

Hypermobility 117: “Neuro-EDS”

Defining Neuro-EDS

A Neuro-Predominant Clinical Phenotype within hEDS/HSD and Related Heritable Connective Tissue Disorders

THE CLINICAL PROBLEM

Current hEDS/HSD patients are classified as a single heterogeneous population

Neurological manifestations are often viewed as isolated diagnoses

- Complex Chiari Malformation
- Craniocervical Instability (CCI)
- Tethered Cord Syndrome
- Intracranial Hypertension (IIH)
- CSF Leaks / Intracranial Hypotension
- Cerebral Venous Outflow Disorders
- Eagle Syndrome
- CSF-Venous Fistulas
- Dysautonomia
- Small Fiber Neuropathy
- Mast Cell Activation Syndrome
- Headache Disorders
- Sleep Disturbance
- Cognitive Dysfunction
- Chronic Fatigue / ME-like Illness
- GI Dysmotility
- Thermoregulatory Dysfunction
- Urinary Dysfunction

↓
**Fragmented diagnosis
Fragmented care**

Neuro-EDS

*A clinically recognizable
neuro-predominant phenotype*

Cranial &
Spinal
Domain

Neuro-
Autonomic-
Inflammatory
Domain

Structural • Physiologic • Neurovascular • Neuroimmune

WHY THIS MATTERS

Recognizes a *reproducible*
clinical phenotype

Provides a framework
for *earlier diagnosis*

Standardizes phenotyping
across centers

Enables prospective *registries*
and natural history studies

Corrects the inappropriate attribution
of symptoms to functional or primary
psychiatric disorders, underrecognition
of potential treatable craniospinal
pathology, and missed opportunities
for meaningful patient stratification.

Creates the foundation for
mechanism-based endotyping
and *precision medicine*

Neuro-EDS represents a proposed working clinical framework that will be refined through an international Delphi consensus process to establish standardized definitions, phenotyping, and diagnostic criteria.

Leslie N Russek,
PT, DPT, PhD, OCS
Clarkson University





Who Am I?

- Professor Emeritus, Physical Therapy Department, Clarkson University
- Retired PT, St. Lawrence Health System, Potsdam NY
 - Clinical specialties: hypermobility, fibromyalgia, headaches, temporomandibular disorders
- Member: Ehlers-Danlos Society Medical and Scientific Board
- Chair: The Allied Health Working Group of the International Consortium of Ehlers-Danlos Syndromes and Hypermobility Spectrum Disorders
- Frequent presenter to professional and patient groups at national and international conferences
- Author of multiple review and research articles on hypermobility
- Author: "Pain Mechanisms in HSD" in Di Bon, *The Integral Movement Method for Hypermobility Management*
- Author: "Chronic Pain" chapter in *Physical Rehabilitation* textbook for PT students
- Lrussek@Clarkson.edu
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**I do not have any
conflicts of interest to report**

Hypermobility Lecture Series Schedule

- HSD 101: Basics of HSD/hEDS and self-care
- HSD 102: POTS and POTS self-care, basics of MCAS
- HSD 103: Pain management in HSD/hEDS
- HSD 104: Safe exercise selection and progression with HSD/hEDS
- HSD 104 part 2: Nuts and bolts of modifying exercise with HSD and POTS
- HSD 105: Posture and joint protection
- HSD 106: Gut issues in HSD/hEDS, POTS, MCAS
- HSD 107: Fatigue in HSD/hEDS and POTS
- HSD 108: Headaches, migraines, & TMJ pain associated with HSD, POTS and MCAS
- HSD 109: Breathing disorders in HSD
- HSD 110: Lumbar instability
- HSD 111: Conservative management of cervical instability
- HSD 112: The vagus nerve
- HSD 113: The role of fascia
- HSD 114: Optimizing your hospital experience with HSD, POTS, MCAS
- HSD 115: Functional Neurological Disorder and HSD/hEDS
- HSD 116: Excessive Bleeding in HSD
- **HSD 117: *NEW* Neuro-EDS**

I will refer to these if
you want more info



Russek: HSD117 - Neuro-EDS



Relevant Handouts Available



I will refer to these if you want more info

<https://webpace.clarkson.edu/~lrussek/research.html>

- **Cervical Instability:**

- [Upper cervical Instability. \(UCI\).](#) Patient handout. [Full text of UCI article.](#)
- A very comprehensive patient guide to [EDS cervical instability by EDSawareness.](#)

- **Self-Care Strategies**

- [Headache Trigger Points.](#) Many headaches are caused by trigger points from overactive muscles trying to stabilize the neck.
- [Temporomandibular Disorder \(TMD\).](#) TMD, or TMJ problems, are common in HSD, and particularly with cervical instability.
- [Self-Care Toolbox.](#) A checklist to help you optimize your self-care toolbox.
- [Breathing.](#) Breathing incorrectly can increase cervical instability, pain sensitivity, headaches, & jaw pain
- [Posture.](#) Good posture decreases strain on muscles and joints, and can prevent many problems.
- [Joint Protection Strategies](#) Learning to protect your joints and muscles is the first step towards healthier and stronger joints.
- [Sleep Hygiene and Positioning.](#) Sleep posture and sleep hygiene strategies.

- **Pain Management**

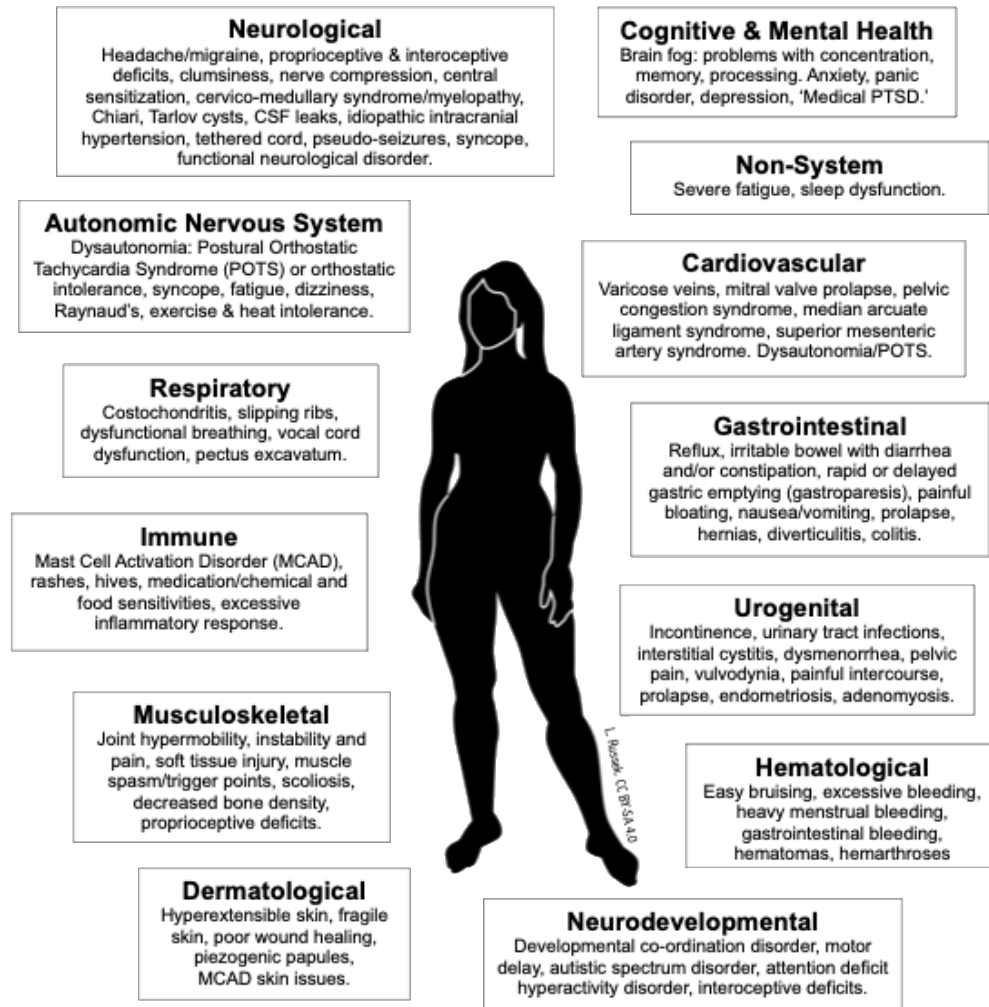
- [Pain flare management plan - PDF version.](#) Create a flare management plan so you know what works when you have a flare.
- [Free chronic pain management apps for teens](#)
- [Pain Sensitization: Nociceptive pain.](#) Explains pain mechanisms, including nociceptive pain.



Relevant Handouts Available



COMMON SYMPTOMS OF HYPERMOBILITY SPECTRUM DISORDERS



• Graphic showing symptoms associated with HSD.

I will refer to these if you want more info

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- [Headache Trigger Points.](#) Many headaches are caused by trigger points from overactive muscles trying to stabilize the neck.
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Disclaimers

The information in this presentation is for general purposes, only, and may or may not apply to your situation.

Check with your health care provider before starting any new treatment approach to ensure that it is appropriate and safe for YOU.

I cannot diagnose or make specific treatment recommendations in this lecture.

This lecture is based in part on an article that has completed peer review and is publicly available as a pre-print.



Caution!

- We will be discussing neurological conditions that can be scary to think about and have.
- Remember that most people with HSD (about 90%) won't have this complex Neuro-EDS phenotype. It is NOT a progression that affects most people with HSD.
- If you do have Neuro-EDS, you are not crazy and you are not a complainer or hypochondriac. You have ONE problem (a connective tissue disorder) that presents in MULTIPLE ways.
- Hopefully this is the beginning of finding better ways to prevent and manage this presentation of HSD.



