosis based on findings in 4 major systems</td>
</tr>
<tr>
<td>• Vascular, skeletal, craniofacial, cutaneous</td>
</tr>
<tr>
<td>• Variable spectrum</td>
</tr>
<tr>
<td>• Caused by mutations in $TGFBR1$, $TGFBR2$, $SMAD3$, and $TGFB2$</td>
</tr>
<tr>
<td>• Autosomal dominant inheritance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LDS – Vascular Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Aortic dissection or dilatation</td>
</tr>
<tr>
<td>• Aggressive dissection</td>
</tr>
<tr>
<td>• Risk of dissection at smaller diameters than seen in MFS</td>
</tr>
<tr>
<td>• Arterial aneurysms and tortuosity</td>
</tr>
<tr>
<td>• 50% aneurysms beyond aortic root, not visible by echocardiogram</td>
</tr>
<tr>
<td>• Tortuosity does not typically cause problems</td>
</tr>
</tbody>
</table>
LDS – Vascular Findings

Marked tortuosity of aorta, aneurysms of aortic root & subclavian artery

Aortic root dilatation, severe tortuosity of abdominal arterial branches

LDS – Vascular Findings

Ped Rad 2009.

**LDS – Craniofacial findings**

- Ocular hypertelorism
- Short, wide, or bifid uvula and/or cleft palate
- Craniosynostosis

**LDS – Skeletal and Skin findings**

**Skeletal:**
- Pectus deformity
- Scoliosis
- Arachnodactyly
- Joint laxity
- Congenital talipes equinovarus

**Skin:**
- Translucent skin
- Easy bruising
- Dystrophic scars
TGFβ receptor-mediated signaling pathway

TGFB-1 and -2 receptors activate Smad-dependent and -independent pathways.

Smads are family of transcription factors critical for transmitting signals from TGFBR to nucleus to regulate expression of:
- Matrix proteins - collagen (COL1A1, COL3A1), fibronectin
- Members of fibrinolytic system

How have LDS patients presented?

65% with TGFBR2 mutations were first identified because of aortic aneurysm, dissection or sudden death.

Circulation 2009.
### LDS Natural History

- Mean age of death 26 years
  - 67% thoracic aortic aneurysm
  - 22% abdominal aortic aneurysm
  - 7% cerebral bleed
- 1/3 patients have dissection, surgery for aneurysm, or died from dissection or rupture by 19 years
- Half of women have complications in pregnancy (aortic dissection, uterine rupture)

### Management of LDS

- Careful monitoring of aorta
  - Surgical correction at smaller size than in MFS (~4cm in adolescents, adults)
- Treatment with ARB or B-blocker
- Supportive care for skeletal, craniofacial features (surgical correction of cleft palate, severe scoliosis or pectus)
Ehlers Danlos Syndrome - Vascular type

- Arterial/intestinal/uterine fragility or rupture
- Hypermobility of small joints
  - Tendon and muscle rupture
- Extensive bruising, acrogeria
- Thin, translucent skin
  - Visible veins (chest and abdomen)
- Characteristic facial appearance
- Autosomal dominant inheritance
  - May have family history of sudden death
- Caused by structural defects in pro a 1(III) chain of collagen type III
- Mutation analysis of COL3A1 gene also recommended

EDS - Vascular type
EDS – Vascular type Outcomes

- 25% experience a major medical complication by 20 years
  - 80% by 40 years
  - Arterial or organ rupture
  - Median age of death 48 years

- 12% risk of death in pregnancy
  - Peripartum arterial or uterine rupture

NEJM 2000.
Joint Hypermobility

- Based on Beighton scale
- Score of 5/9 or more indicates joint hypermobility
  - Passive dorsiflexion of 5th finger beyond 90 degrees - 1 point each hand
  - Passive apposition of thumb to flexor aspect of forearm - 1 point for each hand
  - Hyperextension of elbow beyond 10 degrees - 1 point for each elbow
  - Hyperextension of the knees beyond 10 degrees - 1 point for each knee
  - Forward flexion of the trunk with knees fully extended so that palms rest flat on floor - 1 point
- Some suggest score 6/9 significant pre-puberty, 4/9 significant >50 years

