Long COVID & ME/CFS Clinical Considerations: Hypermobility

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Symptoms of hypermobile spectrum disorders can be myriad and span all aspects of a complete review of systems…

Not dissimilar to those with long-COVID and ME/CFS

TABLE 3

Symptoms Associated with Hypermobile Ehlers-Danlos Syndrome

Organ system	Symptoms/physical findings
Autonomic[27,28]	Neurally mediated hypotension/syncope
	Orthostatic intolerance
	Postural orthostatic tachycardia syndrome
Cardiovascular[29]	Low progressive aortic root dilation
	Mitral valve prolapse/insufficiency
Gastrointestinal[22]	Chronic/recurrent gastritis
	Defecatory dysfunction
	Delayed gastric emptying
	Delayed small bowel and colonic transit
	Dysphagia
	Dysphonia
	Gastroesophageal reflux
	Hiatal hernia
	Unexplained abdominal pain
	Various food intolerances
	Visceroptosis (prolapse of the abdominal viscera)
Gynecologic[26,30]	Disabling dysmenorrhea
	Dyspareunia
	Menorrhagia/metrorrhagia
	Pelvic organ prolapse
	Urinary stress incontinence
Mucocutaneous[31]	Atrophic scars
	Easy bruising
	Gingival inflammation/recessions
	Hernias (inguinal/umbilical/incisional)
	Hypoplastic lingual frenulum
	Keratosis pilaris
	Light blue sclerae
	Mildly hyperextensible skin
	Resistance to local anesthetic drugs
	Velvety/silky/soft skin texture

Organ system	Symptoms/physical findings
Musculoskeletal[2,32-34]	Chronic pain
	Chronic/recurrent noninflammatory joint pain
	Early osteoarthritis
	Fibromyalgia
	Flatfoot
	Generalized joint hypermobility
	High arched/narrow palate
	Involuntary muscle contractions
	Marfanoid habitus (ratio of arm span to height > 1.05)
	Mild scoliosis, dorsal hyperkyphosis, lumbar hyperlordosis
	Myofascial pain
	Nonpostmenopausal reduced bone mass
	Nonsurgical pectus excavatum
	Recurrent dislocations (e.g., hips, shoulders, temporomandibular, fingers)
	Recurrent myalgias and cramps
	Recurrent soft tissue lesions
	Temporomandibular joint dysfunction
Neurologic[32,34,35]	Clumsiness
	Headache and migraines
	Impaired memory and concentration
	Sleep disturbances
	Somatosensory/central sensitization
Ocular[36]	Myopia and/or strabismus
	Palpebral ptosis
Psychological[23,37,38]	Attention-deficit/hyperactivity disorder
	Chronic fatigue/chronic fatigue syndrome
	Depression
	Generalized anxiety
	Obsessive-compulsive disorder
	Panic attacks
	Phobias, kinesiophobia

Information from references 2, 22, 23, and 26-38.

Yew, Kenneth S., et al. "Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorders." *American Family Physician*, American Academy of Family Physicians, 15 Apr. 2021, www.aafp.org/pubs/afp/issues/2021/0415/p481.html.

Comorbidities to Consider & in those with hEDS/HSD:

- Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Long-COVID
- Postural Orthostatic Tachycardia Syndrome (POTS)/ Orthostatic Intolerance
- Mast Cell Activation Syndrome (MCAS)
- Fibromyalgia/Widespread Chronic Pain
- Small Fiber Polyneuropathy (SFPN)
- Gastrointestinal Dysmotility
- Central Nervous System Complications
  - Cranio-cervical Instability/Atlantoaxial Instability
  - Occult/Acquired Tethered Cord
- Vascular Abdominal Pathologies
  - May Thurner's
  - Nutcracker
  - Median Arcuate Ligament Syndrome (MALS)
- Headaches, Neck Pain, Migraine
- Neurodivergent Disorders
  - Autism Spectrum Disorder (ASD)
  - ADHD (Attention Deficit Hyperactivity Disorder)
- Obstructive Sleep Apnea
- Gynecological Complications
  - Dysmenorrhea, Menorrhagia, Dyspareunia, Endometriosis

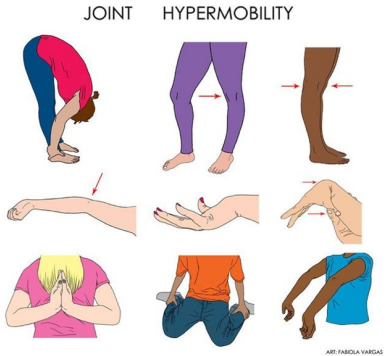
The presence of many of these comorbidities in a patient, likewise, should raise the suspicion for hEDS/HSD!

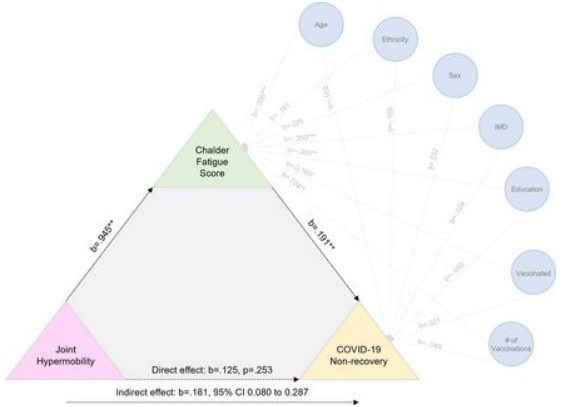
"Are the Ehlers-Danlos Syndromes and Hypermobility Spectrum Disorders Rare or Common?" *The Ehlers Danlos Society*, 31 July 2023, www.ehlers-danlos.com/is-eds-rare-or-common/.

Hypermobile Ehlers Danlos Syndrome (hEDS) (Q79.62) in Long-COVID and ME/CFS

- Self-reported data in a cross-sectional study of those with ME/CFS suggests that 15.5% of those with ME/CFS have joint hypermobility, while 28% of those with Long-COVID ME/CFS report generalized joint hypermobility.

- In a self-reporting prospective observational study, individuals with generalized joint hypermobility were approximately 30% more likely to experience chronic symptoms after recovery from acute infection by Sars-CoV-2, with many of these patients meeting criteria for ME/CFS.