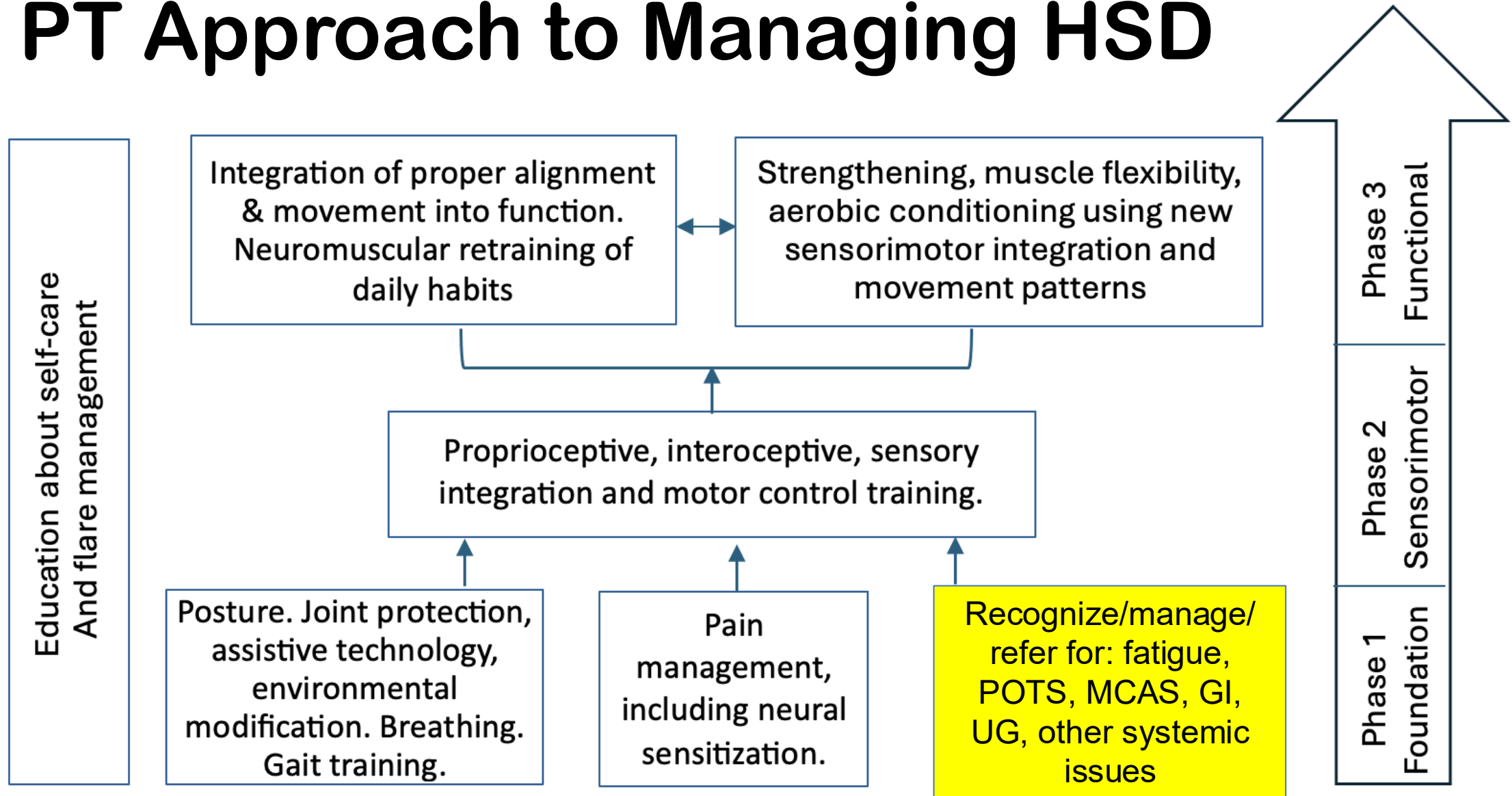
Objectives

By the end of this session, participants should be able to:

1. Describe what the "Neuro-EDS" phenotype looks like.
 2. Describe some of the inter-relationships that contribute to the frequent co-existence of these conditions.
 3. Recognize the benefits and limitations of defining this phenotype.
- Definition: A phenotype is the set of observable characteristics, traits, or physical properties of an organism, such as its appearance, development, biochemical properties, and behavior



PT Approach to Managing HSD



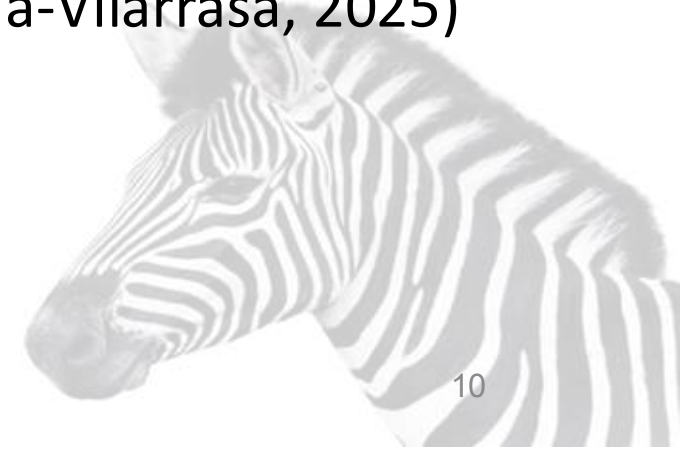
EDS Phenotypes

- There seem to be 3 ‘phenotypes’ or ‘clusters’ of EDS patients
 1. Many musculoskeletal symptoms and many comorbidities (45%)
 2. Mostly musculoskeletal, with fewer comorbidities (43%)
 3. Many neurological symptoms or comorbidities (11%)

Petrucci, 2024

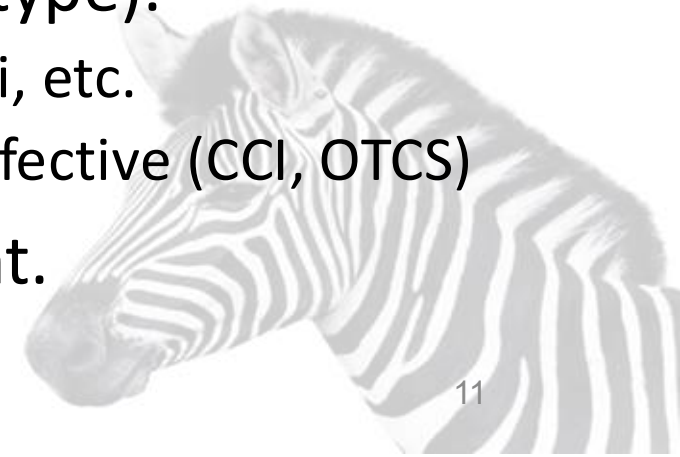
- Other neuro-related phenotypes described
 - Neuroconnective endophenotype

(Bulbena-Vilarrasa, 2025)



Why Does This Matter?

- A subgroup of people with HSD tend to develop multiple neurological problems.
 - These patients seem to have more problems than most people with HSD.
- Recognizing these individuals decreases the chance that their problems will be incorrectly diagnosed as psychiatric.
- Recognition can also facilitate identification of additional associated problems (i.e., other components of the neuro phenotype).
 - For example, providers know to look for CCI, CSF leak, Chiari, etc.
 - Recognize when standard diagnostic testing is not always effective (CCI, OTCS)
- Understanding why this occurs may improve treatment.

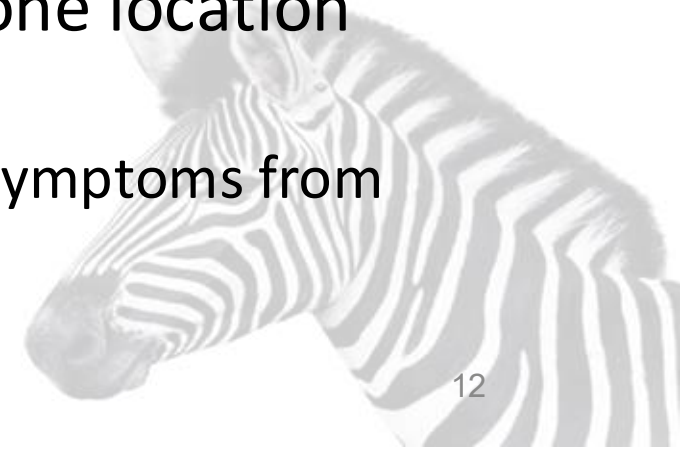


“Network Medicine” Approach

- Rather than viewing each neurological component as a separate diagnosis, the phenotype sees them as interconnected.

For example:

- Craniocervical instability (CCI) appears more common in patients with occult tethered cord syndrome (OTCS).
 - Sometimes treating the OTCS helps the CCI.
- Inflammation affecting the central nervous system in one location probably affects other parts of the nervous system.
 - Sometimes treating the inflammation (MCAS) calms down symptoms from structural problems.