Beighton score

http://www.physio-pedia.com/images/8/82/Beighton_Score.png
Hypermobility syndromes reclassified

- 2017 reclassification of Ehlers Danlos syndromes and hypermobility syndromes
  - Specific criteria for each of 13 types of EDS
  - Classical, classic-like, cardiac-valvular, vascular, hypermobile, arthrochalasia, dermadosparaxis, kyphoscoliotic, brittle cornea syndrome, spondylodysplastic, musculocontractural, myopathic, periodontal

- Further classification of hypermobility into hypermobility spectrum disorders (HSDs)
  - Better classification of those with hypermobility
  - Understanding variability within families, over time
  - Includes hypermobile EDS

Hypermobility spectrum disorders
Hypermobile EDS

- Generalized joint hypermobility
  - Recurrent subluxations or dislocations
  - Chronic joint/limb pain
- Most common form of EDS
- Characterized by skin softness, easy bruising, and/or smooth, velvety skin
- Autosomal dominant inheritance
- Diagnosed clinically
- Molecular testing not available
- Now part of spectrum of HSDs

Complete criteria for hEDS

- 1) Generalized joint hypermobility
- 2) 2 out of 3 of the following:
  - Systemic features
  - Family history
  - Musculoskeletal complications
    - Cannot be used in patients with other autoimmune disease
- 3) Absence of skin fragility or signs of other inherited CTDs
## Complete criteria for hEDS

### Positive Beighton Score

Criteria for Beighton score is based on age, historical recall
- Pubertal and adolescent child: Beighton score ≥ 6
- Prepubertal up to age 50 yo: Beighton score ≥ 5
- Lower Beighton score (1 point lower) is acceptable if SPQ is positive (2/5 questions)

5 Point Questionnaire [Graham and Hakan, 2003]
- 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 thumbs to touch your forearm?
- As a child, did you amuse your friends by contorting your body into strange shapes or could you do splits?
- As a child or teenager, did your shoulder or kneecap dislocate more than one occasion?
- Do you consider yourself “double-jointed”?

### Complete criteria for hEDS

#### Criterion #2

- **Category A**: Systemic Manifestation of generalized CT disorder
- **Category B**: Positive Family History
- **Category C**: Musculoskeletal complications

**Category A**
- Sweating
- Unusually soft or velvety, subjective, recommend high threshold for positivity
- Milia skin hyperextensibility
- 1.5 cm or greater non-dominant forearm; if > 2 cm and other skin features consider Classic EDS
- Unexplained striae
- Back, groin, breasts, abdomen in adolescents, men, prepubertal women without HV weight gain/feats
- Petechiae papules on bilateral feet
- Hemiatrophy of subcutaneous fat present in heels upon standing
- Atrophic scarring of 2 sites
- Without formation of pagetaceous or hemorrhagic scars as in Classic EDS
- Recurrent/multiple hernias

#### Somatic/Skeletal

- Arachnodactyly
- *Thumb and Wrist sign on both sides
- *Aer Spine:Height > 1.05
- *Pelvis: rectal or uterine prolapse
- *Dental crowding and high/normal palate

#### Cardiovascular

- Mitral Valve Prolapse mild or greater
- Aortic root dilatation: *Z score > 2.0
- *Marfanoid features or aortic root dilatation consider Marfan, Loeks Dietz, Congential Contractural Arachnodactyly, Steppinett-Goldberg syndrome, Stickler, Homocystinuria, MEN2B, FTAAD

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AJMG 2017.
Complete criteria for hEDS

**Category B**  Positive Family History
- First degree relative meets updated criteria for hEDS

**Category C**  Musculoskeletal complications
NEED 1 out of 3
- Musculoskeletal pain in ≥ 2 limbs, daily, for > 3 months
- Chronic widespread pain for ≥ 3 months
- Recurrent joint dislocations - not related to trauma
- ≥ 3 dislocations in same joint OR
- > 2 dislocations in 2 different joints OR
- Joint instability at ≥ 2 sites (medically confirmed)

Category C cannot be used in patients with autoimmune disease or other cause for pain