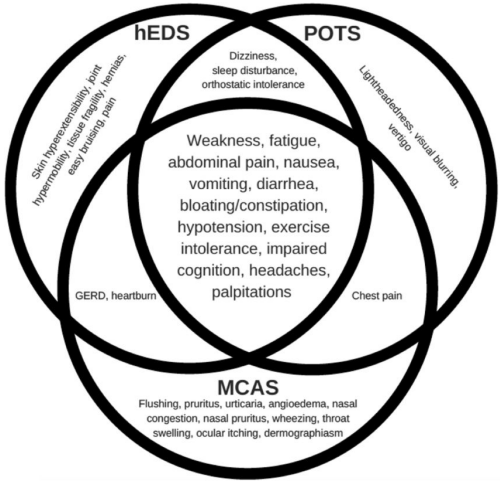




- Patients with hypermobile spectrum disorder were also at higher risk of having higher levels of self-reported fatigue when developing Long-COVID as measured by the Chalder Fatigue Scale

Eccles, Jessica A, et al. "Is joint hypermobility linked to self-reported non-recovery from covid-19? case–control evidence from the British covid symptom study Biobank." *BMJ Public Health*, vol. 2, no. 1, Feb. 2024, https://doi.org/10.1136/bmjph-2023-000478.
"Long Covid and Gjh." *The HMSA*, www.hypermobility.org/longcovid. Accessed 17 Aug. 2024.
Mudie, Kathleen, et al. "Do People with ME/CFS and joint hypermobility represent a disease subgroup? an analysis using registry data." *Frontiers in Neurology*, vol. 15, 13 Mar. 2024, https://doi.org/10.3389/fneur.2024.1324879.

MCAS Prevalence in ME/CFS Comorbidities



- Nearly 1 in 3 patients with MCAS had a comorbid diagnosis of hEDS in a sample of 37,665 patients diagnosed with either disorder
- In one study, 66% of patients with POTS and EDS also met symptoms for MCAS

Afrin LB, Ackerley MB, Bluestein LS, et al. Diagnosis of mast cell activation syndrome: a global “consensus-2”. Diagnosis (Berl). 2020:dex-2020–0005.10.1515/dx-20200005.

Kohn, Alison, and Christopher Chang. “The relationship between Hypermobile Ehlers-Danlos syndrome (heds), postural orthostatic tachycardia syndrome (POTS), and mast cell activation syndrome (MCAS).” *Clinical Reviews in Allergy & Immunology*, vol. 58, no. 3, 2019, pp. 273–297, https://doi.org/10.1007/s12016-019-08755-8.

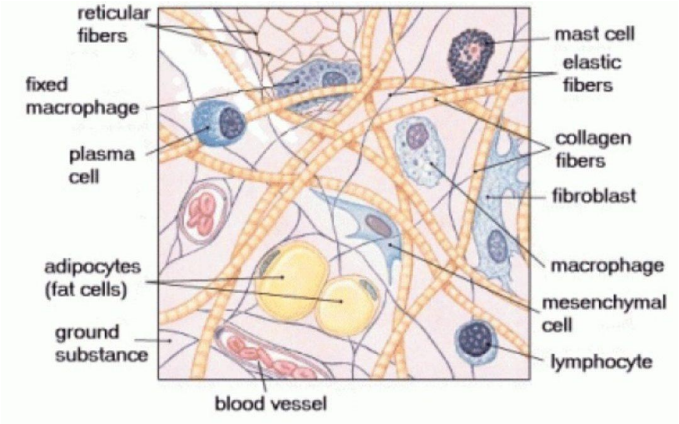
Lyons JL, Yu X, Hughes JD, Le QT, Jamil A, Bai Y, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat Genet.* 2016;48:1564–1569. doi: 10.1038/ng.3696.

Monaco, Ashley, et al. “Association of Mast-cell-related conditions with hypermobile syndromes: A review of the literature.” *Immunologic Research*, vol. 70, no. 4, 2022, pp. 419–431, https://doi.org/10.1007/s12026-022-09280-1.

Seneviratne SL, Maitland A, Afrin L. 2017. Mast cell disorders in Ehlers–Danlos syndrome. Am J Med Genet Part C Semin Med Genet 175C:226–236.

MCAS in Hypermobile Ehlers Danlos (hEDS)

- Irregular, recurrent, or chronic release of mast cell-mediated cytokines (such as proinflammatory molecules, growth factors, and proteases) has been linked to hEDS, HSD, and other heritable connective tissue diseases.
- Mast cells in connective tissue cause microenvironmental changes to the extracellular matrix, including IgE-mediated autoreactivity.
- Mast cell inflammatory changes have been implicated in contributing to laxity of blood vessels with pooling of blood in the extremities (POTS, dysautonomia, etc.).
- In families with heritable mutations in genes encoding elevated tryptase levels (one protease released from activated mast cells), 28% of these patients were found to have joint hypermobility, nearly double that of the general population.



KNMyles, and Name. “Mast Cells, Ehlers-Danlos Syndrome, and Gi Disorders.” *EDS Wellness, Inc.*, 9 Oct. 2016, edswellness.org/mast-cells-ehlers-danlos-syndrome-gi-disorders/.

- One literature review found a lack of evidence suggesting that MCAS or hEDS are even distinct significant clinical entities, though a significant overlapping pool of “vague and subjective symptoms” may have played a confounding role

Afrin LB, Ackerley MB, Bluestein LS, et al. Diagnosis of mast cell activation syndrome: a global “consensus-2”. Diagnosis (Berl). 2020:dex-2020–0005.10.1515/dx-20200005.

Kohn, Alison, and Christopher Chang. “The relationship between Hypermobile Ehlers-Danlos syndrome (heds), postural orthostatic tachycardia syndrome (POTS), and mast cell activation syndrome (MCAS).” *Clinical Reviews in Allergy & Immunology*, vol. 58, no. 3, 2019, pp. 273–297, https://doi.org/10.1007/s12016-019-08755-8.

Lyons JL, Yu X, Hughes JD, Le QT, Jamil A, Bai Y, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat Genet.* 2016;48:1564–1569. doi: 10.1038/ng.3696.

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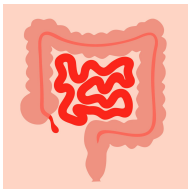
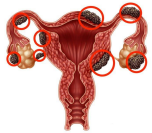
Seneviratne SL, Maitland A, Afrin L. 2017. Mast cell disorders in Ehlers–Danlos syndrome. Am J Med Genet Part C Semin Med Genet 175C:226–236.

EDS Conditions Comorbid with MCAS

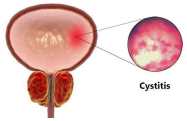
- Postural Orthostatic Tachycardia Syndrome (POTS)
- ME/CFS
- Post-Lyme Syndrome
- Fibromyalgia
- Chronic Migraines

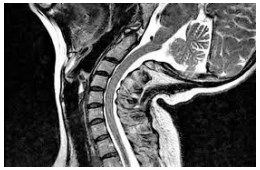
- Multiple Chemical Sensitivity Syndrome
- Irritable Bowel Syndrome
- Post-Traumatic Stress Disorder (PTSD)

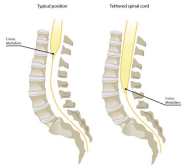




- Endometriosis
- Interstitial Cystitis
- Chronic Prostatitis
- Vulvodynia
- Cranio-cervical Instability (CCI)
- Atlanto-axial Instability (AAI)
- Occult Tethered Cord Syndrome