“EDS Clusters”

Musculoskeletal High Comorbidities

Neuro

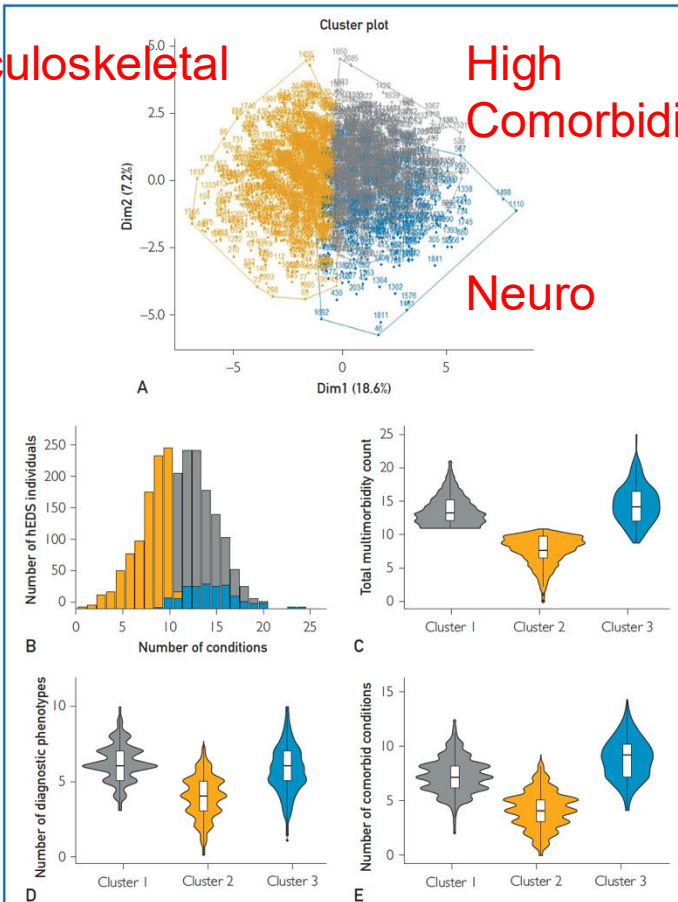


FIGURE 3. K-means clusters and multimorbidity profiles for hEDS. (A) K-means cluster plot illustrating the grouping of all patients with hEDS based on their reported clinical demographic characteristics. The plot reveals the presence of 6 distinct and independent clusters within the patient population with hEDS. (B) Graphical representation of the distribution and frequency of chronic conditions reporting differences between each cluster. (C-E) Prevalence of total multimorbidity, diagnostic phenotypes, and comorbid conditions per cluster.

hEDS diagnostic phenotypes	Cluster 1		Cluster 2		Cluster 3		Total	
	n	%	n	%	n	%	n	%
Chronic pain	951	97.44%	725	78.21%	241	97.97%	1917	89.20%
Joint subluxations	943	96.62%	751	81.01%	233	94.72%	1927	89.67%
Abnormal scarring	837	85.76%	471	50.81%	188	76.42%	1496	69.61%
Poor wound healing	787	80.64%	373	40.24%	167	67.89%	1327	61.75%
Abnormally stretchy skin	768	78.69%	519	55.99%	174	70.73%	1461	67.99%
Joint dislocations	748	76.64%	390	42.07%	160	65.04%	1298	60.40%
Mitral valve prolapse	310	31.76%	112	12.08%	79	32.11%	501	23.31%
Abdominal hernia(s)	264	27.05%	112	12.08%	78	31.71%	454	21.13%
Pelvic organ prolapse	250	25.61%	103	11.11%	52	21.14%	405	18.85%
Other heart valve conditions	195	19.98%	70	7.55%	41	16.67%	306	14.24%

A

Comorbid conditions	Cluster 1		Cluster 2		Cluster 3		Total	
	n	%	n	%	n	%	n	%
Gastrointestinal manifestations	889	91.09%	629	67.85%	222	90.24%	1740	80.97%
Anxiety	844	86.48%	598	64.51%	183	74.39%	1625	75.62%
Migraine	823	84.32%	476	51.35%	205	83.33%	1504	69.99%
Dysautonomia/POTS	807	82.68%	498	53.72%	218	88.62%	1523	70.87%
Depression	744	76.23%	450	48.54%	152	61.79%	1346	62.63%
Raynaud's phenomenon	568	58.20%	235	25.35%	138	56.10%	941	43.79%
Mast cell activation	496	50.82%	194	20.93%	169	68.70%	859	39.97%
ME/CFS	423	43.34%	144	15.53%	120	48.78%	687	31.97%
CCII/AAI	365	37.40%	129	13.92%	185	75.20%	679	31.60%
Bleeding or clotting problems	322	32.99%	86	9.28%	68	27.64%	476	22.15%
Autism spectrum disorder	109	11.17%	43	4.64%	38	15.45%	190	8.84%
Chiari malformation	0	0.00%	20	2.16%	150	60.98%	170	7.91%
Tethered cord	0	0.00%	9	0.97%	136	55.28%	145	6.75%

B

Additional demographics	Cluster 1	Cluster 2	Cluster 3	Total
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Number of conditions	13.37 (1.93)	8.00 (1.93)	14.39 (2.65)	11.17 (3.44)
Mean age	38.30 (12.42)	36.03 (13.73)	39.56 (11.68)	37.46 (12.98)
Total count	976	927	246	2149

C

45% 43% 11%

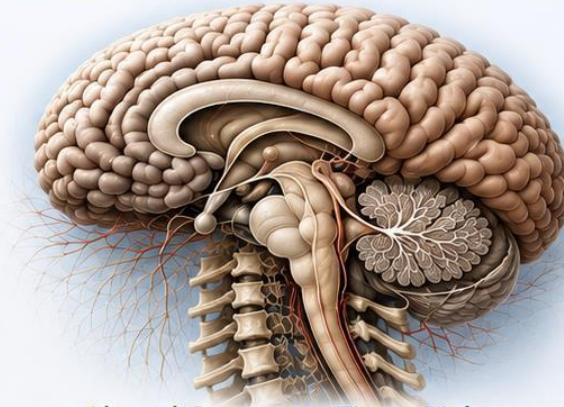
FIGURE 4. Subgroups and prevalence of chronic conditions per hEDS cluster. (A, B) Percentage prevalence of each chronic condition per cluster and totals across all clusters. Note that lower prevalence of diagnostic and comorbid conditions in Clusters 1 and 2 compared with Cluster 3, which has a high prevalence of neurologic conditions. (C) Mean number of conditions, age and total number of patients within each cluster. Note that Cluster 2 individuals have a lower prevalence of nearly all diagnostic and comorbid conditions, whereas Cluster 3 has the highest prevalence.

Neuro-EDS

A CLINICAL FRAMEWORK—NOT A NEW DISEASE.

CRANIOSPINAL MANIFESTATIONS

- Craniocervical instability
- Chiari I malformation / Complex Chiari spectrum
- Syringomyelia
- Tethered cord syndrome
- Intracranial hypertension
- Intracranial hypotension / spontaneous CSF leaks
- Internal jugular venous outflow disorders
- Eagle syndrome



Altered Connective Tissue Biology

↓
Shared Biomechanical, Physiologic
& Inflammatory Mechanisms

↓
Multiple Neurologic Manifestations

*These seemingly disparate neurological disorders
frequently cluster in patients with hEDS/HSD
and related connective tissue disorders.*

NEURO-AUTONOMIC & INFLAMMATORY MANIFESTATIONS

- POTS / Dysautonomia
- Cognitive dysfunction
- Small fiber neuropathy
- Gastrointestinal dysmotility
- Neurogenic bladder
- MCAS
- ME/CFS-like illness

————— A REPRODUCIBLE NEUROLOGIC PHENOTYPE —————

Different Diagnoses. Same Patient.

Bloom, in press: <https://www.preprints.org/manuscript/202608.0567>



CRANIOSPINAL MANIFESTATIONS IN NEURO-EDS

Craniocervical Instability

Chiari I Malformation

Complex Chiari Spectrum Disorders

Syringomyelia

Tethered Cord Syndrome

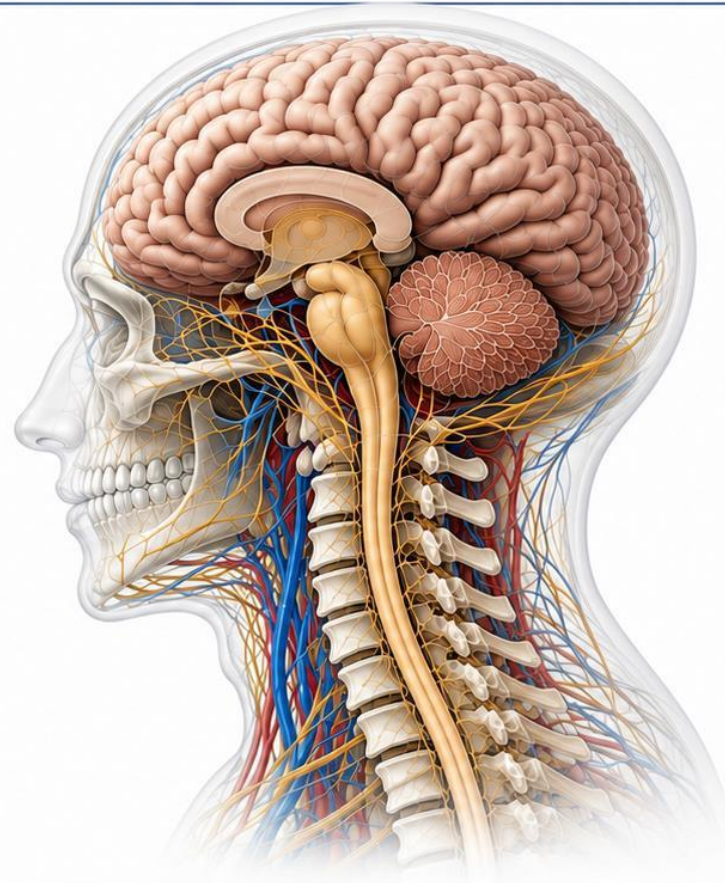
Intracranial Hypertension

Intracranial Hypotension and Spontaneous CSF Leaks

Internal Jugular Venous Outflow Disorders

Styloidogenic Jugular Venous Compression
and Internal Jugular Vein Compression at C1

