Unexplained Pain? Multiple Systemic Complaints? Think Ehlers-Danlos Syndrome

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Harvey Institute for Human Genetics
Baltimore, Maryland
TCAPP Educational Symposium
September 13, 2014
EDS: A Multi-system Disorder

- Chronic pain syndrome
- Chronic fatigue syndrome
- Functional gastrointestinal disorder
- Chronic headache disorders
- Pelvic dysfunction
- Exocrine gland dysfunction
- Cardiovascular – dysautonomia
- Immune dysregulation
- Mast cell dysfunction
- Bleeding/clotting disorders
- Neurologic complications

Castori, ISRN Dermatology, 2012
Review

The Ehlers–Danlos syndrome, a disorder with many faces


A De Paepe and F Malfait
Centre for Medical Genetics, Ghent University Hospital, Ghent University,

- Excellent review of genes causing various forms of EDS as well as the clinical phenotypes.
- “Snapshot” vignettes of typical cases
## EDS Classification

<table>
<thead>
<tr>
<th>EDS subtype</th>
<th>Inheritance pattern</th>
<th>Protein</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>AD</td>
<td>Procollagen type V</td>
<td>COL5A1/COL5A2</td>
</tr>
<tr>
<td></td>
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<td>Procollagen type I</td>
<td>COL1A1</td>
</tr>
<tr>
<td></td>
<td>AR</td>
<td>Tenascin-X</td>
<td>TNXB</td>
</tr>
<tr>
<td>Cardiac-valvular</td>
<td>AR</td>
<td>Deficiency of α2(I) collagen chain</td>
<td>COL1A2</td>
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<tr>
<td>Hypermobility</td>
<td>AD</td>
<td>Unknown (Tenascin X)</td>
<td>TNXB</td>
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<tr>
<td>Vascular</td>
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<tr>
<td>Vascular-like</td>
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<td>Procollagen type I (R-to-C)</td>
<td>COL1A1</td>
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<tr>
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<td>Lysyl hydroxylase-1</td>
<td>PLCD1</td>
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<td>Musculocontractural</td>
<td>AR</td>
<td>Dermatan-4-sulfotransferase-1</td>
<td>CHST14</td>
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<tr>
<td>Spondylocheirodysplastic</td>
<td>AR</td>
<td>ZIP13</td>
<td>SLC39A13</td>
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<tr>
<td>Brittle cornea syndrome</td>
<td>AR</td>
<td>ZNF469</td>
<td>ZNF469</td>
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<tr>
<td>Arthrodialsis</td>
<td>AD</td>
<td>Procollagen type I (deletion of N-propeptide cleavage site)</td>
<td>COL1A1/COL1A2</td>
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<tr>
<td>EDS/OI overlap</td>
<td>AD</td>
<td>Procollagen type I (delay in N-propeptide cleavage)</td>
<td>COL1A1/COL1A2</td>
</tr>
<tr>
<td>Dermatosparaxis</td>
<td>AR</td>
<td>Procollagen-I-N-proteinase</td>
<td>ADAMTS2</td>
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</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; EDS, Ehlers–Danlos syndrome.

De Paepe and Malfait, 2012
Joint Hypermobility and Joint Hypermobility Syndrome

• Joint hypermobility – Beighton score $\geq 4$
• Joint hypermobility syndrome – Brighton criteria
• Ehlers-Danlos syndrome, hypermobility type and the Joint Hypermobility syndrome have overlapping criteria – 2009 report suggests they are the same disorder
Joint Hypermobility Questionnaire

• Can you now or could you ever place your hands on the floor by bending forward with your knees straight?
• 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 knee cap dislocate on more than one occasion?
• Do you consider yourself double-jointed?
Joint Hypermobility Syndrome

• Major Criteria
  – Beighton score $\geq 4/9$
  – Arthralgia for $>3$ months in $4$ or more joints
Joint Hypermobility Syndrome Minor Criteria