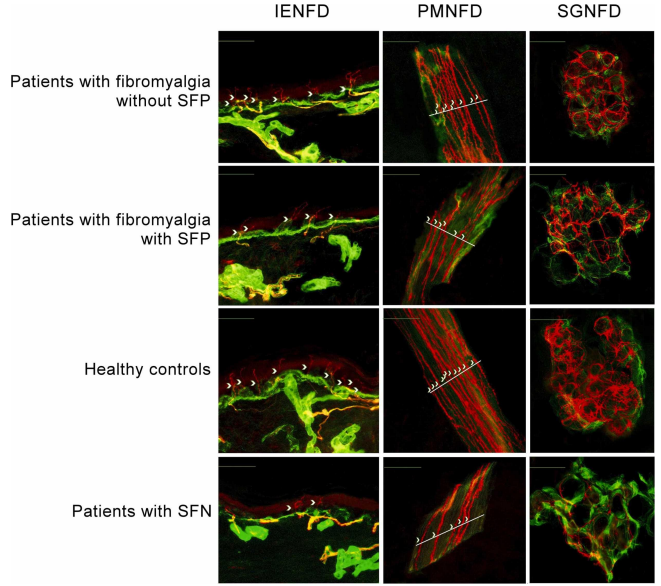


Aich A, Afrin LB, Gupta K. Mast Cell-Mediated Mechanisms of Nociception. Int J Mol Sci. 2015 Dec 4;16(12):29069-92. doi: 10.3390/ijms161226151. PMID: 26690128; PMCID: PMC4691098.
Theoharides, Theoharis C., et al. "Recent advances in our understanding of mast cell activation – or should it be mast cell mediator disorders?" *Expert Review of Clinical Immunology*, vol. 15, no. 6, 2019, pp. 639–656, https://doi.org/10.1080/1744666x.2019.1596800.

Fibromyalgia (M79.7) in hEDS:

- A systematic review of 11 studies showed a prevalence of a concomitant diagnosis of hEDS/HSD and Fibromyalgia from 68-88.9%

- A systematic review and meta-analysis demonstrated a pooled prevalence of SFPN of 49% in those with fibromyalgia
  - SFPN diagnosed by skip biopsy had a 45% prevalence in FM
  - SFPN diagnosed by corneal confocal microscopy was 59%

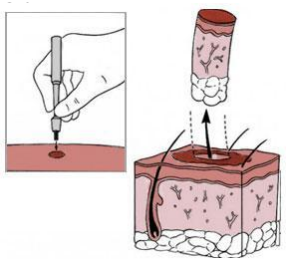


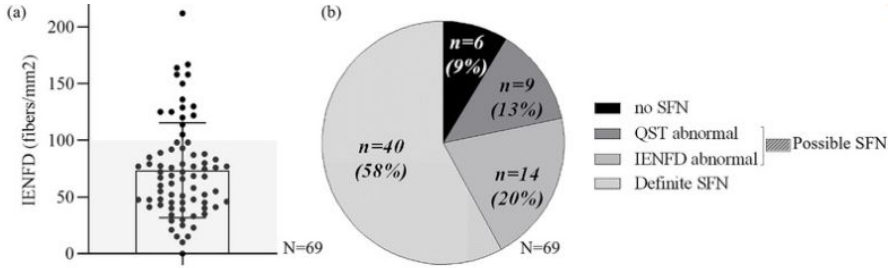
Alsiri, Najla, et al. “The concomitant diagnosis of fibromyalgia and connective tissue disorders: A systematic review.” *Seminars in Arthritis and Rheumatism*, vol. 58, Feb. 2023, p. 152127, https://doi.org/10.1016/j.semarthrit.2022.152127.
Grayston, Rebecca, et al. “A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: Implications for a new paradigm in fibromyalgia etiopathogenesis.” *Seminars in Arthritis and Rheumatism*, vol. 48, no. 5, Apr. 2019, pp. 933–940, https://doi.org/10.1016/j.semarthrit.2018.08.003.

Falco, Pietro, et al. “Autonomic small-fiber pathology in patients with fibromyalgia.” *The Journal of Pain*, vol. 25, no. 1, Jan. 2024, pp. 64–72, https://doi.org/10.1016/j.jpain.2023.07.020.

Small Fiber Polyneuropathy (SFPN) (G62.89)

- Quantitative Sensory Testing (QST) performed on 79 hEDS patients with anamnestic complaints and 55/79 (70%) met criteria for SFPN
- Skin biopsy to evaluate for intraepidermal nerve fiber density (IENFD), the gold-standard for SFPN diagnosis, performed on 69 of the same hEDS patients and found 54/69 (78%) met criteria f SFPN



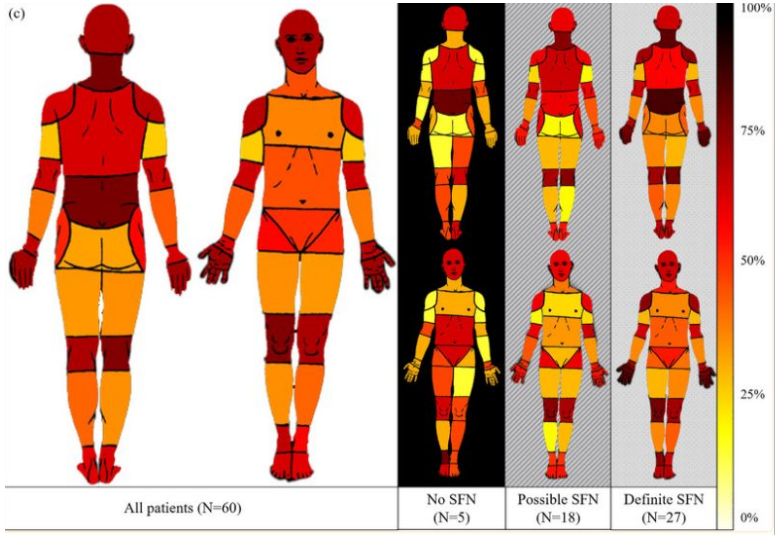


Distribution of the intraepidermal nerve fiber density (IENFD) count in the hypermobile Ehlers–Danlos syndrome (hEDS)/hypermobility spectrum disorders (HSD) population (a); subdivision of the hEDS/HSD population according to the likelihood of small fiber neuropathy based on quantitative sensory testing (QST) and IENFD (b)

"Fernandez, Aurore, et al. "Small fiber neuropathy in hypermobile Ehlers Danlos syndrome/hypermobility spectrum disorder." *Journal of Internal Medicine*, vol. 292, no. 6, 2022, pp. 957–960, https://doi.org/10.1111/joim.13539.