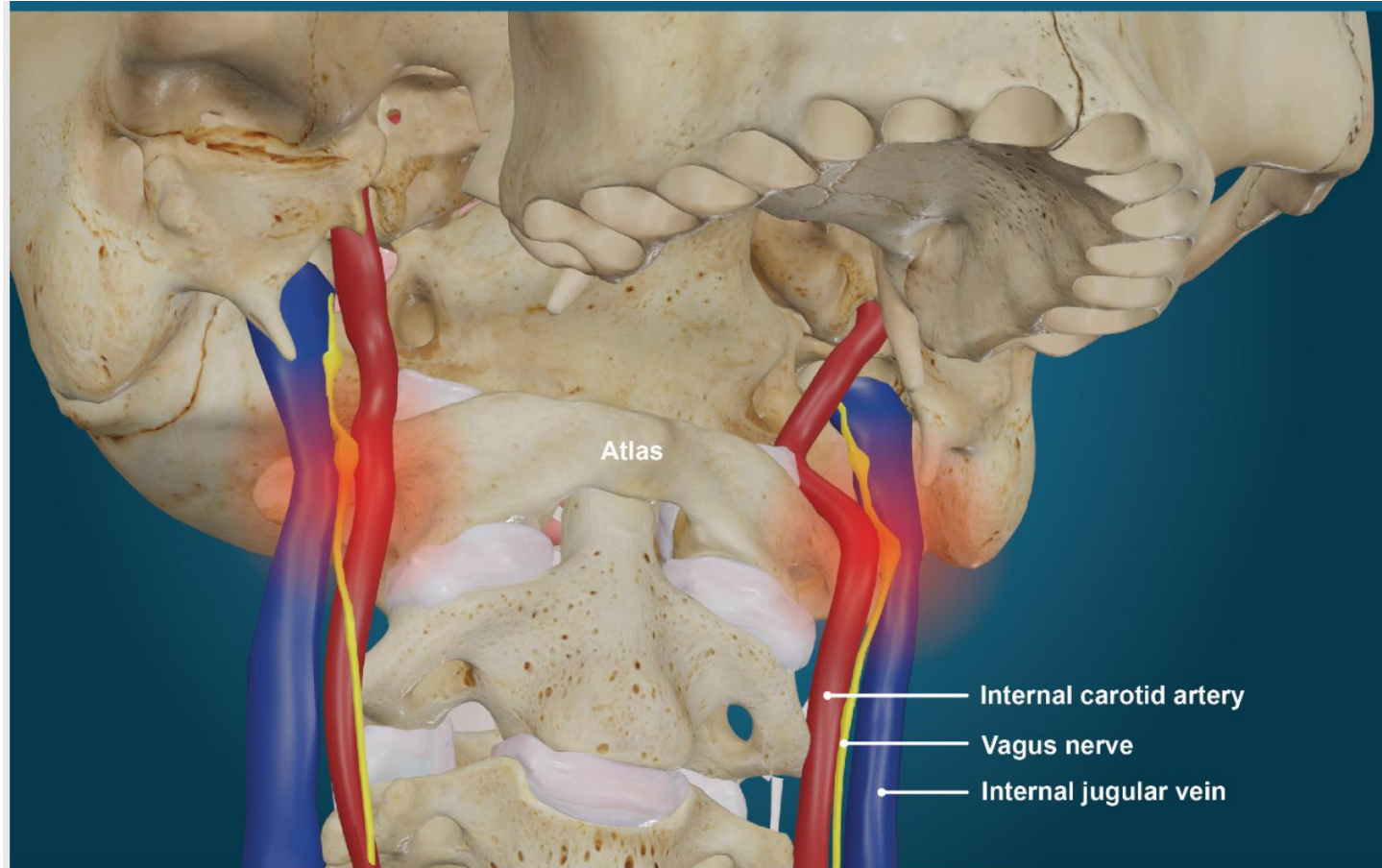
Eagle Syndrome



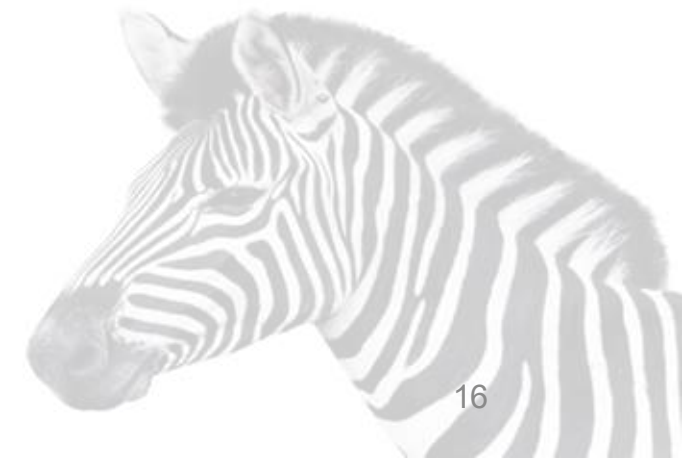
A common connective tissue substrate. Diverse neurological manifestations.



Neck Anatomy: Blood Flow & Vagus



This view is looking from the front, with the lower jaw and soft tissue of the throat removed.



Craniocervical Instability (CCI)



Heavy Head?
Symptoms of Upper Cervical Instability
(Russek et al., 2023)

Musculoskeletal-type

- Heavy/bobble head
- Apprehension about neck movement in vehicle
- Swallowing difficulties
- Clicking in neck with movement
- Tinnitus, dizziness

Neurological-type

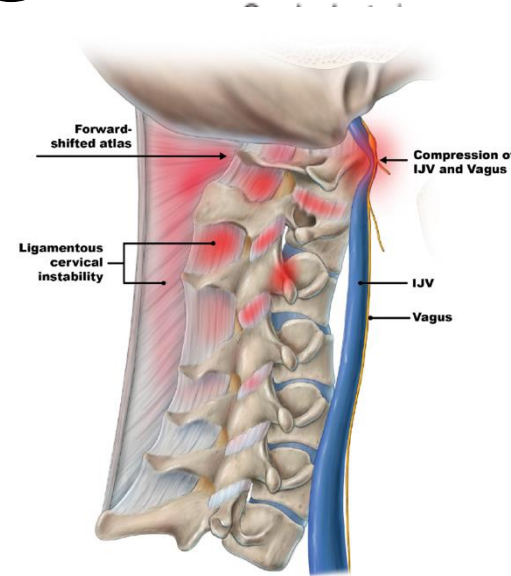
- Non-epileptic seizures
- Drop attacks from neck motion
- Swallow/vocal changes
- Boat rocking instability
- Ataxia
- Facial tingling/numbness
- Vision changes
- Dystonia and more...

@EMILYRICHOT >>> @CHALELAPTI

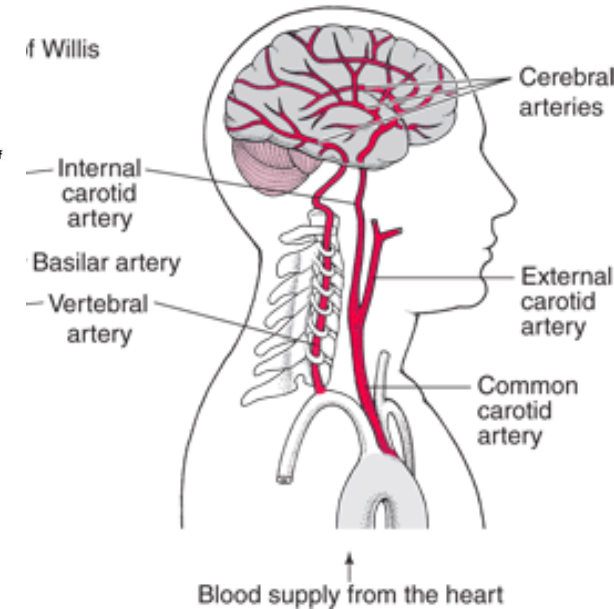
- In HSD, Often develops gradually over time due to connective tissue insufficiency.
 - In contrast to traumatic cervical instability in non-hypermobile people.
- Presents with symptoms of cervico-medullary syndrome .
 - The medulla is part of the brainstem most affected, and causes a lot of the symptoms.

Craniovascular Issues

- CCI can interfere with blood flow to the brain.
 - Rotational instability can compress the vertebral artery.
 - Excessive cervical extension (or forward head) can compress common carotid.
- Obstruction of venous (jugular) drainage from the brain
 - From cervical malalignment.
- Vascular compression: dizziness, fainting, drop attacks, headaches triggered by neck movement, visual changes
- Eagle syndrome: feels like severe ear infection, aching tongue and throat, lump in throat. Symptoms aggravated with head rotation, tilting, swallowing.