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**Complete criteria for hEDS**

- Criterion #3 ALL requirements must be met
- Absence of unusual skin fragility
  - if present consider other forms of EDS
- Exclude other Disorders with Joint Hypermobility as a feature
  - exclude acquired CT disorders, autoimmune rheumatologic conditions (lupus, Rheumatoid arthritis)
  - exclude alternative diagnoses that can include joint hypermobility:
    - Neur muscular disorders including hypotonia
    - Heritable disorders of CT (other EDS, Loeyes Dietz, Marfan, OI)
    - Skeletal dysplasias
    - Chromosomal and single gene disorders (with associated features such as dysmorphic features, intellectual disability, developmental delay, autism spectrum disorders, congenital anomalies)

AJMG 2017.
Hypermobility spectrum disorders

Classical EDS

- Generalized joint hypermobility
  - Recurrent subluxations or dislocations
  - Chronic joint/limb pain
- Characterized by skin hyperextensibility, widened atrophic scars
- Autosomal dominant inheritance
- Diagnosed clinically
- Can evaluate for abnormal electrophoretic mobility of collagen type V
- Molecular diagnosis by \textit{COL5A1} or \textit{COL5A2} genes
  - Genetic testing now highly sensitive
  - Utility for such testing unclear
EDS – Classical and Hypermobility types

Joint laxity is an important problem
- Can cause chronic joint and limb pain
- Often leads to early osteoarthritis and pain
- Worsened by excess weight
- Strengthening the muscle surrounding the joints for stabilization
- Avoiding body movements that cause undue stress on the joints including high impact activities
- Physical therapy important for life-long strengthening of the muscles
- Aquatic therapy and swimming are especially helpful

HSDs – Musculoskeletal Features

- Orthotics provide support for lax joints
- Pain Management teams
### HSDs – Musculoskeletal Features

- **Low bone density is frequently seen**
  - Abnormality in the collagen formation and interaction with bones vs decreased level of activity that in some patients with EDS
  - Calcium and vitamin D supplementation is recommended
- **Headaches**
  - Cervical instability, with neck muscle overuse and strain

### HSDs – Skin Features

- **Easy bruising**
- **Molluscoid pseudotumors**
  - Fleshy lesions associated with scars found over pressure points
- **Subcutaneous spheroids**
  - Small spherical hard bodies, frequently mobile and palpable on the forearms and shins
  - May be calcified and detectable radiologically
- **Surgical concerns**
  - May require deep sutures as well as superficial sutures in the closure of wounds to allow for better healing
  - Sutures should be left in for twice as long as usual
  - May require the use of mesh with major surgeries to prevent future herniation in the surgical incision site
HSDs – Cardiac Features

- Likely does not predispose to mitral valve prolapse, aortic dilatation
- Screening echocardiogram recommendations unclear
- New AJMG guidelines conflicting – state baseline echo not recommended but include MVP or AoD in dx criteria for hEDS
- 2017 study of 325 patients, ~½ over 18 years
  - AoD Z-score >2 in 14.2% (46)
  - AoD z-score >3 in 5.5% (18)
  - No significant increases in size of AoD seen over time
- Recent Penn study of 209 adults with HSDs showing lower rates of AoD, no significant increase in MVP

HSDs – Cardiac Features

- MVP in 13/209 (6.2%)
  - 2 trivial, 5 mild, 1 moderate (5 unspecified)
- Only 3 patients had AoD
  - 2 had follow up echo with stable diameter
**Dysautonomia in H-EDS**

- Autonomic dysfunction reported as a frequent feature of EDS
- Non-musculoskeletal complaints are varied
  - Palpitations
  - Syncope
  - Orthostatic hypotension
  - Diarrhea and/or constipation
  - Abnormal temperature regulation

**2014 study of 39 patients with H-EDS**

- All female
- Resting heart rate higher in H-EDS versus controls
- Other signs of autonomic dysfunction included abnormal sweating and abnormal responses to Valsalva maneuver
- Orthostatic intolerance found in 74% patients
  - Seen earlier than in controls
  - More patients prematurely ended tilt testing due to symptoms
  - However, 3 patients ended tilt test due to symptoms despite adequate blood pressure
  - POTS in 41%, gradual orthostatic hypotension in 26%
- Findings suggestive of reduced sympathetic nervous system reactivity with resting overactivity
### Why dysautonomia in H-EDS?