Small Fiber Polyneuropathy (SFPN) (G62.89)

- SFPN diagnosis was considered “definite” when both QST and IENFD criteria (representing abnormal function and structure, respectively) and was noted in 40/69 (58%)
- Additional 23/69 (33%) of patients met one of the two criteria, leaving only 9% without signal for SFPN

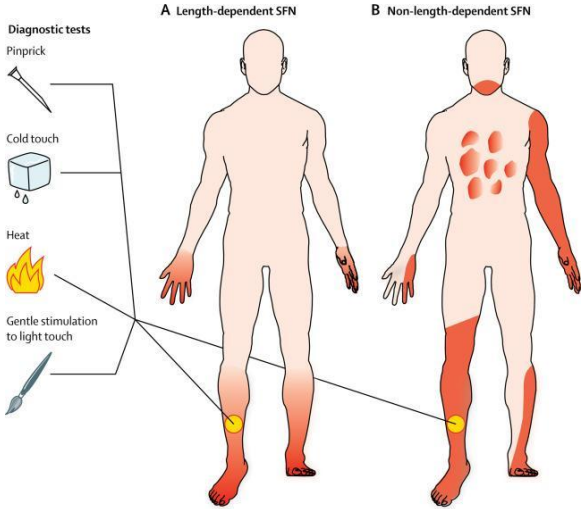


Pain distribution heat map (c). The left part of panel c represents the frequency of pain localization of hEDS/HSD patients as reported on pain drawings; the right panel shows the body map representations in sub-groups of patients based on their small fiber neuropathy (SFN) likelihood. The color gradient represents the percentage of patients reporting pain in each body area from light yellow (0%) to dark red (100%). Definite SFN = both QST and IENFD abnormal. No SFN = both QST and IENFD normal. Possible SFN = either QST or IENFD abnormal.

“Fernandez, Aurore, et al. “Small fiber neuropathy in hypermobile Ehlers Danlos syndrome/hypermobility spectrum disorder.” *Journal of Internal Medicine*, vol. 292, no. 6, 2022, pp. 957–960, https://doi.org/10.1111/joim.13539.

Small Fiber Polyneuropathy (G62.89) in hEDS and POTS

- 61% of hEDS patients in a prospective study were found to have SFPN
  - 63% had length-dependent SFPN
  - 32% had non-length dependent SFPN
  - 89% had a reduced proximal intra-epidermal nerve fiber density (IENFD)



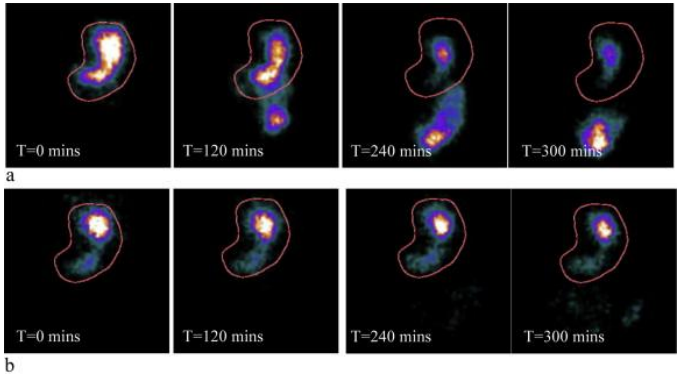
- 53% of those with hEDS and SFPN (32% of all with hEDS) found to meet criteria for POTS on a tilt-table test
- Autonomic dysfunction has been identified as a result of SFPN with impaired autonomic innervation potentially resulting in a loss of compensatory vasoconstriction after tilt
- SFPN, in particular, is thought to play an active role in the underlying physiology of neuropathic POTS

Igharo, Denver, et al. "Skin biopsy reveals generalized small fibre neuropathy in Hypermobile Ehlers–danlos syndromes." *European Journal of Neurology*, vol. 30, no. 3, 13 Dec. 2022, pp. 719–728, https://doi.org/10.1111/ene.15649.

Gastrointestinal Dysmotility (K31.84)

- One study evaluated 129 patients referred to a tertiary neurogastroenterology clinic
- 63 (49%) of these patients were found to meet criteria for “joint hypermobility syndrome”
- An unknown etiology for GI symptoms was significantly more likely in those with “joint hypermobility syndrome” vs those without (P<0.0001)
- 12 of 17 of these patients evaluated were found to have delayed gastric emptying

Upright vs Supine Gastrointestinal Motility Studies May Yield Different Results!



Kar, Palash, et al. “Measurement of gastric emptying in the critically ill.” *Clinical Nutrition*, vol. 34, no. 4, 2015, pp. 557–564, https://doi.org/10.1016/j.clnu.2014.11.003.

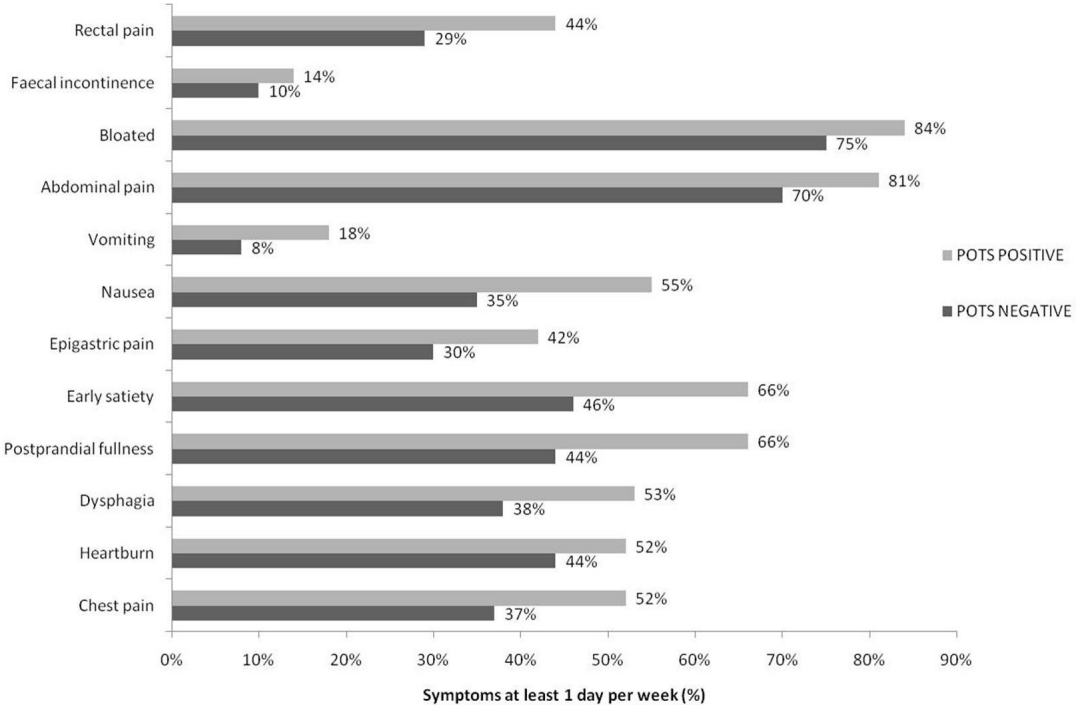
- Another study of EDS patients at Mayo Clinic noted abnormal gastric emptying observed in 22.3% of EDS patients
- 11.8% of these patients had delayed gastric emptying
- 10.5% had accelerated gastric emptying

Nelson, A. D., Mouchli, M. A., Valentin, N., Deyle, D., Pichurin, P., Acosta, A. and Camilleri, M, Ehlers Danlos syndrome and gastrointestinal manifestations: a 20-year experience at Mayo Clinic. Neurogastroenterology & Motil 2015; 27: 1657–1666.