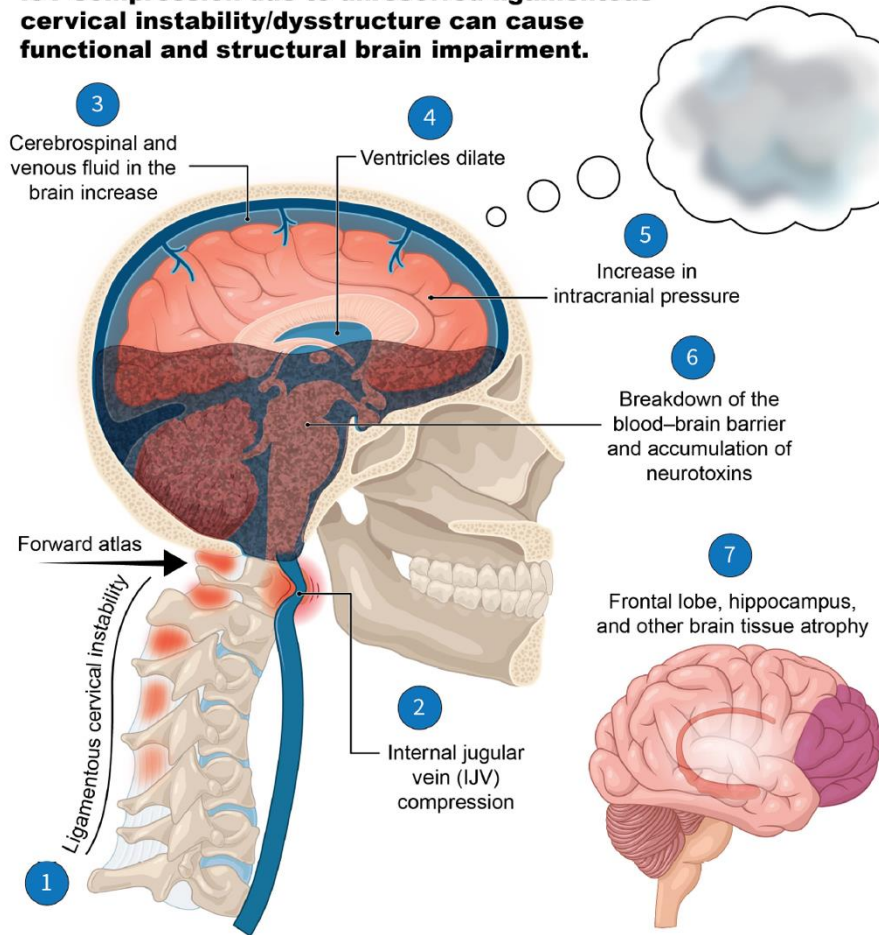


Hauser, 2026



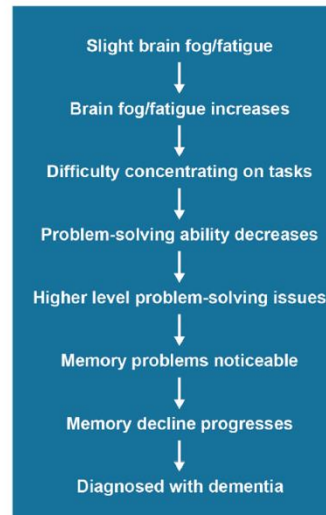
Secondary Effects of CCI

IJV compression due to unresolved ligamentous cervical instability/dysstructure can cause functional and structural brain impairment.



Ligamentous cervical instability leads to venous fluid outflow obstruction. As the condition progresses, brain pressure increases, the blood–brain barrier breaks down, neurotoxins accumulate, and these and other factors ultimately lead to the death of brain tissue. When the frontal lobe and hippocampus atrophy, cognitive abilities decline.

Cascade of Symptoms



Ligamentous Cervical Instability

cervical dysstructure

dynamic carotid sheath compression

internal jugular vein compression

vagus nerve degeneration

- elevated intracranial pressure
- headaches
- brain fog
- concentration difficulty
- fatigue
- memory problems
- dizziness
- lightheadedness
- fainting (syncope)
- visual disturbances
- light sensitivity
- eye pain/pressure
- tinnitus
- noise sensitivity
- sleep disturbances
- cerebrospinal fluid (CSF) disorders
- mental health/mood disorders
- balance difficulties
- other cognitive difficulties

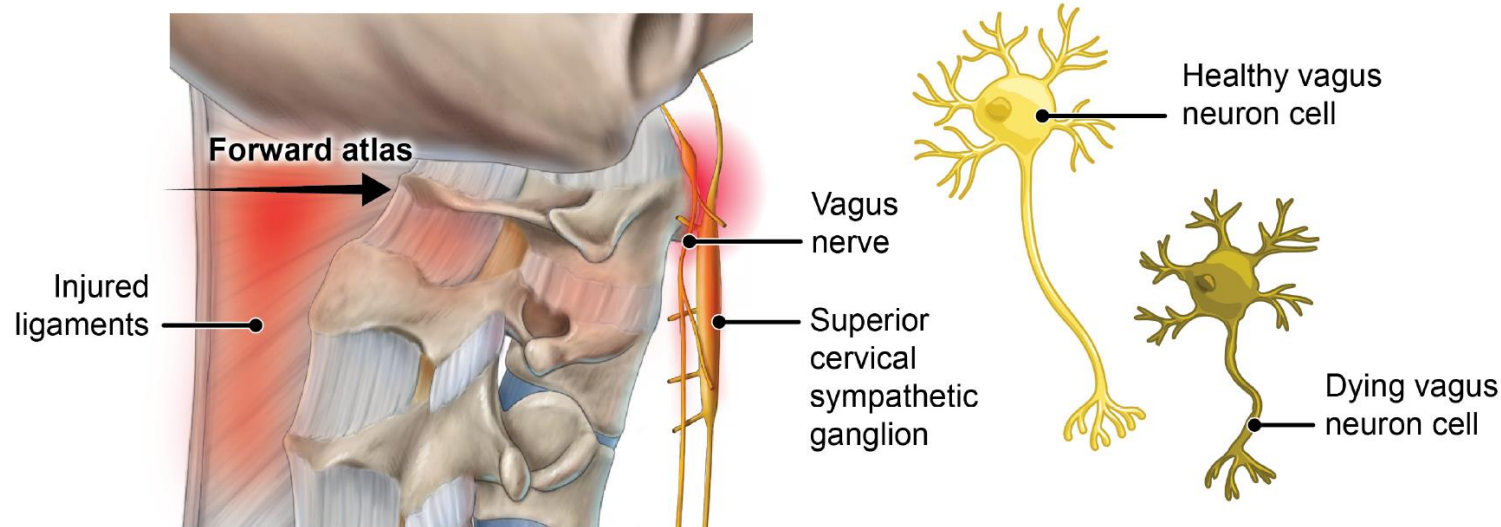
- Postural orthostatic tachycardia syndrome (POTS)
- orthostatic intolerance, presyncope, syncope
- visual dimming / tunnel vision
- dizziness
- heart palpitations
- inappropriate sinus tachycardia
- reduced heart rate variability/poor stress recovery
- gastrointestinal dysmotility
- nausea
- abdominal pain and bloating
- air hunger
- anxiety
- mast cell activation syndrome
- chronic pain
- chronic inflammation
- sympathetic overdrive
- other dysautonomia

Hauser, 2026

Russek: HSD117 - Neuro-EDS

BRAIN BODY

CCI and Vagus Nerve Function



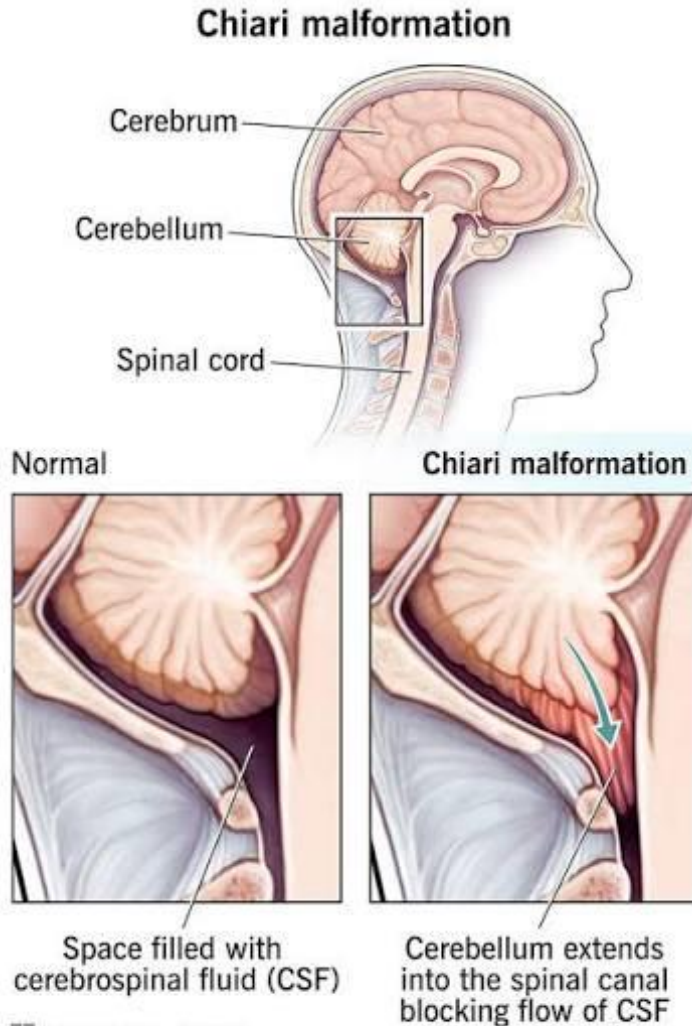
Vagus nerve degeneration leads to imbalanced sympathetic/parasympathetic system (chronic fight/flight or reduced rest and digest), affecting multiple systems:

- Irregular heart rate (high heart rate, slow heart rate recovery)
- Reduced baroreflex (blood pressure instability, fainting, lightheaded)
- GI dysfunction (poor digestion, acid reflux, constipation)
- Vasoconstriction (increased blood pressure, reduced blood flow)
- Pupil dilation (visual changes)
- Altered inflammatory response (chronic inflammation)
- Emotional distress (anxiety, depression, mood changes)
- Neurologic difficulties (brain fog, sleep disturbance, swallowing difficulties, headaches, hoarseness, tinnitus)