- A Beighton score of 1, 2, or 3 of 9 points (0, 1, 2, or 3 points if ≥ 50 years old)
- Arthralgia (≥ 3 months) in one to three joints or back pain (≥ 3 months), spondylosis, or spondylolisthesis
- Dislocation/subluxation in more than one joint, or in one joint on more than one occasion
- Soft tissue rheumatism: ≥ three lesions (eg, epicondylitis, tenosynovitis, bursitis)
- Marfanoid habitus (tall, slim, span/height ratio of > 1.03; upper/lower segment ratio of < 0.89; arachnodactyly [positive Steinberg/wrist signs])
- Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring
- Eye signs: drooping eyelids, myopia, or antimongoloid slant
- Varicose veins, hernia, or uterine/rectal prolapse
Brighton Criteria: 
Joint Hypermobility Syndrome

• Joint hypermobility syndrome is diagnosed if the patient presents with two major criteria; one major and two minor criteria; or four minor criteria.

• Two minor criteria will suffice if there is an unequivocally affected first-degree relative. Major 1 and Minor 1 criteria are mutually exclusive, as are Major 2 and Minor 2.
Skin Features

Pain in Ehlers-Danlos Syndrome

- Muscular
- Myofascial
- Neuropathic
- Headache
- Abdominal pain
- Pelvic pain
- Complex regional pain syndrome
Brief Pain Inventory (Short Form)

Study ID# ____________________________ Hospital # ____________________________

Do not write above this line.

Date: ____________________________

Time: ____________________________

Name: ____________________________

Last __________ First ____________ Middle Initial ____________

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

   1. yes  
   2. no

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

3) Please rate your pain by circling the one number that best describes your pain at its WORST in the past 24 hours.

4) What treatments or medications are you receiving for your pain?

   ____________________________________________

5) In the past 24 hours, how much RELIEF have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

   0%  10%  20%  30%  40%  50%  60%  70%  80%  90%  100%  Complete Relief
   No Relief
   6) Circle the one number that describes how, during the past 24 hours, PAIN HAS INTERFERED with your:

   A. General Activity:

   0  1  2  3  4  5  6  7  8  9  10  Completely Interferes
   Does not Interfere

   B. Mood

   0  1  2  3  4  5  6  7  8  9  10  Completely Interferes
   Does not Interfere

   C. Walking Ability

   0  1  2  3  4  5  6  7  8  9  10  Completely Interferes
   Does not Interfere

   D. Normal work (includes both work outside the home and housework)

   ____________________________________________
3) Please rate your pain by circling the one number that best describes your pain at its WORST in the past 24 hours.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
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<th>7</th>
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<th>10</th>
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</thead>
<tbody>
<tr>
<td>No Pain</td>
<td>Pain as bad as you can imagine</td>
<td></td>
<td></td>
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4) Please rate your pain by circling the one number that best describes your pain at its LEAST in the past 24 hours.

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</table>

5) Please rate your pain by circling the one number that best describes your pain on the AVERAGE.

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</table>

6) Please rate your pain by circling the one number that tells how much pain you have RIGHT NOW.

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</tbody>
</table>

D. Normal work (Includes both work outside the home and housework)

<table>
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<tr>
<th>0</th>
<th>1</th>
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<th>3</th>
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<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not Interfere</td>
<td>Completely Interferes</td>
<td></td>
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</table>

E. Relation with other people

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<th>4</th>
<th>5</th>
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<th>7</th>
<th>8</th>
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<th>10</th>
</tr>
</thead>
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<td>Does not Interfere</td>
<td>Completely Interferes</td>
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</table>

F. Sleep

<table>
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<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does not Interfere</td>
<td>Completely Interferes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>

G. Enjoyment of life

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<tr>
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<th>4</th>
<th>5</th>
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<th>7</th>
<th>8</th>
<th>9</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Does not Interfere</td>
<td>Completely Interferes</td>
<td></td>
<td></td>
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Copyright © 1991 Charles S. Cleeland, PhD
## Brief Pain Inventory

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<tr>
<th></th>
<th>HYPERMOBILE</th>
<th>CLASSICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average pain score</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Worst pain score**</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;18</th>
<th>18-29</th>
<th>30-39</th>
<th>40-49</th>
<th>&gt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average pain score</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Worst pain score</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>
Chronic Fatigue Syndrome