**Possible mechanisms in H-EDS:**
- Peripheral neuropathy
- Increased distensibility of blood vessels with increased venous pooling during upright posture
- Medication use may contribute
  - Opiates cause vasodilatation
  - Trazodone, some blood pressure medications inhibit sympathetic activation
  - Tricyclic antidepressants block sympathetic receptors
- Depression
- Deconditioning
- Pain-induced sympathetic arousal

### HSDs - Other Features

**GI**
- Constipation (bowel and abdominal wall may have low tone) or IBS symptoms
- Diverticula and diverticulitis
- Gastroesophageal reflux disease (GERD)

**Dental**
- High-arched palate, tooth crowding
- TMJ dysfunction with pain and headaches

**Respiratory**
- Lung blebs or pneumothorax

**Psychiatric**
- Increased risk of depression due to having a chronic painful disease
# Pain in hEDS/HSDs

## Impact of H-EDS

### Comparative study looking at 206 patients (all female)
- 72 with EDS, hypermobility type
- 69 with fibromyalgia
- 65 with rheumatoid arthritis

### Assessed functional impairment with Sickness Impact Profile (SIP)
- Scale 0-100 with higher scores indicating more functional impairment
- Score >10 indicates significant clinical dysfunction
- Score 0-10 indicates slight dysfunction lacking clinical importance
- Score = 0 indicates no dysfunction

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### Table 1: Review of Literature of Types of Pain in hEDS

<table>
<thead>
<tr>
<th>Type of Pain</th>
<th>Number of Patients</th>
<th>Score</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>60</td>
<td>6.20*</td>
<td>Harvis et al. (2013)</td>
</tr>
<tr>
<td>Neck pain</td>
<td>58</td>
<td>6.79</td>
<td>Gallacher et al. (2006)</td>
</tr>
<tr>
<td>Jaw pain</td>
<td>58</td>
<td>6.79</td>
<td>Gallacher et al. (2006)</td>
</tr>
<tr>
<td>Shoulder pain</td>
<td>58</td>
<td>6.79</td>
<td>Gallacher et al. (2006)</td>
</tr>
<tr>
<td>Knee pain</td>
<td>58</td>
<td>6.79</td>
<td>Gallacher et al. (2006)</td>
</tr>
<tr>
<td>Temporomandibular joint pain</td>
<td>42</td>
<td>7.14</td>
<td>*Fuchs et al. (2004); Huygen et al. (2004)</td>
</tr>
<tr>
<td>Meningalgia</td>
<td>387</td>
<td>77.57</td>
<td>Grapin (2014)</td>
</tr>
<tr>
<td>Depression</td>
<td>71</td>
<td>6.42</td>
<td>Grapin (2014)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>71</td>
<td>6.42</td>
<td>Grapin (2014)</td>
</tr>
</tbody>
</table>

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*Note: * denotes significant *P* values.
Impact of H-EDS

Table 2. Type and frequency of symptoms reported by the EDS-HT group as compared to the FM and RA groups