Zarate, N., Farmer, A. D., Grahame, R., et al. Unexplained gastrointestinal symp-toms and joint hypermobility: Is connective tissue the missing link? Neurogastroenterology & Motility 2010; 22: 252–278.

Functional Gastrointestinal Disorders (K59.9)

- Up to 62% of patients with hEDS suffer from “irritable bowel syndrome”
- Of those with hEDS and POTS, patients with both diagnoses were more likely to fulfill criteria for Rome IV Functional Gastrointestinal Disorders (FDIG’s) across various organ domains with increased upper and lower gastrointestinal symptoms beyond an already elevated baseline in hEDS

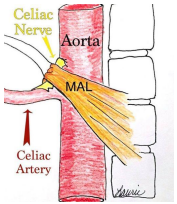


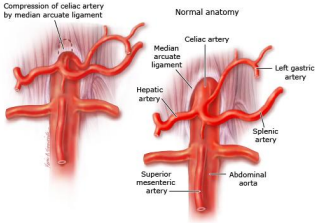
Choudhary, Anisa, et al. “Overlap between irritable bowel syndrome and hypermobileEhlers–DanlosSyndrome: An unexplored clinical phenotype?” *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, vol. 187, no. 4, 6 Nov. 2021, pp. 561–569, https://doi.org/10.1002/ajmg.c.31938.

Tai, Foong Way, et al. “Functional gastrointestinal disorders are increased in joint hypermobility-related disorders with concomitant postural orthostatic tachycardia syndrome.” *Neurogastroenterology & Motility*, vol. 32, no. 12, 16 Aug. 2020, https://doi.org/10.1111/nmo.13975.

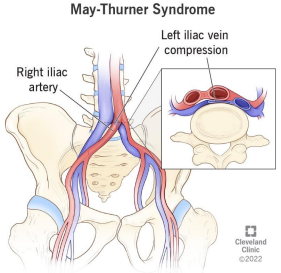
Abdominal Vascular Compression Syndromes

- Median Arcuate Ligament Syndrome (MALS) /Celiac Artery Compression Syndrome (I77.4)
  - Post-prandial abdominal pain, weight loss, abdominal bruit due to compression of the celiac artery or celiac nerve plexus by the median arcuate ligament





Modified from: Kim EN, Lamb K, Relles D, et al. Median arcuate ligament syndrome—Review of this rare disease. JAMA Surg 2016; 151:471.



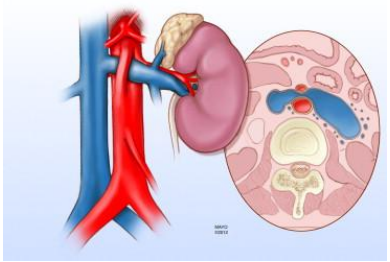
Cleveland Clinic medical. "May-Thurner Syndrome: Causes, Symptoms & Treatment." *Cleveland Clinic*, my.clevelandclinic.org/health/diseases/17213-may-thurner-syndrome. Accessed 30 Sept. 2023.

May-Thurner Syndrome /Iliac Vein Compression (I87.1)

- Extrinsic venous compression of the left common iliac vein by the right iliac artery causing left lower extremity pain, swelling, venous claudication, or venous insufficiency

Nutcracker Syndrome (Q27.8)

- Compression of the left renal vein between the aorta and the proximal superior mesenteric artery causing hematuria, orthostatic proteinuria, left flank pain

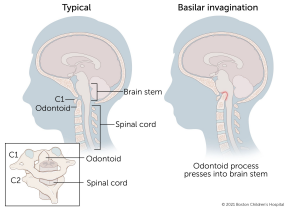


Said, Sameh M., et al. "Renal nutcracker syndrome: Surgical options." *Seminars in Vascular Surgery*, vol. 26, no. 1, 2013, pp. 35–42, https://doi.org/10.1053/j.semvascsurg.2013.04.006.

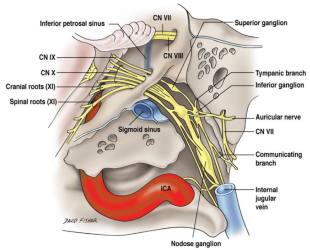
Neuroanatomical Complications:

Craniocervical Instability (CCI) /Atlantoaxial Instability (AAI) (M53.2X2)

- Incompetence or hyperlaxity of ligamentous and bony elements supporting the cranio-cervical junction (C0-C1, C1-C2) allowing increased mechanical motion and resulting deformation of the brainstem or upper spinal cord



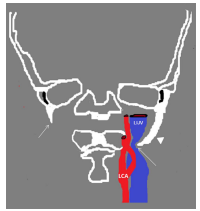
"Basilar Invagination." *Basilar Invagination | Boston Children's Hospital*, www.childrenshospital.org/conditions/basilar-invagination. Accessed 1 Oct. 2023.



Gutierrez S;Warner T;McCormack E;Werner C;Mathkour M;Iwanaga J;Uz A;Dumont AS;Tubbs RS; "Lower Cranial Nerve Syndromes: A Review." *Neurosurgical Review*, U.S. National Library of Medicine, pubmed.ncbi.nlm.nih.gov/32638140/. Accessed 18 Oct. 2024.

Increased Intracranial Hypertension/Hypotension (IIH) (H47.11)

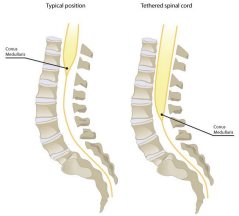
- Venous compression and outflow tract obstruction leading to transient (often positional) increases in intracerebral pressure and (sometimes) resulting spontaneous CSF leaks with associated headaches, tinnitus, vision changes, brain fog



Farina, Renato, et al. "Stylo-Jugular Venous Compression Syndrome: Lessons based on a case report." *American Journal of Case Reports*, vol. 22, 13 July 2021, https://doi.org/10.12659/ajcr.932035.

Acquired Tethered Cord Syndrome (G95.89)

- Anatomical restriction of the normal movement of the spinal cord via anchoring of the filum terminale, causing flexion stretching of the cord and triggering symptoms of lower extremity weakness & sensory loss, lower back pain, and/or neurogenic bladder

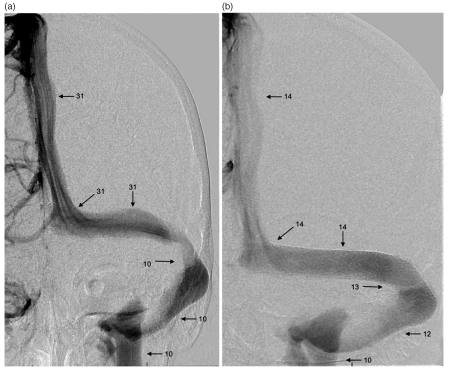


partnership, London Neurosurgery. "Tethered Cord – Condition and Symptoms - How to Treat." *London Neurosurgery Partnership - Spine & Neurosurgery*, 28 May 2021, lnpuk.com/tethered-cord-condition-and-symptoms/.

