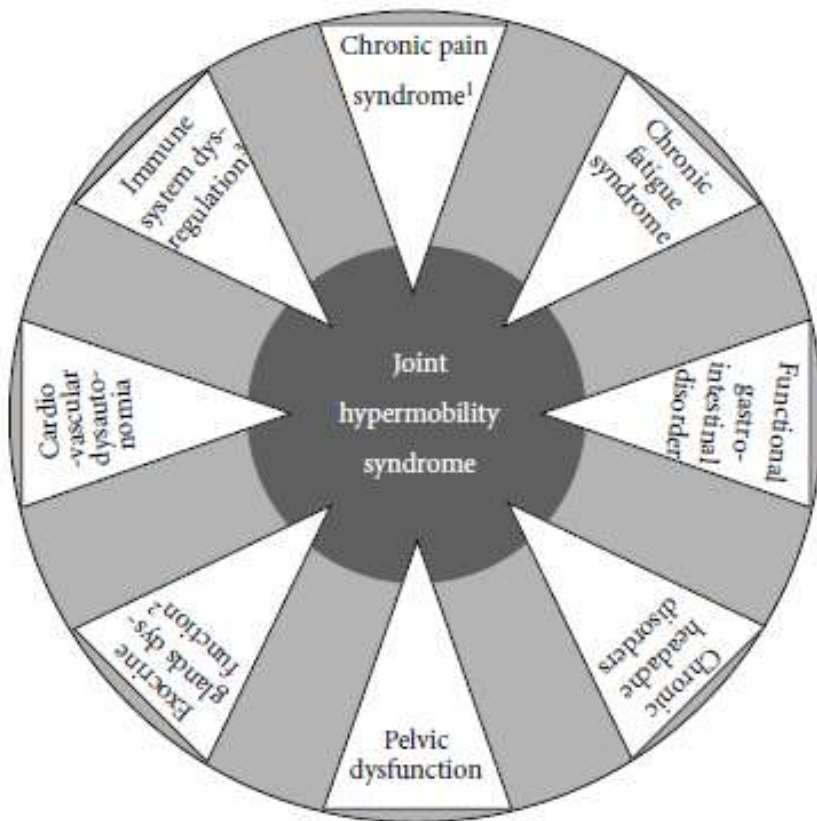


Unexplained Pain? Multiple Systemic Complaints? Think Ehlers-Danlos Syndrome

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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



Review

The Ehlers–Danlos syndrome, a disorder with many faces

De Paepe A, Malfait F. The Ehlers–Danlos syndrome, a disorder with many faces.
Clin Genet 2012; 82: 1–11. © John Wiley & Sons A/S, 2012

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 2. Updated EDS classification

| EDS subtype | Inheritance pattern | Protein | Gene |
|--------------------------|---------------------|---|-------------------------------|
| Classic | AD | Procollagen type V | <i>COL5A1/COL5A2</i> |
| | AR | Procollagen type I Tenascin-X | <i>COL1A1</i> <i>TNX-B</i> |
| Cardiac-valvular | AR | Deficiency of $\alpha 2(I)$ collagen chain | <i>COL1A2</i> |
| Hypermobility | AD | Unknown | ? |
| | | (Tenascin X) | <i>TNX-B</i> |
| Vascular | AD | Procollagen type III | <i>COL3A1</i> |
| Vascular-like | AD | Procollagen type I (R-to-C) | <i>COL1A1</i> |
| Kyphoscoliotic | AR | Lysyl hydroxylase-1 | <i>PLOD1</i> |
| Musculocontractural | AR | Dermatan-4-sulfotransferase-1 | <i>CHST14</i> |
| Spondylocheirodysplastic | AR | ZIP13 | <i>SLC39A13</i> |
| Brittle cornea syndrome | AR | ZNF469 | <i>ZNF469</i> |
| | | PRDM5 | <i>PRDM5</i> |
| Arthrochalasia | AD | Procollagen type I (deletion of N-propeptide cleavage site) | <i>COL1A1/COL1A2</i> |
| EDS/OI overlap | AD | Procollagen type I (delay in N-propeptide cleavage) | <i>COL1A1/COL1A2</i> |
| Dermatosparaxis | AR | Procollagen-I-N-proteinase | <i>ADAMTS2</i> |

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

Joint Hypermobility and Joint Hypermobility Syndrome

- Joint hypermobility – Brighton score ≥ 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?

Beighton Score



Current Pain & Headache Reports (2009) 13:427–433
Childs Nerv Syst (2011) 27:365–371

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 spondylolysis/spondylolisthesis
- Dislocation/subluxation in more than one joint, or in one joint on more than one occasion
- Soft tissue rheumatism: \geq 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



Childs Nerv Syst (2011) 27:365–371

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: _____

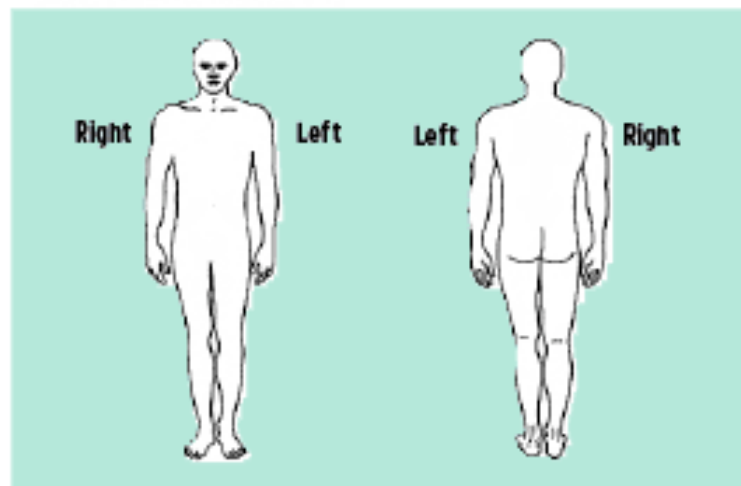
Time: _____

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.