- Profound, disabling exhaustion
- May be more disabling than pain
- Sleep disturbance is major contributor
- Other possible contributors
  - Adrenal dysfunction
  - Hypothyroid
  - Mitochondrial
My Joints
go out more
than I do
FEELING THE EFFECTS OF SLEEP DEPRIVATION

- Irritability
- Cognitive impairment
- Memory lapses or loss
- Impaired moral judgement
- Severe yawning
- Hallucinations
- Symptoms similar to ADHD
- Impaired immune system
- Risk of diabetes Type 2

- Increased heart rate variability
- Risk of heart disease
- Decreased reaction time and accuracy
- Tremors
- Aches

Other:
- Growth suppression
- Risk of obesity
- Decreased temperature
Gastrointestinal Complications In EDS

- Dysphagia
- Esophageal dysmotility
- Esophageal spasm
- Gastro-esophageal reflux
- Hiatal hernia
- Gastroparesis
- Bowel dysmotility
- Rectal prolapse
Gastrointestinal symptoms

- **Dysphagia**: Classical 11, Hypermobile 12
- **Nausea**: Classical 55, Hypermobile 54
- **Emesis**: Classical 11, Hypermobile 28
- **Abdominal pain**: Classical 56, Hypermobile 46
- **Constipation**: Classical 50, Hypermobile 55
- **Diarrhea**: Classical 31, Hypermobile 45
- **Incontinence**: Classical 10, Hypermobile 9

**Note**: Nausea includes *nausea* with an asterisk.
Headache in Ehlers-Danlos Syndrome

- Muscular
- Myofascial
- Neurogenic
- Migraine
- Temporo-mandibular joint dysfunction
- CSF leaks
  - Decreased intracranial pressure
- Chiari I malformation
  - Increased intracranial pressure
- Disruption of venous drainage
  - Chronic Cerebral Sinus Venous Insufficiency
Symptoms:
- Pressure headache, sensitive to changes in barometric pressure
- May present with evidence of CSF leak
- Some women report increased symptoms around menses
- Documented by increased pressure on lumbar puncture or intracranial pressure monitoring

Multiple potential causes
- Chiari, disruption of CSF or venous blood flow
- Responsive to diamox therapy
- Decreases bicarbonate levels, so monitor closely
Pelvic Dysfunction in Ehlers-Danlos Syndrome

- Pelvic pain
- Uterine prolapse
- Bladder prolapse
- Dysfunctional uterine bleeding
- Sexual dysfunction
Urinary symptoms

- Urge Incontinence: Classical 30, Hypermobile 21
- Incontinence: Classical 21, Hypermobile 26
- Frequency: Classical 40, Hypermobile 38
- Recurrent UTI: Classical 9, Hypermobile 10
Exocrine Gland Dysfunction

- Pituitary
- Thyroid
- Pancreas
- Adrenal
- Ovaries
- Testes
Cardiovascular Manifestations

- Mitral valve prolapse
- Aortic root dilation
- Venous insufficiency
- Tachycardia
- Orthostatic intolerance
- Chest pain
Cardiovascular symptoms

- **PALPITATIONS**
  - Classical: 56
  - Hypermobile: 52
- **SYNCOPE**
  - Classical: 19
  - Hypermobile: 26
- **DIZZINESS**
  - Classical: 66
  - Hypermobile: 66
- **CHEST PAIN**
  - Classical: 40
  - Hypermobile: 37
Immune Dysfunction

- Common Variable Immunodeficiency
- Auto-immune disorders
  - Systemic Lupus Erythematosus
  - Rheumatoid Arthritis
  - Psoriasis
  - Behcet’s disease
  - Mixed connective tissue disorder
- Mast cell activation disorder
Mast Cell Disease

- There is a subset of EDS patients who develop symptoms of mast cell disease (flushing, hives, anaphylaxis)
- Many of these people respond to therapy for mast cell activation disorder (H1 and H2 blockers, cromolyn sodium)
- May reflect increased stress levels and/or autonomic dysfunction
Hematologic Complications

- Easy bruising
- Bleeding complications – von Willebrand syndrome
- Clotting complications – cause??
- Iron deficiency - malabsorption
Neurologic Complications