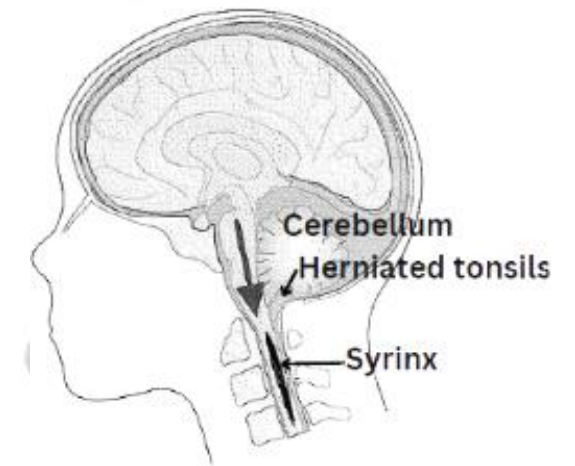
Hauser, 2026



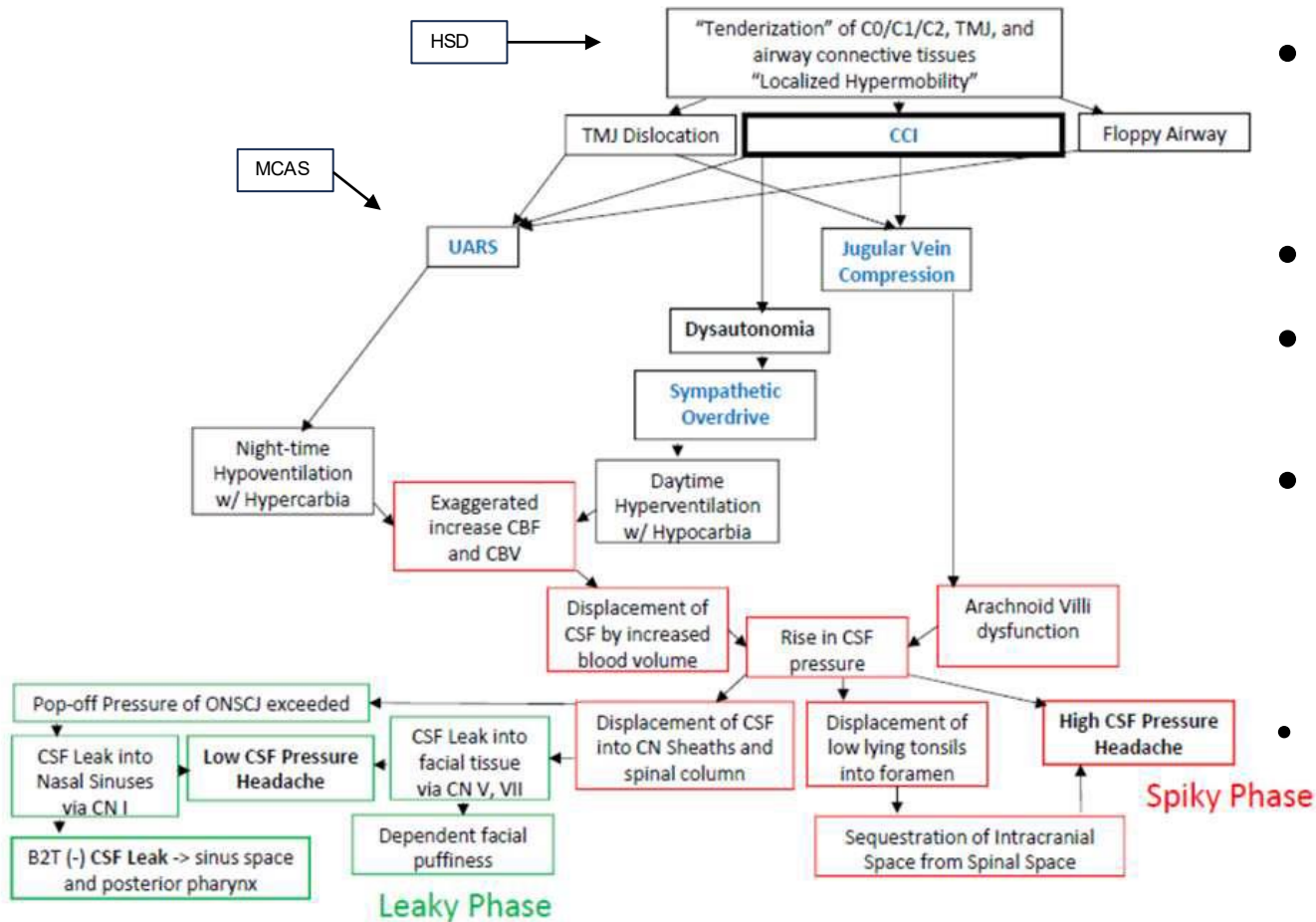
Chiari & Syringomyelia



- Chiari I malformation when portions of the cerebellum sink into the spinal canal.
- Syringomyelia occurs when a fluid-filled pocket forms within the spinal canal and compresses the spinal cord.
- Symptoms:
 - Loss of sensitivity to hot and cold
 - Numbness and tingling
 - Bowel and bladder function may be affected
 - Scoliosis
 - Pain
 - Muscle weakness
 - Spasticity
 - Paralysis



Cerebrospinal Fluid Pressure Disorder



- Cerebrospinal fluid (CSF) is formed in the brain and naturally drains down the spinal canal.
- CSF leak leads to low CSF pressure.
- Intracranial hypertension if there is an obstruction to fluid flow.
- “Spiky-Leaky” can occur where people alternate between the two states.

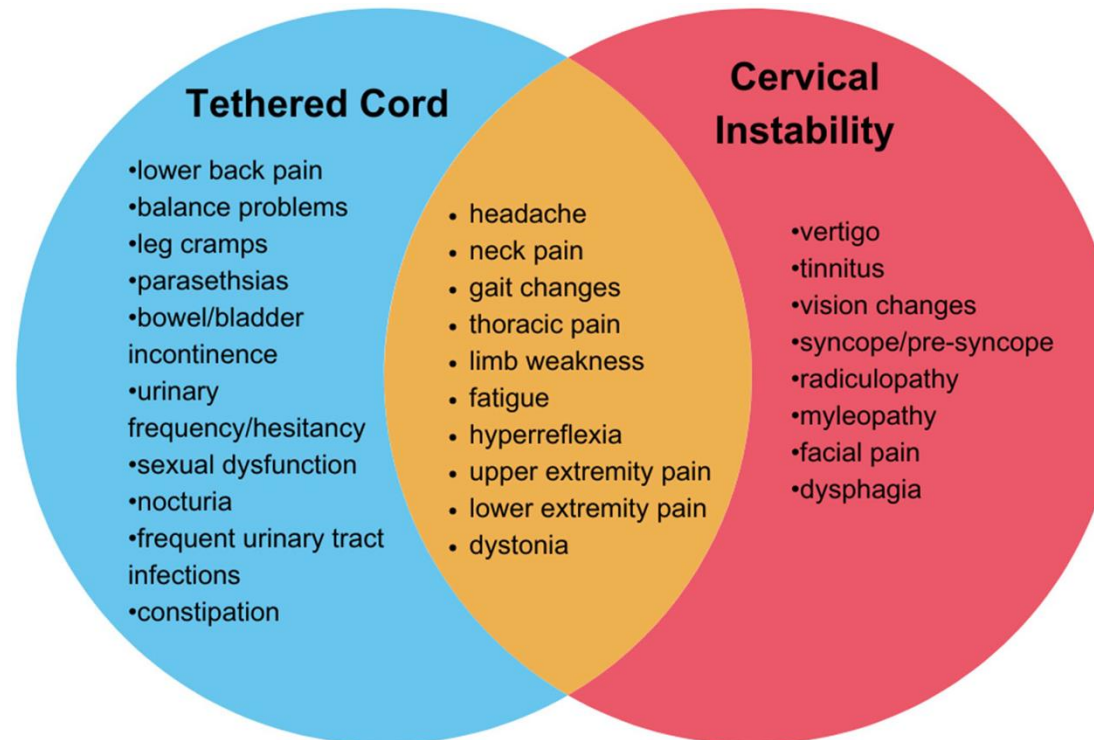
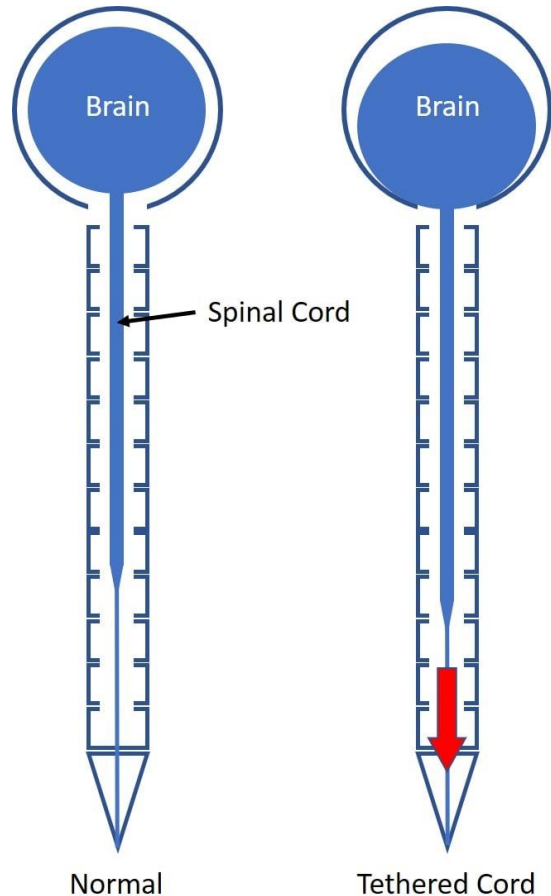
Maxwell, 2024

Abbreviations:

- MCAS: mast cell activation syndrome
- CCI: craniocervical instability
- UARS: upper airway resistance syndrome

Occult Tethered Cord Syndrome (OTCS)

- Spinal cord is fixed to fibrous tissue at the bottom of the spinal cord.
- If the tethering is not visible on MRI (often true in HSD) it is “occult tethered cord syndrome”. Special diagnostic tests need to be done (prone vs. supine MRI).
- It can pull on the brain and aggravate cervicomedullary symptoms due to CCI.
- OTCS symptoms can be similar to CCI, and CCI can co-exist.