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

8) 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%
No Complete
Relief Relief

9) 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
Does not Completely
Interfere Interfere

B. Mood

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

C. Walking Ability

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

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain as bad as you can imagine

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

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain as bad as you can imagine

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

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain as bad as you can imagine

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

0 1 2 3 4 5 6 7 8 9 10
No Pain Pain as bad as you can imagine

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

0 1 2 3 4 5 6 7 8 9 10
Does not interfere Completely interferes

E. Relation with other people

0 1 2 3 4 5 6 7 8 9 10
Does not interfere Completely interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
Does not interfere Completely interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
Does not interfere Completely interferes


Brief Pain Inventory

| | HYPERMOBILE | CLASSICAL |
|--------------------|-------------|-----------|
| Average pain score | 5 | 5 |
| Worst pain score** | 8 | 7 |

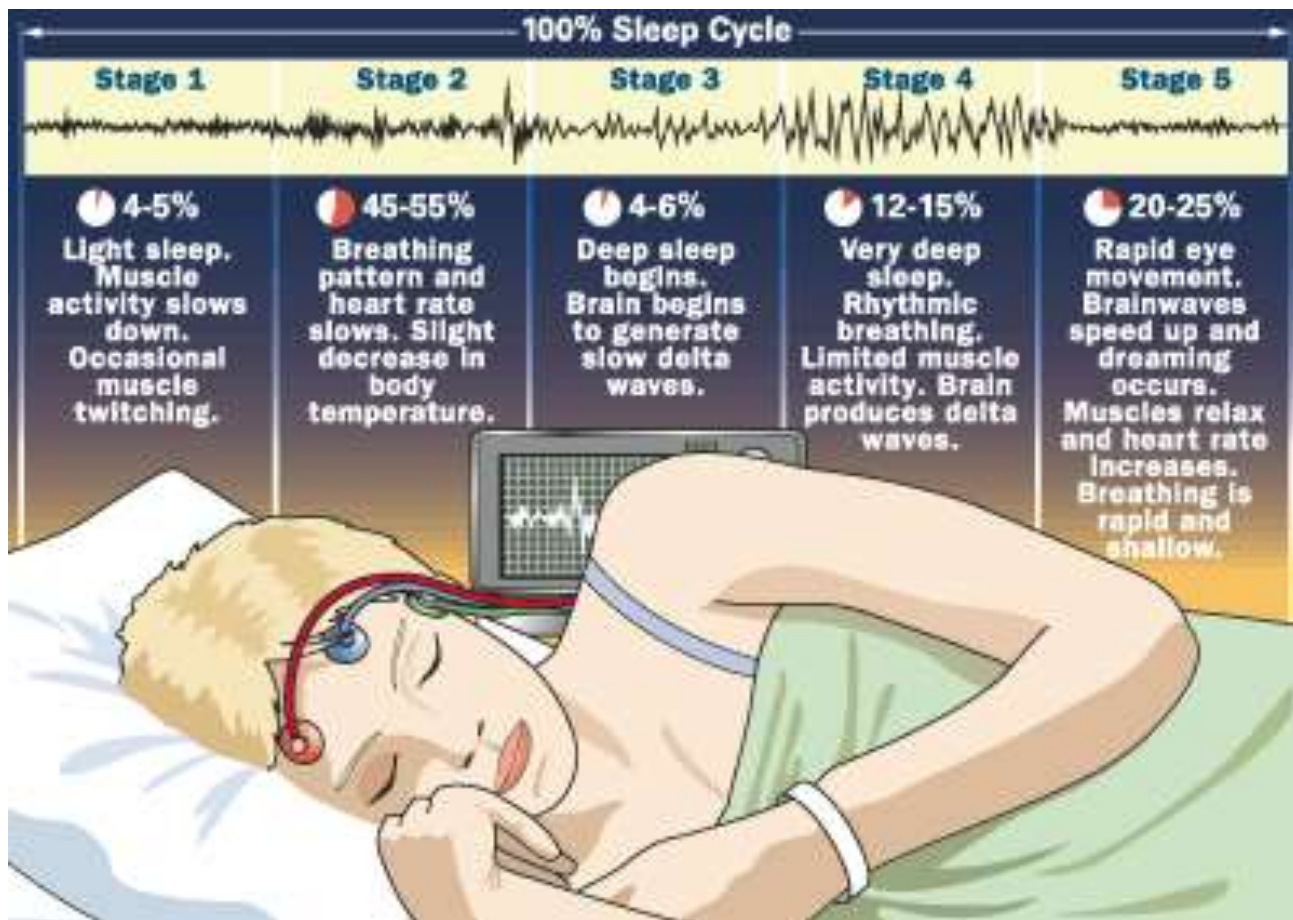
| Age | <18 | 18-29 | 30-39 | 40-49 | >50 |
|--------------------|-----|-------|-------|-------|-----|
| Average pain score | 4 | 5 | 5 | 5 | 5 |
| Worst pain score | 7 | 8 | 7 | 8 | 8 |