<table>
<thead>
<tr>
<th>Symptom</th>
<th>EDS-HT group (n = 72)</th>
<th>FM group (n = 48)</th>
<th>RA group (n = 67)</th>
<th>P* EDS vs. RA</th>
<th>P* EDS vs. FM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>100</td>
<td>100</td>
<td>87.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint pain</td>
<td>100</td>
<td>100</td>
<td>87.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>32.4</td>
<td>78.8</td>
<td>1.8</td>
<td>&lt;0.001 (&lt;0.004)</td>
<td></td>
</tr>
<tr>
<td>Muscle pain</td>
<td>68.7</td>
<td>21.1</td>
<td>26.7</td>
<td>&lt;0.001 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Joint dysfunction</td>
<td>68.7</td>
<td>0.0</td>
<td>9.7</td>
<td>&lt;0.001 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Pelvis instability/locking hip</td>
<td>68.7</td>
<td>0.0</td>
<td>0.0</td>
<td>&lt;0.001 (&lt;0.001)</td>
<td></td>
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<tr>
<td>Joint locking</td>
<td>9.8</td>
<td>0.0</td>
<td>3.2</td>
<td>&lt;0.001 (&lt;0.001)</td>
<td></td>
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<tr>
<td>Joint swelling</td>
<td>5.6</td>
<td>7.3</td>
<td>8.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscular problems</td>
<td>67.6</td>
<td>87.0</td>
<td>62.8</td>
<td>0.004 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>55.6</td>
<td>27.1</td>
<td>32.9</td>
<td>0.003 (&lt;0.001)</td>
<td></td>
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<tr>
<td>Tendinitis</td>
<td>31.1</td>
<td>27.1</td>
<td>32.9</td>
<td>0.004 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>23.9</td>
<td>17.4</td>
<td>9.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle stiffness</td>
<td>7.0</td>
<td>84.1</td>
<td>62.8</td>
<td>&lt;0.001 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Skin problems</td>
<td>60.8</td>
<td>9.7</td>
<td>3.2</td>
<td>&lt;0.001 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Dermatitis</td>
<td>67.9</td>
<td>56.3</td>
<td>2.4</td>
<td>NS (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>25.4</td>
<td>59.9</td>
<td>4.8</td>
<td>&lt;0.001 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Neuropathic problems</td>
<td>16.9</td>
<td>37.5</td>
<td>3.2</td>
<td>NS (&lt;0.004)</td>
<td></td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>7.0</td>
<td>82.6</td>
<td>0.0</td>
<td>&lt;0.001 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Cognitive problems</td>
<td>1.4</td>
<td>44.9</td>
<td>0.0</td>
<td>&lt;0.001 (&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Emotional problems</td>
<td>1.4</td>
<td>47.8</td>
<td>0.0</td>
<td>&lt;0.001 (&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

* Values are the percentage of patients. EDS-HT = Ehlers-Danlos syndrome, hypermobile type. FM = fibromyalgia, RA = rheumatoid arthritis. NS = not significant.  
† Determined by logistic regression analysis, with adjustment for age, education status, household characteristics, and employment status, or by Fisher's exact test if group proportion was equal to zero.

Impact of H-EDS

- All have frequent joint pain, HA
- Joint dysfunction, dislocation suggests EDS
- Weakness suggests EDS
- Stiffness suggests FM or RA
- Dysautonomia not distinguishing (EDS & FM)
- Fatigue? (FM > EDS)
- Cognitive issues suggest FM

Arth & Rheum 2011.
Common Features Elicited by PT

PT Treatment Recommendations

- Education – “Education is probably the most important treatment that physical therapists can provide to individuals with HMS.”
  - Education about ergonomics and body mechanics may decrease back pain
  - Education about joint protection has been shown to increase function and decrease pain
  - Splints, braces, and taping may be helpful to protect vulnerable joints

- Exercise
  - Strengthening and proprioceptive exercises are recommended for musculature surrounding affected joints
  - “It appears reasonable...to advise individuals with HMS to use stretching exercises cautiously, distinguishing between stretching muscles and stretching joints, as the former may be beneficial but the latter may be harmful.”
PT Treatment Recommendations

• “Helping patients with HMS understand their disorder may help them cope with the pain they experience.”
  • Goldman study found that presence of HMS in patients was associated with increased participation in a treatment regimen
  • Attributed this increase to improved understanding and acceptance patients had for disorder

Controlled Trials for HMS

• First randomized controlled trial for children with HMS
  • 2010
  • Diagnosed by Beighton score
• Compared generalized program focusing on muscle strength and fitness to targeted program focusing on correcting motion control in symptomatic joints
• Improvements were seen in both children’s assessment of pain and parents’ assessment of pain in both groups
Pain Management in H-EDS

Medication, Surgery, and Physiotherapy Among Patients With the Hypermobility Type of Ehlers-Danlos Syndrome