Venous Congestion/Outflow Obstruction Syndromes:

Idiopathic Intracranial Hypertension (IIH) (G93.2)

- Increasing recognition that many with hEDS may have symptoms of idiopathic intracranial hypertension
- 20% of people with ME/CFS (and hEDS) had elevated CSF pressures upon a lumbar puncture
- 85% of the ME/CFS (and hEDS) patients who DID NOT have elevated CSF pressures on lumbar puncture noted symptomatic improvements (diminished headache, improved fatigue, less brain fog) after the lumbar puncture and removal of some CSF, with these symptomatic benefits sometimes lasting for weeks
- Obstructions can arise from abnormal venous pathology with venous stenosis or tortuosity, as well as from anatomical impingements (Eagle Syndrome, CCI/AAI, spinal stenosis, disc herniations), perhaps even venous congestion syndromes (May-Thurner, Nutcracker's) elsewhere



Example patient with severe left transverse sinus stenosis and 21 mmHg gradient across the site of stenosis (left panel; arrows denote venous pressures at each location in mmHg). Following transverse sinus stenting, the stenosis has resolved, the gradient has been reduced to 1 mmHg, and upstream venous pressures have reduced from 31 mmHg to 14 mmHg.

Fargen KM, Coffman S, Torosian T, Brinjikji W, Nye BL, Hui F. "Idiopathic" intracranial hypertension: An update from neurointerventional research for clinicians. *Cephalalgia*. 2023;43(4). doi:10.1177/03331024231161323
Higgins JNP, Axon PR, Lever AML. Life changing response to successive surgical interventions on cranial venous outflow: A case report on chronic fatigue syndrome. Front Neurol. 2023 Mar 30;14:1127702. doi: 10.3389/fneur.2023.1127702. PMID: 37064208; PMCID: PMC10097901.
Higgins JNP, Pickard JD. A paradigm for chronic fatigue syndrome: caught between idiopathic intracranial hypertension and spontaneous intracranial hypotension; caused by cranial venous outflow obstruction. Fatigue. 2021 Jul 3;9(3):139-147. doi: 10.1080/21641846.2021.1956223. Epub 2021 Jul 26. PMID: 36514384; PMCID: PMC7613918.
Higgins JNP, Pickard JD, Lever AML. Chronic fatigue syndrome and idiopathic intracranial hypertension: Different manifestations of the same disorder of intracranial pressure? Med Hypotheses. 2017 Aug;105:6-9. doi: 10.1016/j.mehy.2017.06.014. Epub 2017 Jun 24. PMID: 28735654.

Venous Congestion/Outflow Obstruction Syndromes:

Idiopathic Intracranial Hypertension (IIH) (G93.2)

- People with ME/CFS and/or hEDS may have uncharacteristic forms of IIH that do not meet traditional definitions for elevated opening pressures on lumbar puncture and who do not have papilledema (swelling of the optic nerve)
  - Dynamic status based on volume, positioning (supine vs upright), spontaneous CSF leaks relieving pressure…
- Postulated that many cases of spontaneous CSF leaks and intracranial hypotension in ME/CFS actually arise from IIH as an underlying condition

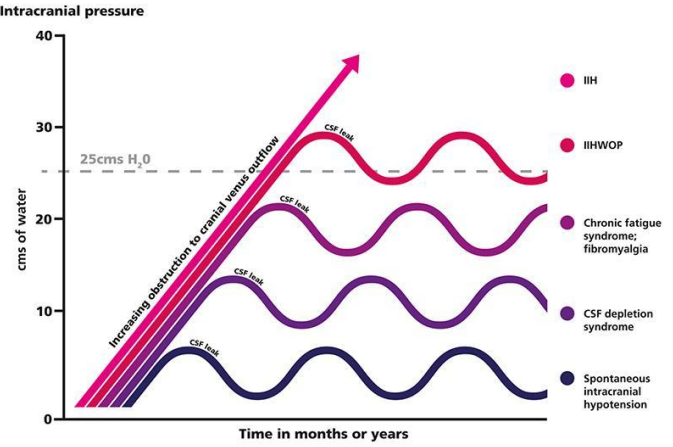


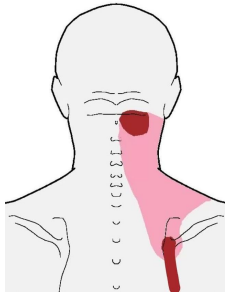
Figure 2

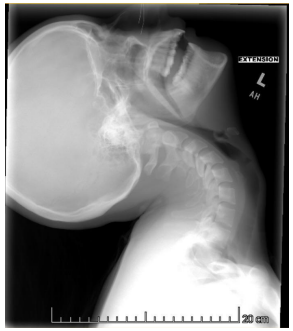
Pictorial representation of the forces on intracranial pressure generated by obstruction to cranial venous outflow and the subsequent development of a CSF leak. Depending on the site and degree of venous obstruction and the compensating or overcompensating effects of CSF depletion, patients will manifest at different points on the IIH spectrum. A normal intracranial pressure, therefore, does not exclude significant physiological disturbance. IIH : idiopathic intracranial hypertension; IIHWOP: idiopathic intracranial hypertension without papilloedema.

Higgins JNP, Axon PR, Lever AML. Life changing response to successive surgical interventions on cranial venous outflow: A case report on chronic fatigue syndrome. Front Neurol. 2023 Mar 30;14:1127702. doi: 10.3389/fneur.2023.1127702. PMID: 37064208; PMCID: PMC10097901.
Higgins JNP, Pickard JD. A paradigm for chronic fatigue syndrome: caught between idiopathic intracranial hypertension and spontaneous intracranial hypotension; caused by cranial venous outflow obstruction. Fatigue. 2021 Jul 3;9(3):139-147. doi: 10.1080/21641846.2021.1956223. Epub 2021 Jul 26. PMID: 36514384; PMCID: PMC7613918.
Higgins JNP, Pickard JD, Lever AML. Chronic fatigue syndrome and idiopathic intracranial hypertension: Different manifestations of the same disorder of intracranial pressure? Med Hypotheses. 2017 Aug;105:6-9. doi: 10.1016/j.mehy.2017.06.014. Epub 2017 Jun 24. PMID: 28735654.

Headache and Migraine (G43.9) in EDS/HSD

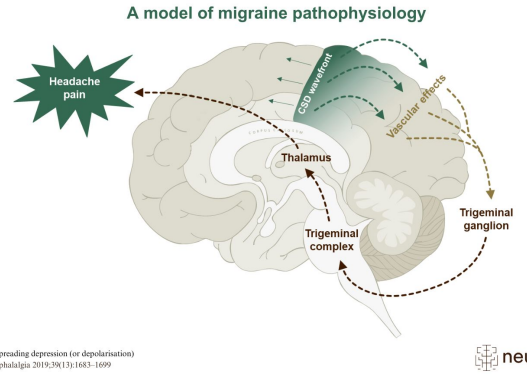
- In a single-center retrospective study, 66% of 140 patients reported headache or neck pain with 53% of these reporting both headache and neck pain





- Migraine was reported as the most common headache type among those with headache disorders (83%)

- Perivascular mast cells, particularly in or near the dura mater, can be activated by trigeminal, cervical, or sphenopalatine ganglion stimulation and then release neuropeptides like calcitonin gene-related peptide (CGRP) as well as other vasoactive, pro-inflammatory, and neurosensitizing mediators that may play a significant role in migraine pathogenesis



"A Model of Migraine Pathophysiology." *Neurotorium*, 7 May 2024, neurotorium.org/image/a-model-of-migraine-pathophysiology/.