Chronic Fatigue Syndrome

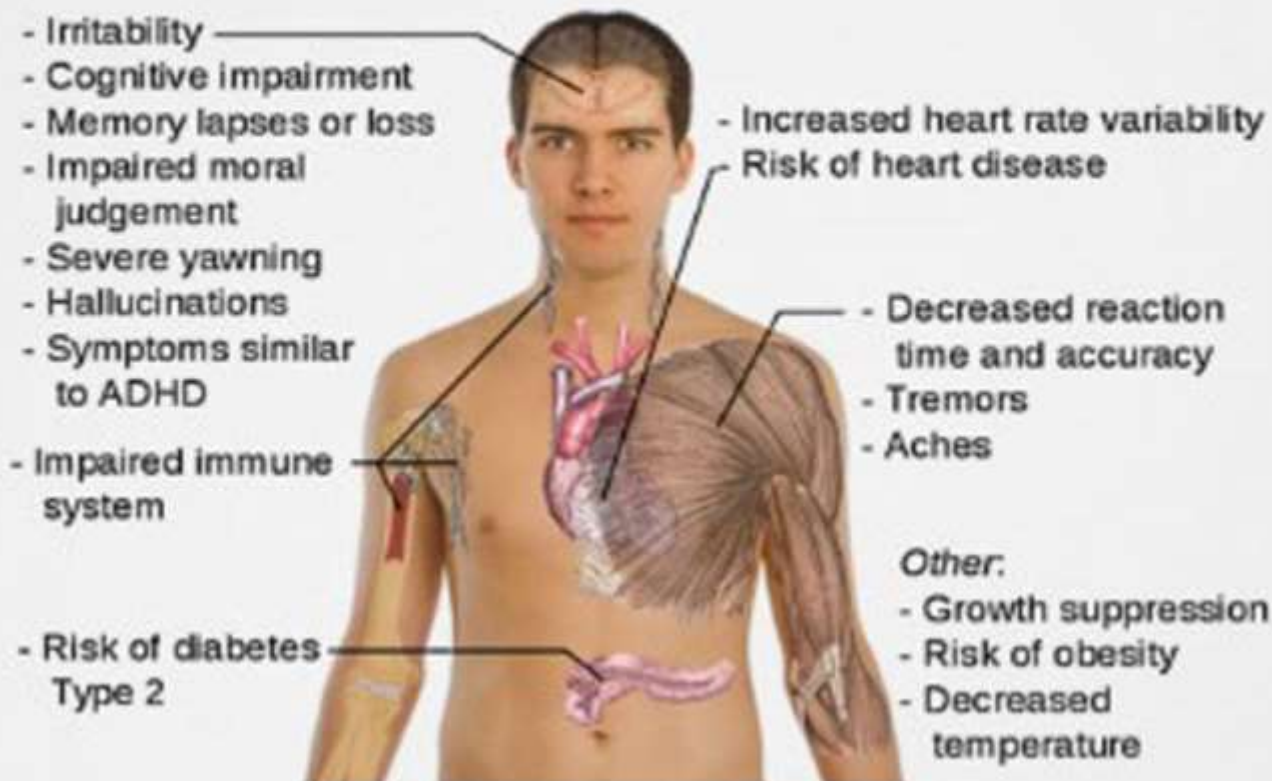
- Profound, disabling exhaustion
- May be more disabling than pain
- Sleep disturbance is major contributor
- Other possible contributors
 - Adrenal dysfunction
 - Hypothyroid
 - Mitochondrial

A person is shown from the chest up, wearing a white t-shirt. The t-shirt has a blue text graphic on the front. The text is arranged in three lines: "MY Joints", "go out More", and "than I do". The font is a casual, slightly irregular sans-serif style. The person's arms are visible, and they appear to be wearing a dark watch or bracelet on their left wrist. The background is plain white.

MY Joints
go out More
than I do



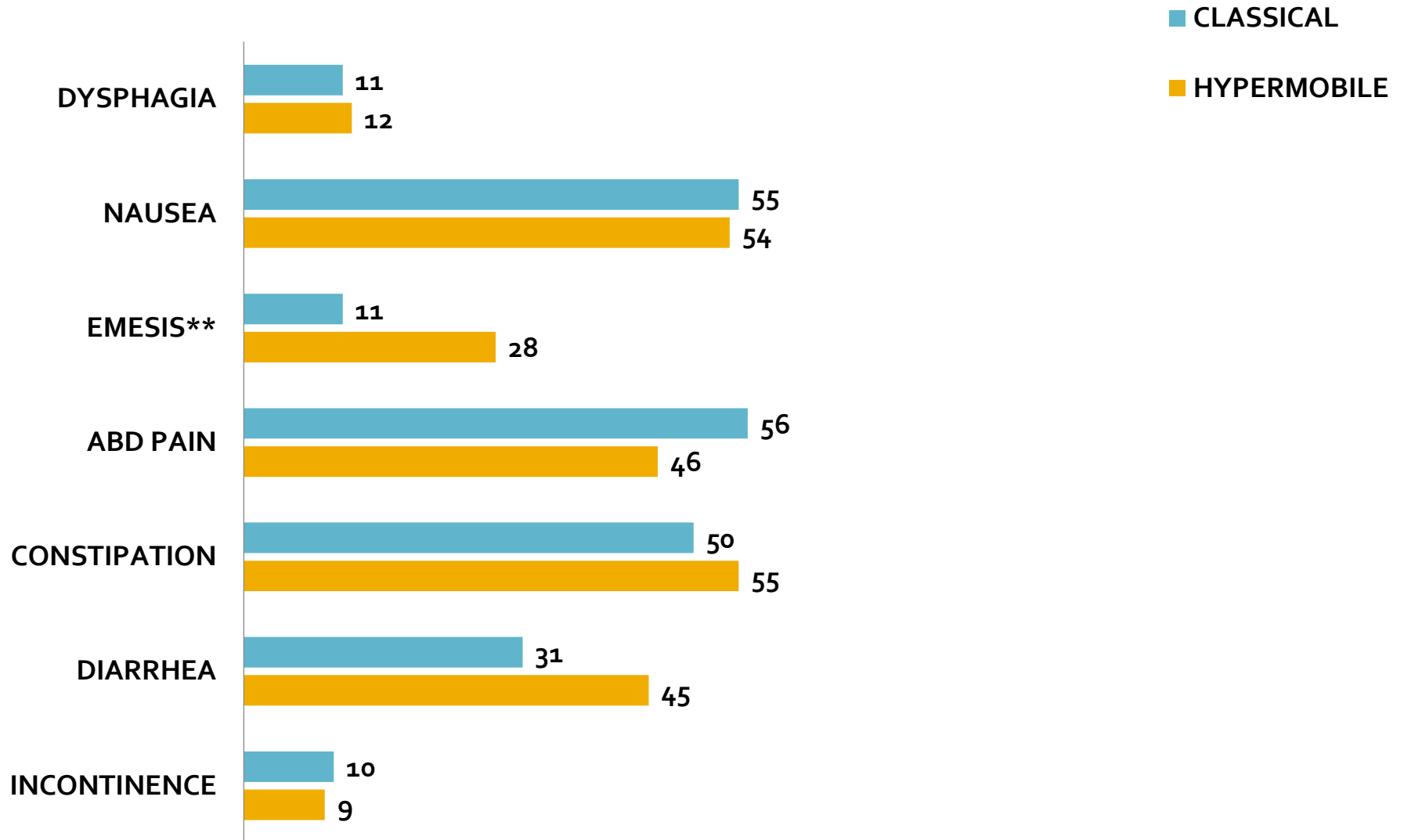
FEELING THE EFFECTS OF SLEEP DEPRIVATION