Lies Rombaut, PT, MSc, Franviska Malfit, MD, PhD, Inge De Wande, PT, MSc, Ann Cools, PT, PhD, Youri Thijs, PT, PhD, Anne De Paep, MD, PhD, Patrick Calders, MSc, PhD

- Study of 79 patients with EDS, hypermobility type (EDS-H)
- Diagnosed by Revised Villefranche Criteria
  - Generalized joint hypermobility
  - Skin hyperextensibility or velvety texture without atrophic scars

Self-Reported Complaints in H-EDS

<table>
<thead>
<tr>
<th>Type of Complaints</th>
<th>EDS-HT Group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (joint pain, muscle pain)</td>
<td>79 (100)</td>
</tr>
<tr>
<td>Joint problems (dislocation, distortion, pelvic instability, swelling, joint lock)</td>
<td>67 (84.4)</td>
</tr>
<tr>
<td>Muscle problems (muscle cramps, muscle weakness, muscle stiffness, tendinitis)</td>
<td>51 (64.6)</td>
</tr>
<tr>
<td>Skin fragility (easy bruising and rupture, difficult wound healing, papaya scars)</td>
<td>50 (63.3)</td>
</tr>
<tr>
<td>Symptoms suggestive of dysautonomia (dizziness, nausea, feeling faint after standing up, syncope, palpitations, constipation, heat flashes, urine retention)</td>
<td>46 (58.2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>39 (49.4)</td>
</tr>
<tr>
<td>Headaches</td>
<td>29 (36.7)</td>
</tr>
<tr>
<td>Neurologic symptoms (paresthesia, paroxysms, paresthesia, sciatica, spasticity)</td>
<td>23 (29.1)</td>
</tr>
<tr>
<td>Infections/infections (recurrent infections, repeated odds, recurrent infections)</td>
<td>22 (27.9)</td>
</tr>
<tr>
<td>Cardiorespiratory symptoms (tachypnea, hypotension, hypertension, breathing difficulty, asthnia)</td>
<td>12 (15.6)</td>
</tr>
<tr>
<td>Sleep problems (difficulties falling asleep, difficulties staying asleep, early awakening)</td>
<td>13 (16.5)</td>
</tr>
<tr>
<td>Excessive irritability (had physical condition, exhaustion after walking a short distance)</td>
<td>12 (15.2)</td>
</tr>
<tr>
<td>Inflammation (warm red joints)</td>
<td>12 (15.2)</td>
</tr>
<tr>
<td>Cognitive problems (forgetfulness, making mistakes)</td>
<td>8 (10.1)</td>
</tr>
<tr>
<td>Logopropic problems (difficulties with swallowing, vocal problems)</td>
<td>6 (7.6)</td>
</tr>
</tbody>
</table>

NOTE: Values are n (%)
**Treatment Modalities Used**

Table 3: Medication, Surgical Treatment, and Physiotherapy Reported by the ED5-HT Group

<table>
<thead>
<tr>
<th>Variables</th>
<th>ED5-HT Group (N=75)</th>
<th>Total Reported Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>73(92.4)%</td>
<td>241</td>
</tr>
<tr>
<td>Analgesics</td>
<td>73(100)%</td>
<td>141</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory (NSAIDs)</td>
<td>49(65.6)%</td>
<td>51</td>
</tr>
<tr>
<td>Opioids (eg, tramadol, codeine, morphine, fentanyl)</td>
<td>59(78.4)%</td>
<td>47</td>
</tr>
<tr>
<td>Other</td>
<td>2(2.7)%</td>
<td>0</td>
</tr>
<tr>
<td>Antidepressants (eg, amitriptyline, duloxetine, trazodone)</td>
<td>15(20.5)%</td>
<td>19</td>
</tr>
<tr>
<td>Sedatives (benzodiazepines)</td>
<td>15(20.5)%</td>
<td>18</td>
</tr>
<tr>
<td>Cardiovascular medication (beta-blockers, diuretics, ACE inhibitors)</td>
<td>11(15.1)%</td>
<td>10</td>
</tr>
<tr>
<td>Pulmonary medication (beta-sympathomimetics)</td>
<td>10(13.3)%</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>29(39.4)%</td>
<td>35</td>
</tr>
</tbody>
</table>