Malhotra, Anuj, et al. "Headaches in hypermobility syndromes: A pain in the neck?" *American Journal of Medical Genetics Part A*, vol. 182, no. 12, 17 Sept. 2020, pp. 2902–2908, https://doi.org/10.1002/ajmg.a.61873.
Theoharides, Theoharis C., et al. "The role of mast cells in migraine pathophysiology." *Brain Research Reviews*, vol. 49, no. 1, July 2005, pp. 65–76, https://doi.org/10.1016/j.brainresrev.2004.11.006.

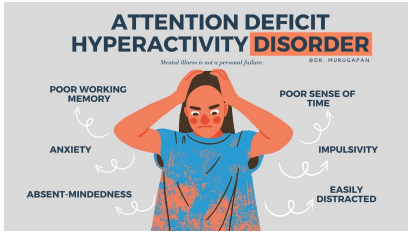
Neurodivergence in Hypermobile Spectrum Disorder (HSD) (F84.0 for Autism Spectrum Disorder, F90.9 for ADHD)

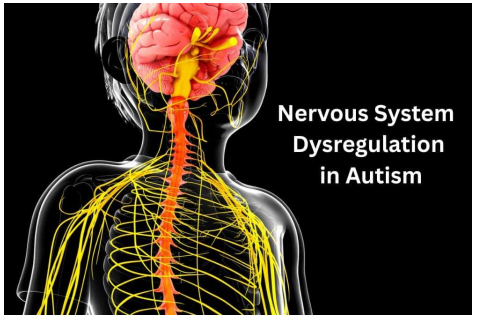
- Incidence of autism spectrum (ASD) disorder or attention-deficit hyperactivity disorder (ADHD) was 39% in family members of those with HSD and fibromyalgia, compared to a neurodivergent disorder prevalence of 2.8% in a control group with osteoarthritis

- Interestingly, females are disproportionately over-represented in contrast to the more predominantly male distribution of neurodivergent conditions in the general population

- Females with FM and HSD were more likely to have autism while males were more likely to carry a diagnosis of ADHD

- Appears to be a common genetic or familial etiology between HSD, FM, and neurodivergence





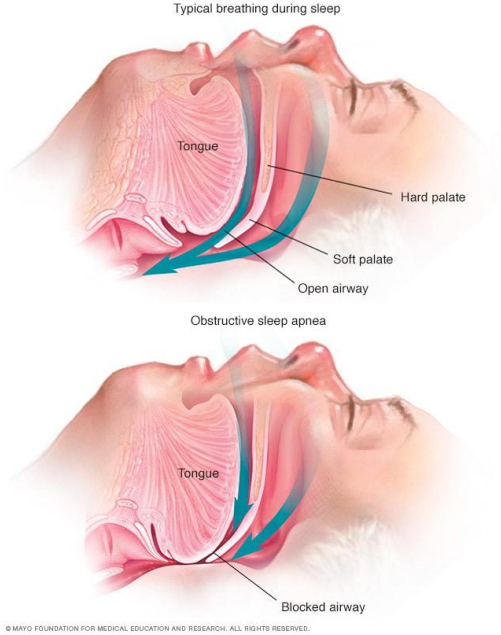
- Those with autism often found to have high basal sympathetic tone, lower parasympathetic activation, and low sympathetic reactivity to certain stimuli including tests of orthostatic intolerance

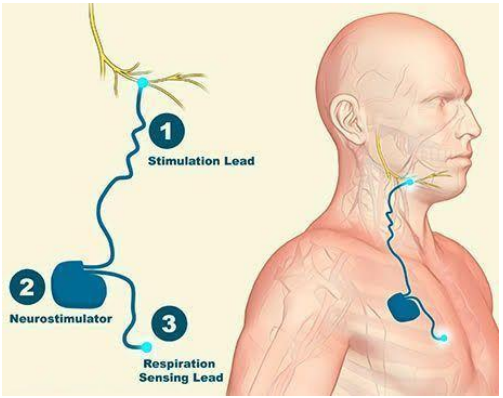
- Those with autism also have higher sympathetic tone during certain stages of sleep and during social interactions with peers

Harder, René, et al. "Heart rate variability during sleep in children with autism spectrum disorder." *Clinical Autonomic Research*, vol. 26, no. 6, 4 Aug. 2016, pp. 423–432, https://doi.org/10.1007/s10286-016-0375-5.
Kelly, Clive, et al. "The links between fibromyalgia, hypermobility and Neurodivergence." *Rheumatology*, vol. 1, no. 1, 2022, p. 3, https://doi.org/10.17925/rmd.2022.1.1.3.
Ganesh, Ravindra, and Bala Munipalli. "Long Covid and hypermobility spectrum disorders have shared pathophysiology." *Frontiers in Neurology*, vol. 15, 5 Sept. 2024, https://doi.org/10.3389/fneur.2024.1455498.
O'Haire, Marguerite E., et al. "Animals may act as social buffers: Skin conductance arousal in children with autism spectrum disorder in a social context." *Developmental Psychobiology*, vol. 57, no. 5, 27 Apr. 2015, pp. 584–595, https://doi.org/10.1002/dev.21310.
Yearoo, Tasnime B, and Clive Kelly. "P033 the intriguing association between fibromyalgia, hypermobility and neurodivergence: A pilot study." *Rheumatology*, vol. 61, no. Supplement_1, 23 Apr. 2022, https://doi.org/10.1093/rheumatology/keac133.032.

Obstructive Sleep Apnea in EDS (G47.3)

- Those with EDS are at a 6 times higher rate of developing OSA (OR 6.28) compared to the general US population prevalence of 39.4% compared to 26%
- Increased tissue laxity and upper airway and nasal-maxillary cartilaginous defects may lead to increased nasal airway resistance and collapse and increase pharyngeal collapsibility
- May also see features like mandibular retrognathia, high arched palate, vocal cord abnormalities, chest deformities, and scoliosis





- Hypoglossal nerve stimulator implantation (HNSI) may be a developing therapy for OSA in EDS, especially in those who have failed CPAP and oral appliances

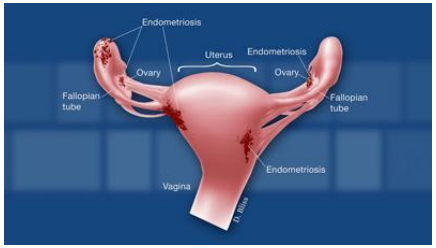
Miller, Stefanie M., and Mitchell B. Miller. "Treatment of obstructive sleep apnea with hypoglossal nerve stimulation in a patient with Ehlers-Danlos syndrome." *Journal of Clinical Sleep Medicine*, vol. 19, no. 3, Mar. 2023, pp. 631–632, https://doi.org/10.5664/jcsm.10368.
Sedky, Karim, et al. "Prevalence of obstructive sleep apnea in joint hypermobility syndrome: A systematic review and meta-analysis." *Journal of Clinical Sleep Medicine*, vol. 15, no. 02, 15 Feb. 2019, pp. 293–299, https://doi.org/10.5664/jcsm.7636.