Gastrointestinal Complications In EDS

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

Gastrointestinal symptoms



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

Increased Intracranial Pressure

- 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

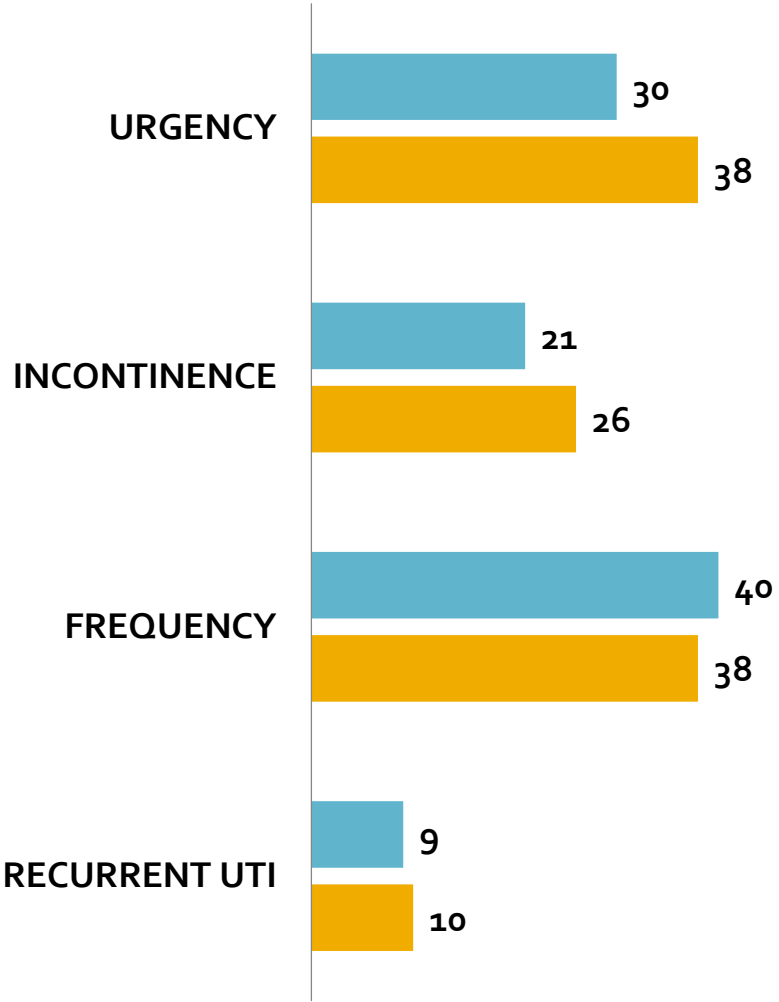
Pelvic Dysfunction in Ehlers-Danlos Syndrome