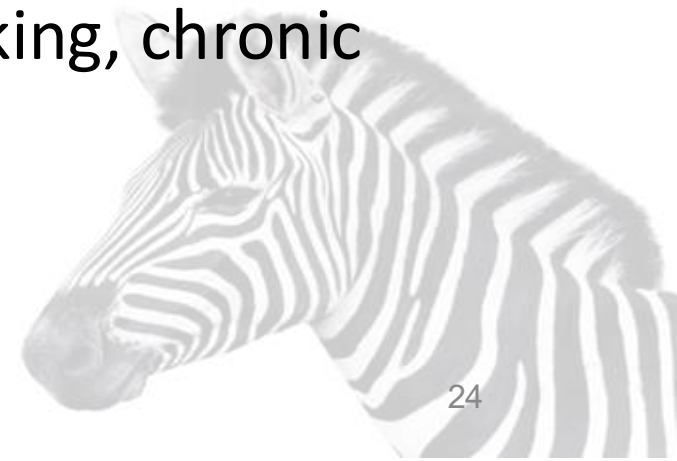


Gensemer, 2024



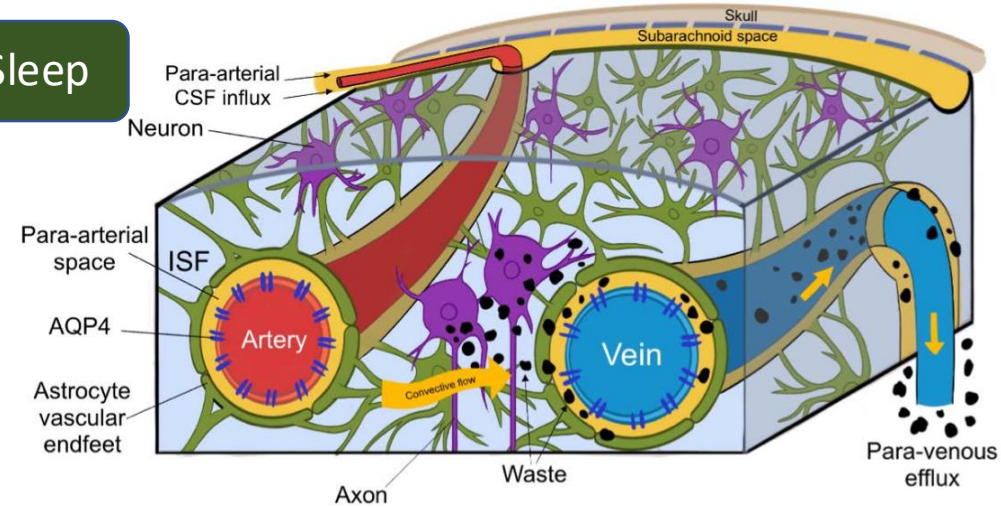
Neuro-Autonomic-Inflammatory Domain

- Dysautonomia/POTS
- GI dysfunction
- Temperature regulation dysfunction
- Bladder dysfunction
- Mast cell activation syndrome (MCAS)
- Small fiber neuropathy
- Symptoms: headache, sleep disturbance, trouble thinking, chronic fatigue, exercise intolerance
- Chronic fatigue syndrome presentation



Glymphatics and Sleep

- “Glymphatics” from ‘glial’ cells and ‘lymphatics’
- The fluid flow system that removes metabolic waste products from your brain
- Glymphatics are 10x more active during sleep than waking
 - Primarily during nREM (non rapid-eye-movement) stage 3 sleep
- Flushes out metabolic waste from brain cells
- Transports increased oxygen to brain cells
- Inadequate sleep interferes with glymphatics, stresses brain neurons and may contribute to:
 - Symptoms such as fatigue, brain fog, headaches, poor memory, low mood
 - Diseases such as Alzheimer’s, Parkinson’s, slow recovery from head trauma



Reddy, 2020

- Yang, 2026; Reddy, 2020
- <https://pmc.ncbi.nlm.nih.gov/articles/PMC7698404/pdf/brainsci-10-00868.pdf>

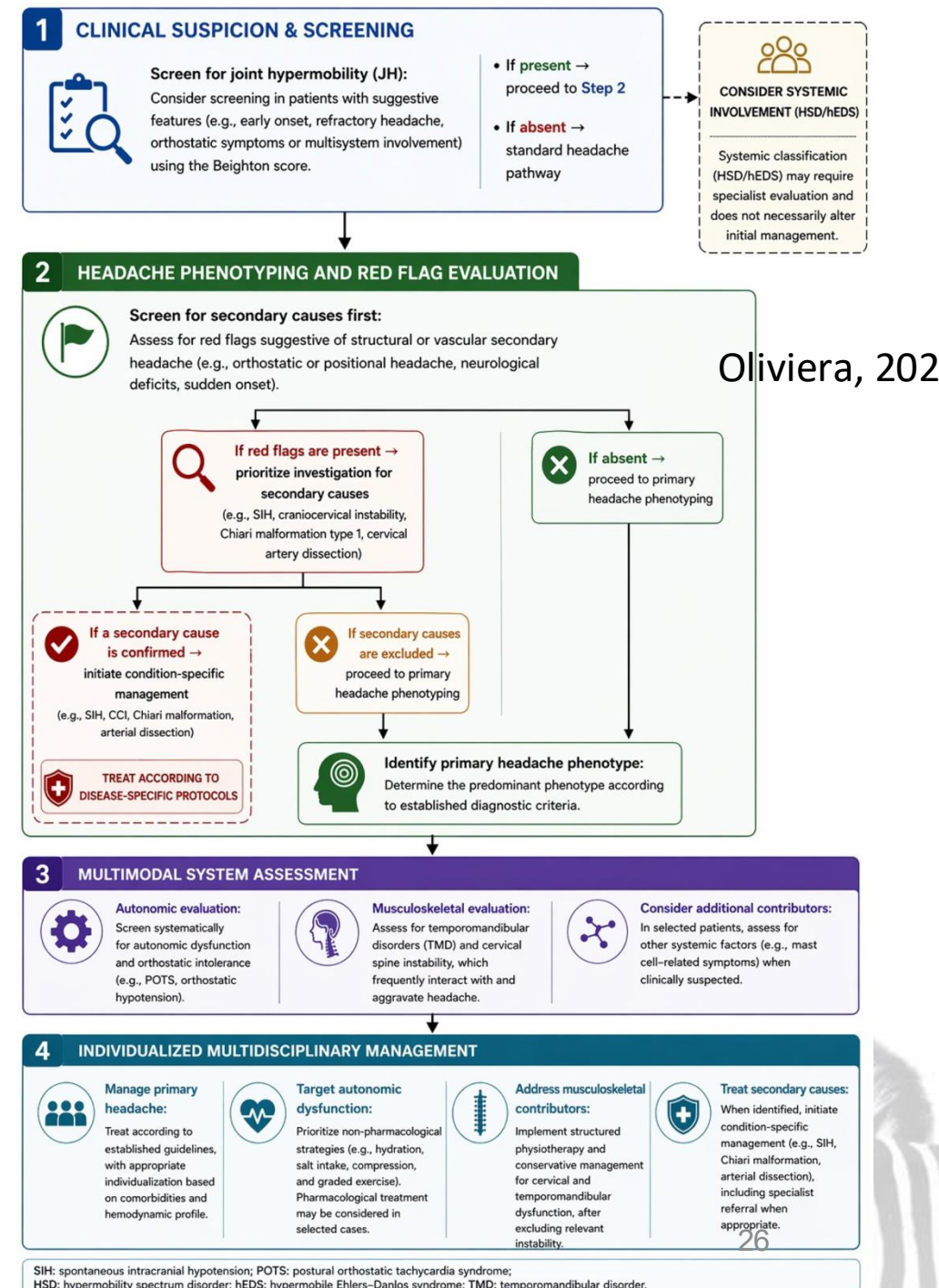
Headaches (HA)

- There are many potential causes of HA in HSD. Most are not due to Neuro-EDS.
- Neuroinflammation:
 - Migraines:
 - Neuroinflammation due to MCAS
 - Dysautonomia due to POTS
 - Sleep disturbance (poor glymphatics)
- Craniospinal factors
 - E.g., CCI, OTCS, CSF leak...
- Musculoskeletal
 - Poor posture
 - Myofascial trigger points (TrP)
 - Temporomandibular joint problems

HSD 108 Discusses HA NOT associated with CNS problems

HA TrP & TMJ

Oliviera, 2026; Mehta, 2024



WHY DOES IT MATTER?