- Cranio-cervical instability
- Chiari malformation
- Syrinx
- Cervical instability - C1-2 or lower
- Degenerative Disc disease
- Occult tethered cord
- Autonomic nervous system dysfunction
Autonomic Dysfunction

- Postural orthostatic tachycardia syndrome
- Neurally mediated hypotension
- Sleep disturbance
- Exocrine dysfunction
- Gastrointestinal dysmotility
- Temperature instability
Neurologic symptoms

- **HEADACHES**: CLASSICAL 69, HYPERMOBILE 71
- **MIGRAINES**: CLASSICAL 56, HYPERMOBILE 52
- **INSOMNIA**: CLASSICAL 65, HYPERMOBILE 77
- **BRAIN FOG**: CLASSICAL 47, HYPERMOBILE 48
- **MEMORY LOSS**: CLASSICAL 40, HYPERMOBILE 33
Neurologic symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Classical</th>
<th>Hypermobile</th>
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</thead>
<tbody>
<tr>
<td>Falls</td>
<td>21</td>
<td>33</td>
</tr>
<tr>
<td>Tremors</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>Seizures</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Numbness</td>
<td>56</td>
<td>52</td>
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</table>
Neurologic symptoms

- TINNITUS:
  - Classical: 24
  - Hypermobile: 28

- HEARING LOSS:
  - Classical: 17
  - Hypermobile: 15

- FLOATERS:
  - Classical: 40
  - Hypermobile: 52

- HYPEROPIA:
  - Classical: 16
  - Hypermobile: 17

- MYOPIA:
  - Classical: 48
  - Hypermobile: 54
Constitutional symptoms

- Temperature Instability
  - Classical: 47
  - Hypermobile: 54
- Weight Gain
  - Classical: 6
  - Hypermobile: 9
- Weight Loss
  - Classical: 5
  - Hypermobile: 6
Psychiatric symptoms

- Mood Swings**: CLASSICAL: 31, HYPERMOBILE: 15
- Withdrawn: CLASSICAL: 14, HYPERMOBILE: 10
- Anxious: CLASSICAL: 48, HYPERMOBILE: 54
- Depressed: CLASSICAL: 38, HYPERMOBILE: 41
- ADD: CLASSICAL: 13, HYPERMOBILE: 14
Many EDS patients do not metabolize drugs as expected.
Many patients have reported that they are slow to respond to the “caine” derivatives in the dental office – need multiple injections; wears off very slowly
Metabolism of many drugs either prolonged or accelerated
Ehlers-Danlos Syndrome Can Be Disabling
Karnofsky performance status scale

100: I feel normal, no complaints, no evidence of disease
90: I am able to carry on normal activity with minor symptoms
80: I carry on normal activity with effort and some symptoms
70: I am able to care for myself, but unable to carry on normal activities
60: I require occasional assistance, but can care for most of my needs
50: I require considerable assistance and frequent care by others
40: I am disabled. I require considerable assistance and frequent care by others
30: I am severely disabled. I am hospitalized, but death is not imminent
20: I am very sick. I require active supportive care by others
10: I have fatal processes that are rapidly progressing. I am near death

<table>
<thead>
<tr>
<th>Age</th>
<th>HYPERMOBILE</th>
<th>CLASSICAL</th>
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<tbody>
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<td>&lt;18</td>
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<td>67</td>
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<th>Karnofsky score</th>
<th>HYPERMOBILE</th>
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<td>18-29</td>
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<td>30-39</td>
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<td>69</td>
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<td>66</td>
<td>&gt;50</td>
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<tr>
<td>71</td>
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</table>

70: I am able to care for myself, but unable to carry on normal activities
Can’t Connect the Issues?

Think Connective Tissues!!

Dr. Heidi Collins, 2012
Thanks to

- Ms. Christy Haakenson
- Ms. Jessica Adcock
- Dr. Fraser Henderson
- Dr. Alan Pocinki
- Dr. Robert Gerwin
- Dr. Anil Mankee
- Dr. Saqib Baig
- Dr. Ezza Khan
- All our patients and their families