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

Urinary symptoms

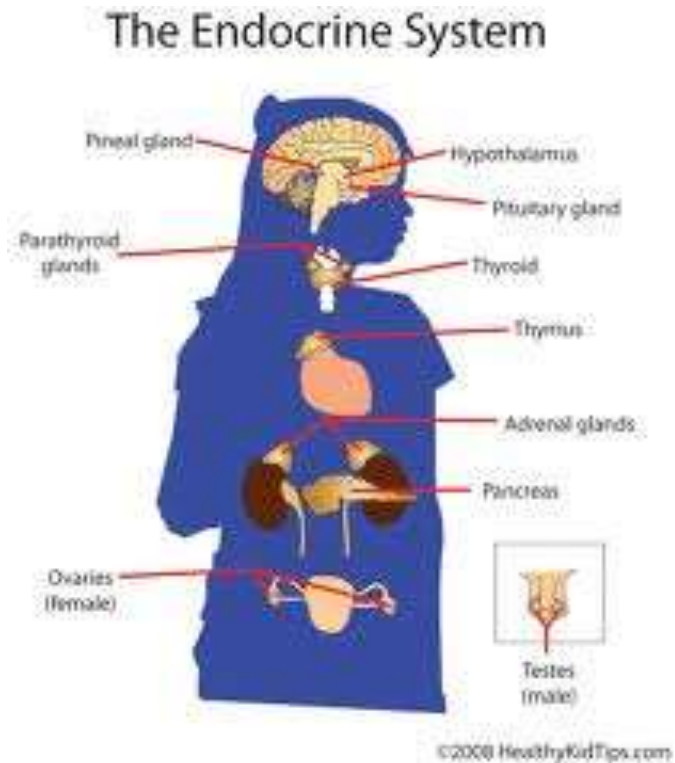
■ CLASSICAL

■ HYPERMOBILE



Exocrine Gland Dysfunction

- Pituitary
- Thyroid
- Pancreas
- Adrenal
- Ovaries
- Testes

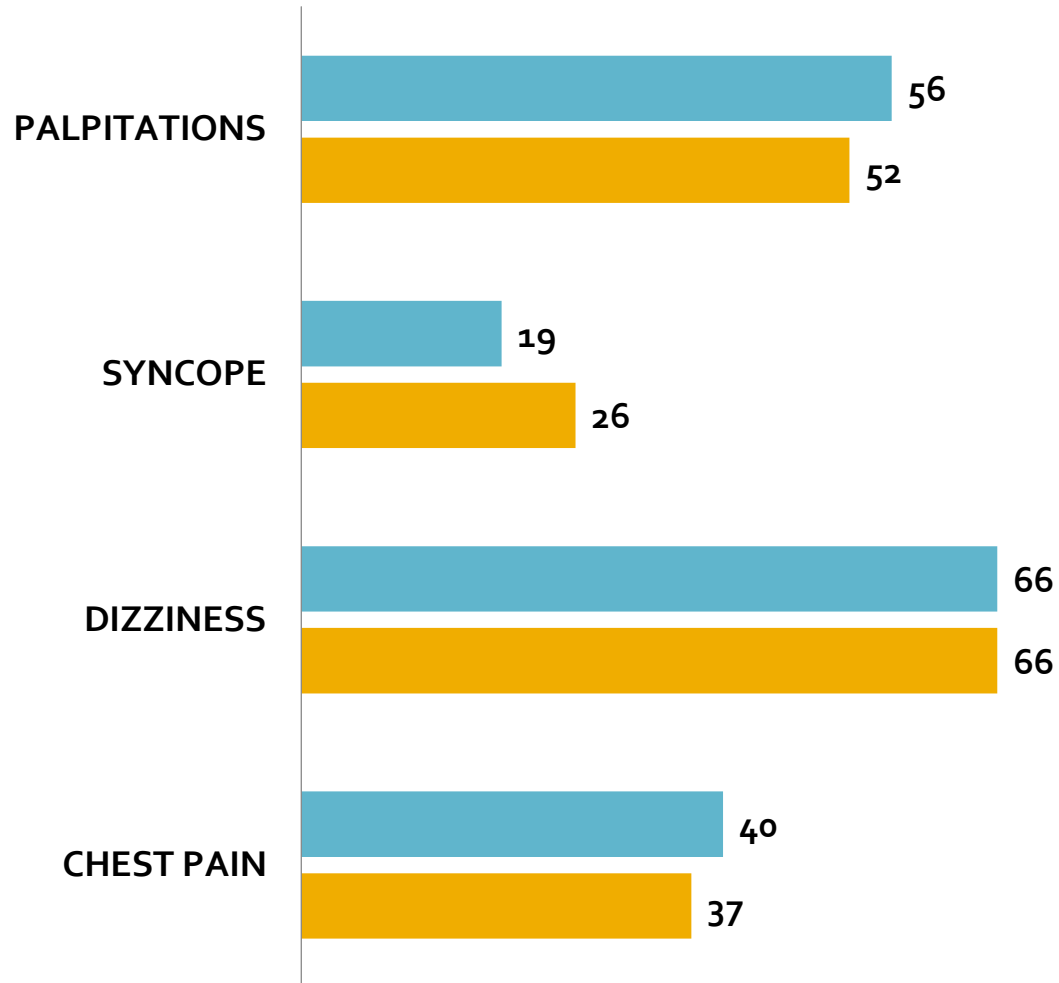


Cardiovascular Manifestations

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

Cardiovascular symptoms

■ CLASSICAL
■ HYPERMOBILE



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

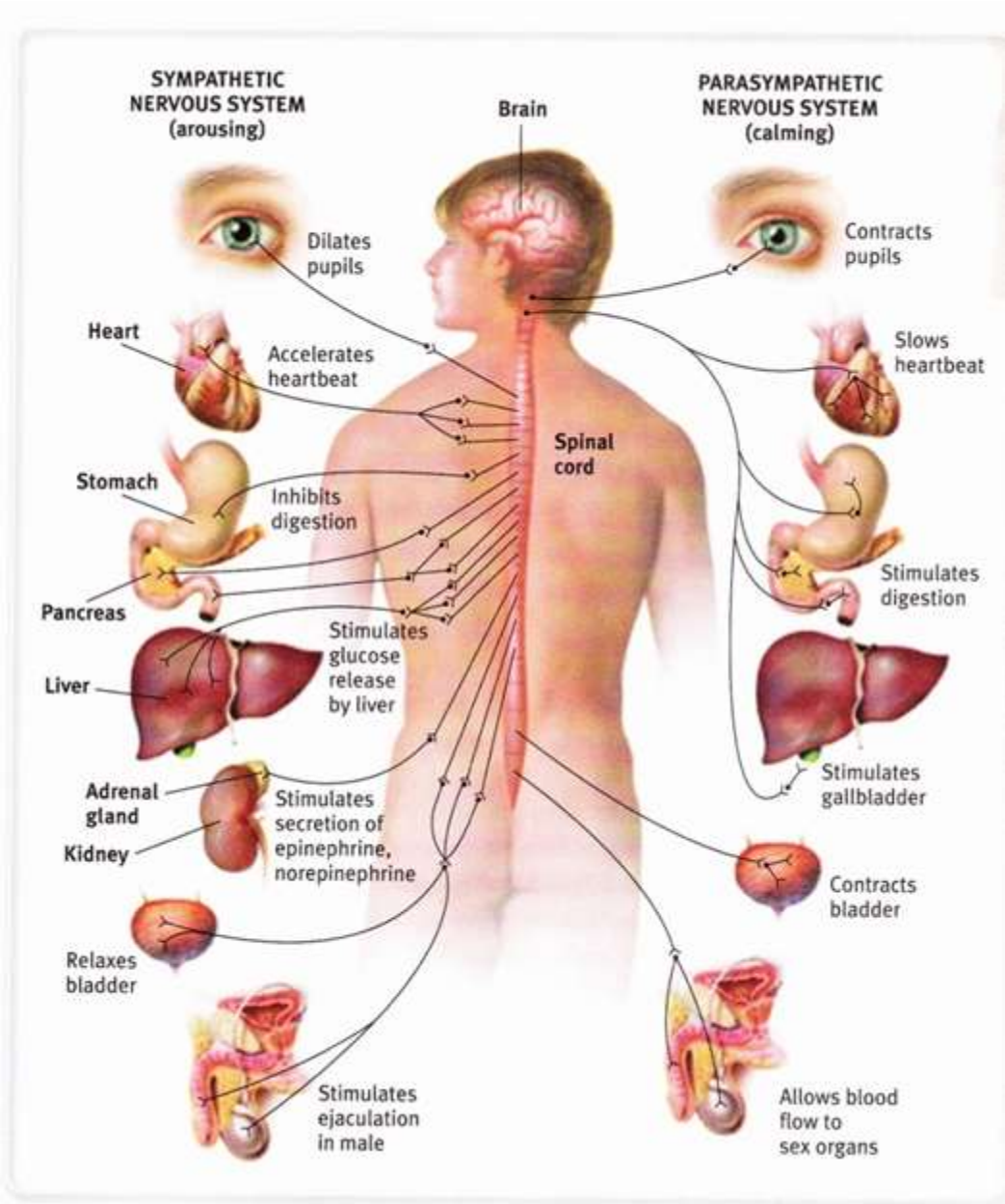
- There is a subset of EDS patients who develop symptoms of mast cell disease (flushing, hives, anaphylaxis)
- Many of these people respond to therapy for mast cell activation disorder (H₁ and H₂ blockers, cromolyn sodium)
- May reflect increased stress levels and/or autonomic dysfunction