Recognition of reproducible clinical phenotypes allows us to:

TRANSFORM PATIENT CARE

Unified neurological phenotype

Reduced diagnostic delay and
fragmented care

Coordinated multidisciplinary evaluation

Earlier identification of treatable disease

More precise, biology-informed management

Validate patient experience

ADVANCE RESEARCH

Standardized phenotyping

Multicenter collaboration

Longitudinal natural history studies

Biomarker discovery

Mechanistic discovery

Conduct prospective research

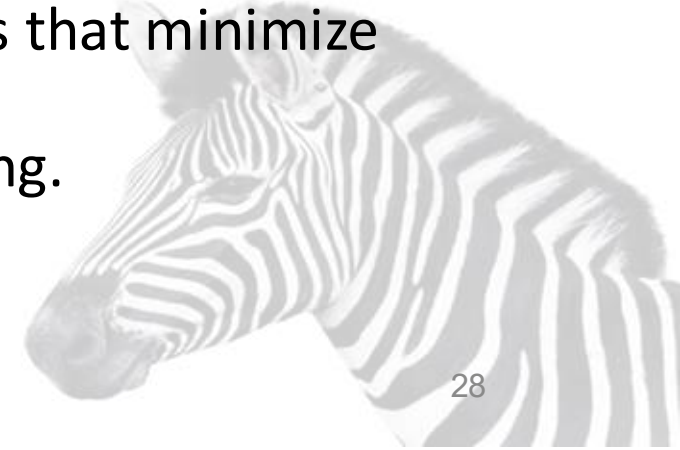
Recognizing Patterns. Understanding Biology. Transforming Care.

————— Develop Education and Awareness —————



What Can You Do About It?

- Improve diagnosis.
 - Recognize that there is a reason that these conditions are often not “either-or” but “also”. Encourages recognition of all the EDS-related neuro issues.
 - Think about what order of treatment is most likely to be most effective.
 - Best to manage inflammation (e.g., MCAS) BEFORE AND AFTER any surgery!
 - E.g., surgery for OTCS often decreases CCI symptoms, and is less invasive.
- What can you do for yourself?
 - Manage MCAS.
 - Manage CCI and OTCS through posture and body mechanics that minimize strain on the nervous system.
 - Manage CCI through sensory motor training and neck bracing.
 - What else? We don't know, yet... this is all so new!



Other Neuro Phenotypes



Neuroconnective Endophenotype

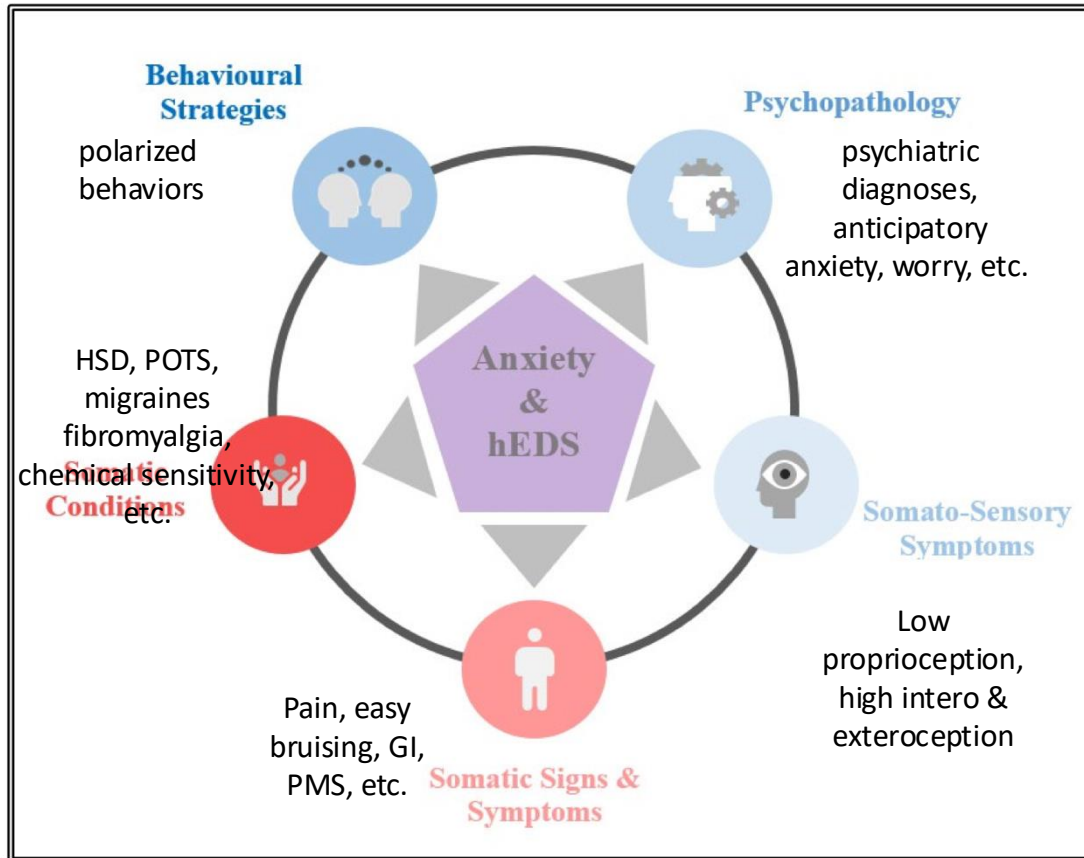


Figure S8. Schematic representation of the Neuroconnective Phenotype with its five dimensions and Anxiety and hEDS as the core.

- Proposed as link between physical and psychiatric symptoms common in HSD.
- Encourages psychiatrists to look for physical causes of psychological presentations.
 - *“The relevance of the NEP model stems from its potential to evaluate psychiatric patients globally, focusing on both classically defined “mental” and “physical” signs and symptoms.”*
- Highly correlated to Functional Neurological Disorder (FND).
- Goal: Inform psychiatrists about physiological factors contributing to psychological presentations.

Bulbena-Vilarrasa, 2025

Summary

- People with HSD are vulnerable to a variety of neurological problems.
- It is better to think of this as one condition presenting in multiple ways.
- These different conditions, whether structural or physiological, influence one another.
- Treating one part can sometimes benefit other parts.
- This concept is new and should evolve over time and will hopefully improve diagnosis and management.



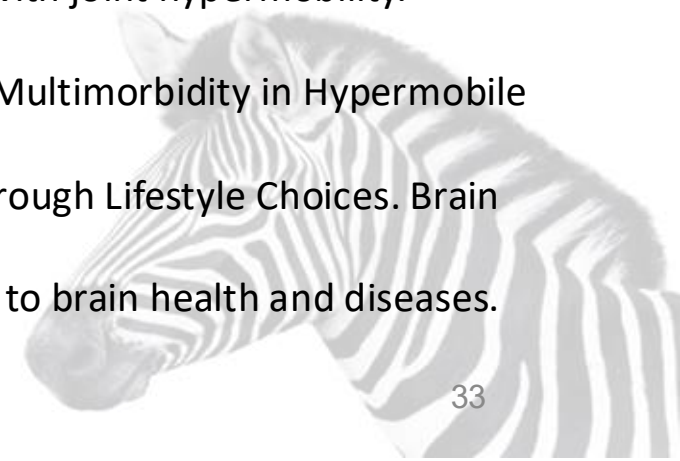
Special Journal Issue...

- I am one of the guest editors for a Frontiers in Neurology Special Topic issue: ***“Complex Neuropresentions in Hypermobility Spectrum Disorders: Interacting Mechanisms and Comorbid Conditions”*** that is due to come out in December.
- The Bloom article, and several other relevant articles will be available as open access.
- You should be able to find the issue by searching for the topic title, above.



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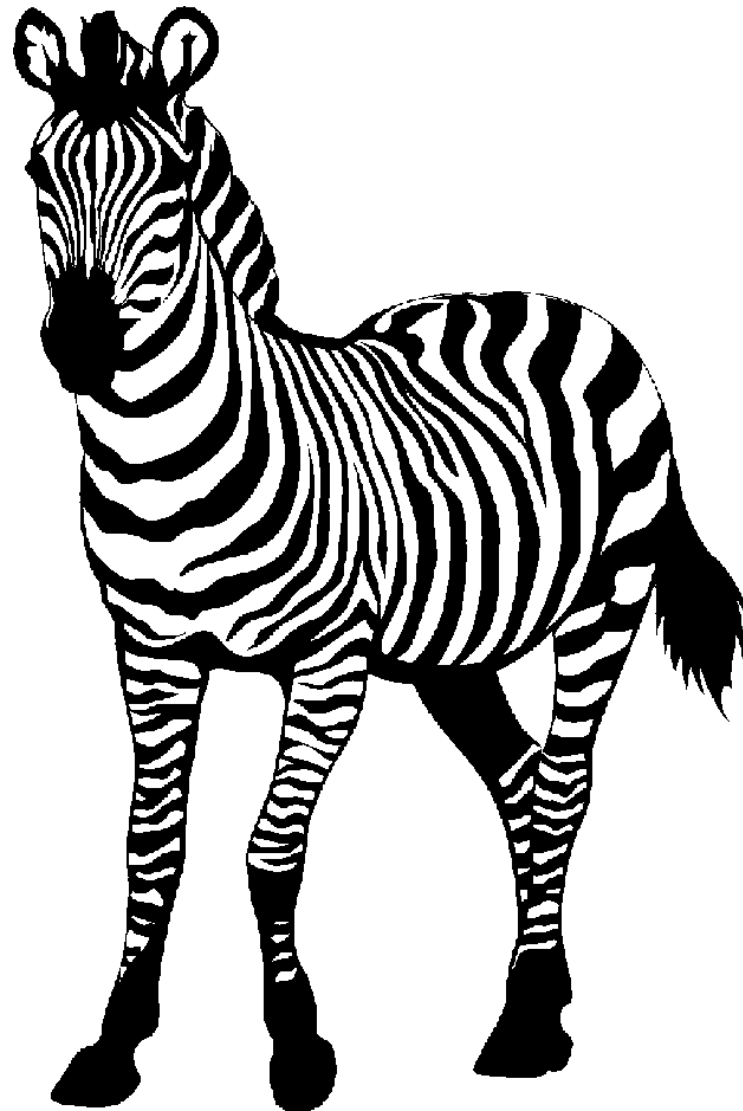
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Web Resources



Thank You!





Questions?