**Surgery**
- Upper limb: 56(75.6)% 175
- Lower limb: 33(44.8)% 112
- Spine: 9(12.1)% 11
- Abdominal: 20(27.3)% 33
- Eye: 5(6.7)% 11
- Other: 5(6.7)% 6

**Physiotherapy**
- Muscle strength training: 41(54.7)% NA
- Massage: 25(33.3)% NA
- Stabilization training: 20(26.7)% NA
- Electrotherapy: 14(18.7)% NA
- Manual therapy: 12(16.0)% NA
- Aquatic therapy: 12(16.0)% NA
- Heat therapy: 6(8.0)% NA
- Stretching: 5(6.7)% NA
- Other: 5(6.7)% NA

Abbreviation: ACE, angiotensin-converting enzyme; NA, not applicable
*Number of patients consuming a therapeutic modality (percentage of total sample).
Detailed therapeutic information was expressed as number of patients (percentage of sample consuming that therapeutic modality).
*WHO steps use of analgesia was categorized according to the 3-step pain-relief ladder of the WHO (see methodology).

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**Functional Impairment**

Table 4: Functional Impairment in the ED5-HT Group

<table>
<thead>
<tr>
<th>Category</th>
<th>SIP Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall functioning</td>
<td>15.7±11.50</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>14.3±12.89</td>
</tr>
<tr>
<td>Ambulation</td>
<td>18.4±17.20</td>
</tr>
<tr>
<td>Body care and movement</td>
<td>13.2±12.21</td>
</tr>
<tr>
<td>Mobility</td>
<td>12.6±16.09</td>
</tr>
<tr>
<td>Psychosocial functioning</td>
<td>17.5±13.16</td>
</tr>
<tr>
<td>Emotional behavior</td>
<td>19.0±17.88</td>
</tr>
<tr>
<td>Social interaction</td>
<td>14.7±16.51</td>
</tr>
<tr>
<td>Alertness behavior</td>
<td>26.5±23.50</td>
</tr>
<tr>
<td>Communication</td>
<td>8.1±10.91</td>
</tr>
</tbody>
</table>

Independent scales:
- Sleep and rest: 27.8±21.74
- Home management: 27.4±20.93
- Work: 48.6±31.99
- Recreation and pastimes: 33.2±16.60
- Eating: 34.4±4.17

*NOTE: Values are mean ± SD.*

- Using Sickness Impact Profile (SIP)
- Scores range 0-100
  - Higher scores indicate more functional impairment
  - Score >10 indicates clinically significant dysfunction
  - Score 0-10 indicated mild dysfunction lacking clinical importance
  - Score = 0 indicates no dysfunction
Pain Severity

- Pain severity was assessed using a visual analog scale (VAS)
- Score of 0 indicates no pain, 100 indicates unbearable pain
- Mean VAS scores were:
  - 48.9 for current pain
  - 56.2 for average pain over last week
  - Indicate presence of severe daily pain

Summary from Arch Phys Med Rehab 2011

- Pain, joint problems, and muscle problems are “omnipresent”
- Large number of non-MS problems are reported
- Patients with EDS-H use many medications
  - Include analgesics and antidepressants
- High prevalence of surgery
  - Effect of surgical intervention was favorable in only 33.9% patients
  - Surgical results are often disappointing to both patients and surgeons
- Physiotherapy (in its various modalities) forms a mainstay of treatment
  - Low dose muscle strength exercises and joint stabilization exercises, including proprioceptive enhancement and re-education of muscle control are likely appropriate
  - Proprioceptive and muscular system play large role in joint stability
  - Muscle strength training also relevant treatment modality
  - “Proven physiotherapeutic treatment techniques are absent in EDS-H”
  - 63.4% of patients reported a positive effect after physical therapy
Approach to Patients

- Diagnosis requires careful history and examination
- Many disorders diagnosed clinically
- Patients with CT disorders require multidisciplinary care to manage complications
- Team approach
  - Physical & Occupational Therapy
  - Orthopedics
  - Physical Medicine & Rehabilitation
  - Pain Management
  - Others based on extra-articular symptoms

References

References


Thank you!

Any questions?