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

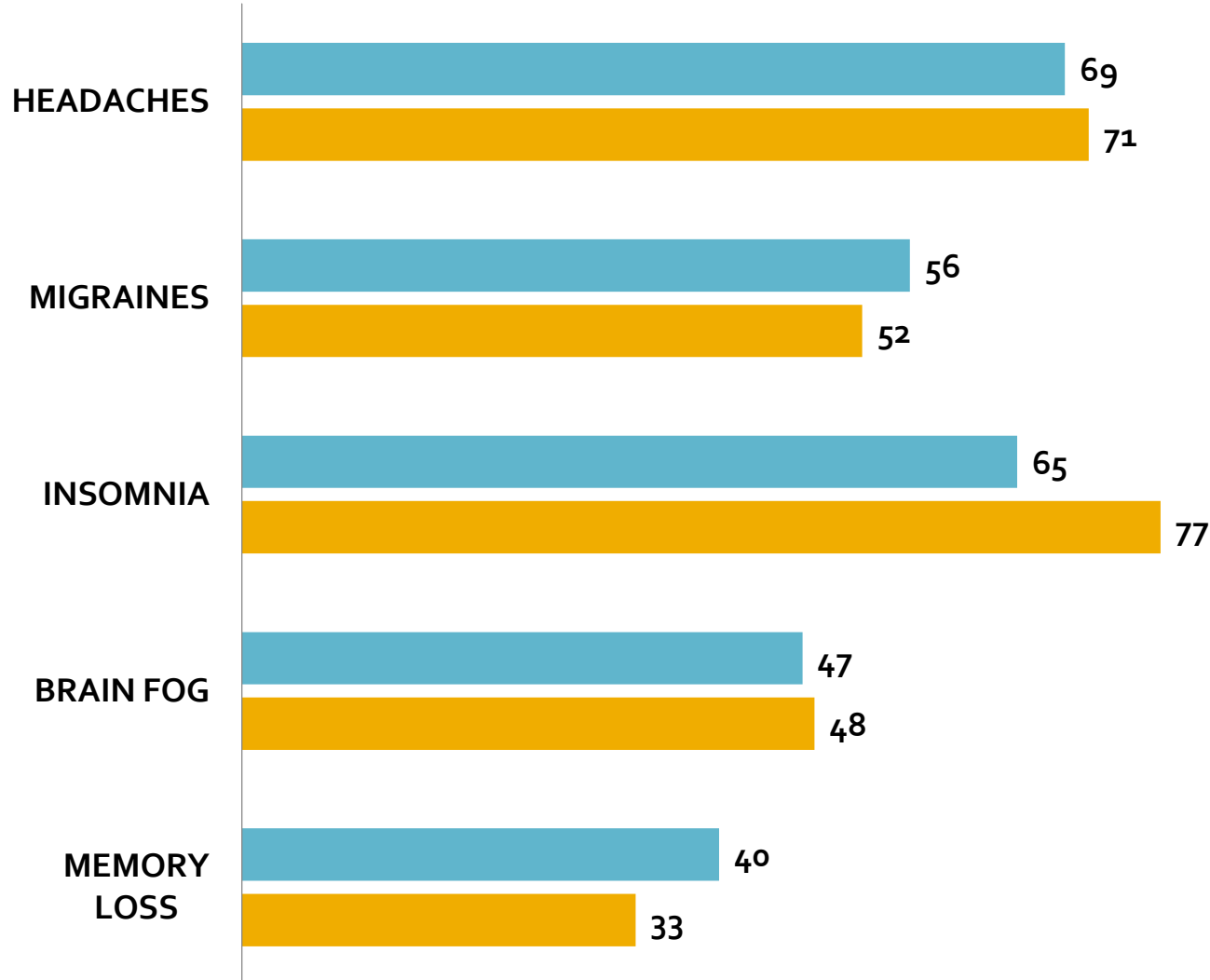


Autonomic Dysfunction

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

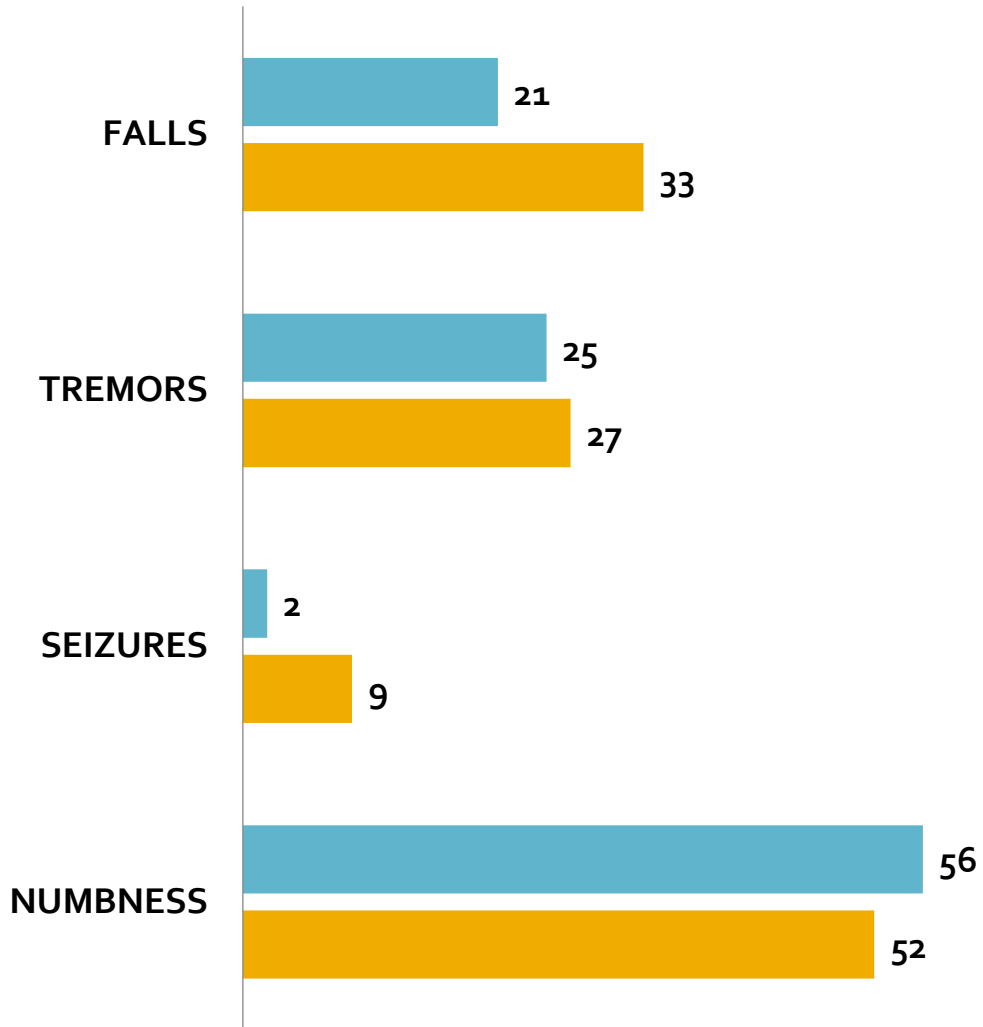
Neurologic symptoms

■ CLASSICAL
■ HYPERMOBILE



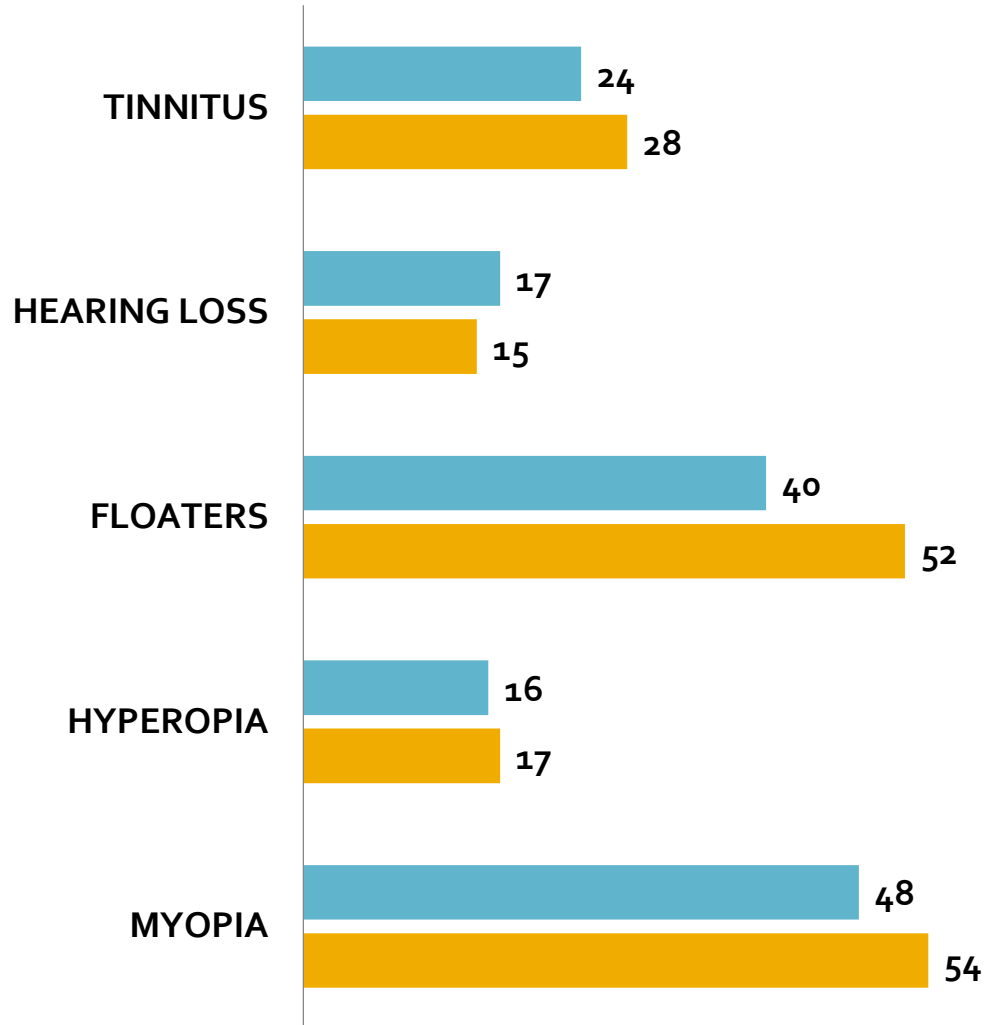
Neurologic symptoms

■ CLASSICAL
■ HYPERMOBILE

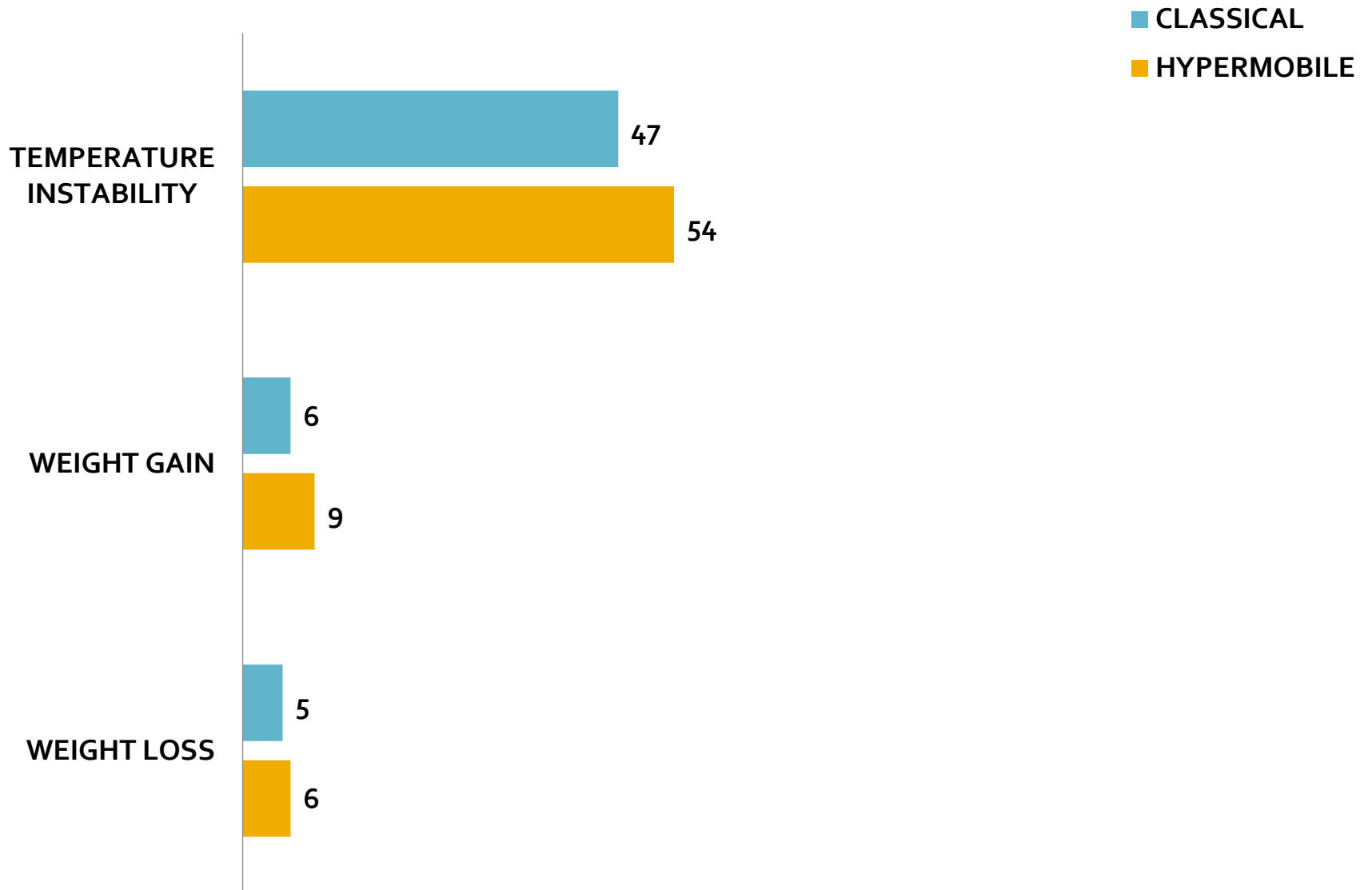


Neurologic symptoms

■ CLASSICAL
■ HYPERMOBILE

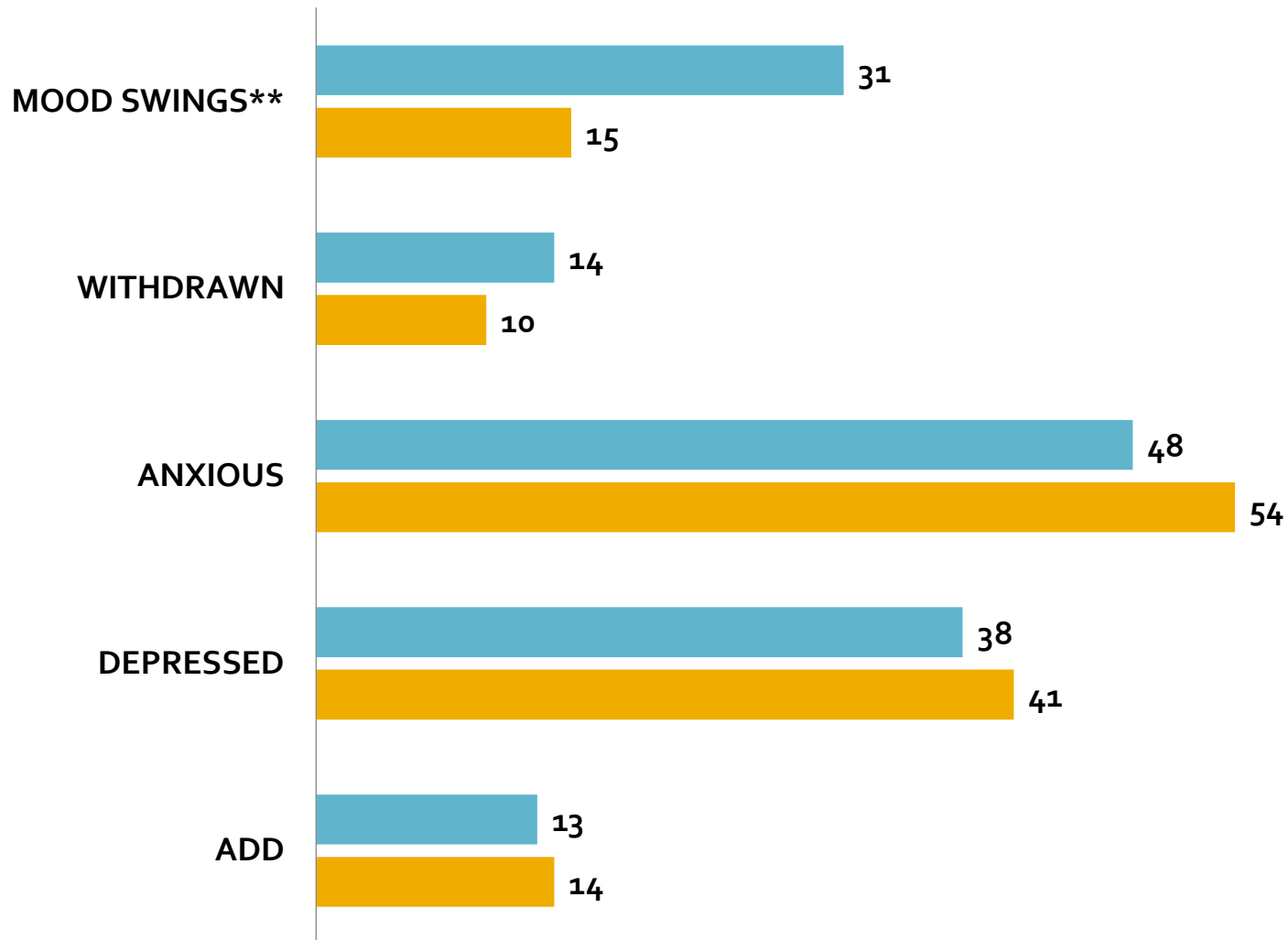


Constitutional symptoms



Psychiatric symptoms

■ CLASSICAL
■ HYPERMOBILE



Drug Metabolism

- 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

Saltzstein B.J., Wyshak G, Hubbusch J.T. Perry J.C. A Naturalistic study of the chronic fatigue syndrome among women in primary care. *Gen Hosp Psychiatry* 1998; 20(5): 307-16

Mean Karnofsky scores

HYPERMOBILE

71

CLASSICAL

67

| Age | <18 | 18-29 | 30-39 | 40-49 | >50 |
|-----------------|-----|-------|-------|-------|-----|
| Karnofsky score | 72 | 70 | 69 | 66 | 71 |

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
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