Sedky, Karim, et al. "Prevalence of obstructive sleep apnea in joint hypermobility syndrome: A systematic review and meta-analysis." *Journal of Clinical Sleep Medicine*, vol. 15, no. 02, 15 Feb. 2019, pp. 293–299, https://doi.org/10.5664/jcsm.7636.

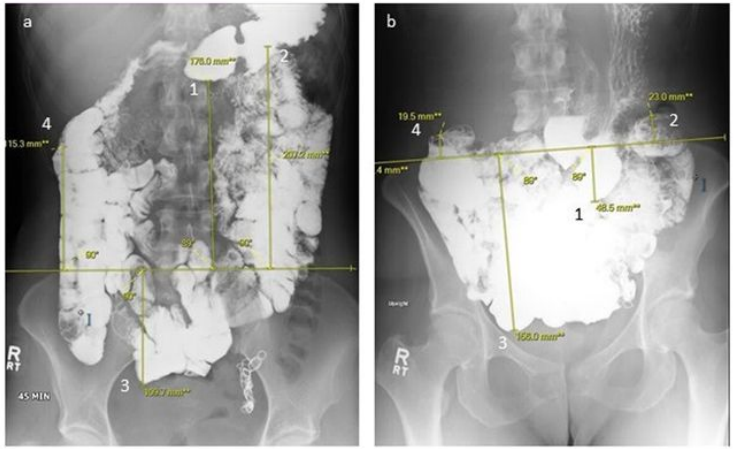
Gynecological Considerations with EDS:

- In a study of 386 women diagnosed with hEDS
  - 76% reported menorrhagia
  - 72% reported dysmenorrhea
  - 43% reported dyspareunia

- Unclear evidence if endometriosis is found at a higher prevalence in hEDS though it appears to have increased concurrence with MCAS



- **Viscerotropic**, or the downward displacement of abdominal and pelvic organs below their natural position occurring when upright compared to supine, is now beginning to be recognized in those with hypermobility spectrum disorders
  - May affect gynecological or gastrointestinal functioning



Example measurements for supine (a), and erect (b) film. 1) lowest point of the stomach, 2) highest point of jejunal column, 3) lowest point of small bowel column, 4) inferior tip of the liver.

Grassetto A, Vicenti R, Garolla A, et al. Mast cells as key players in endometriosis. Am J Reprod Immunol. 2018;80(5):e12998.
Hugon-Rodin, Justine, et al. "Gynecologic symptoms and the influence on reproductive life in 386 women with hypermobility type Ehlers-Danlos Syndrome: A cohort study." *Orphanet Journal of Rare Diseases*, vol. 11, no. 1, 13 Sept. 2016, https://doi.org/10.1186/s13023-016-0511-2.
Takakura, Will, et al. "S3153 hypermobile Ehlers-Danlos syndrome and visceroptosis." *American Journal of Gastroenterology*, vol. 115, no. 1, Oct. 2020, https://doi.org/10.14309/01.ajg.0000714660.32906.3b.

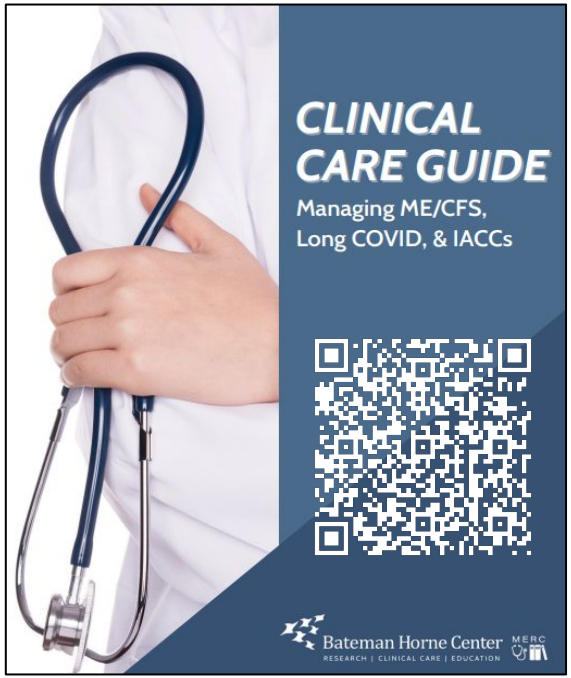
Don’t Forget to Collaborate with our Multidisciplinary Healthcare Colleagues to Provide Comprehensive Care for those with Hypermobile Spectrum Disorders!

Physical Therapy
Occupational Therapy
Speech Therapy
Behavioral Health
Pelvic Floor Therapy
Acupuncture/Massage
Medical Genetics

Learning Objectives

1. Emphasize why multidisciplinary care is vital for ensuring patient safety, tolerance, and effectiveness
2. Describe how to communicate in a multidisciplinary model of care
3. Introduce the BHC ME/CFS and Long COVID Clinical Care Guide
4. Outline how rehabilitation providers play a key role in caring for patients with connective tissue disorders and/or hypermobility spectrum disorders
5. Illustrate how rehab providers can navigate the complexities of managing Long COVID with comorbid joint hypermobility/connective tissue issues

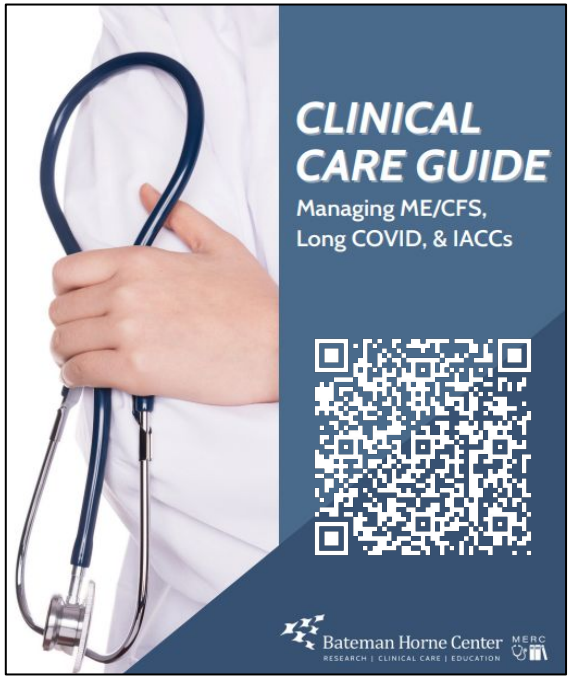
Chapter 15: Collaboration



BHC Clinical Care Guide

- Multidisciplinary Care Model
  - Know each person's role
  - Don't overwhelm with appts
  - Prioritize most impactful interventions/testing

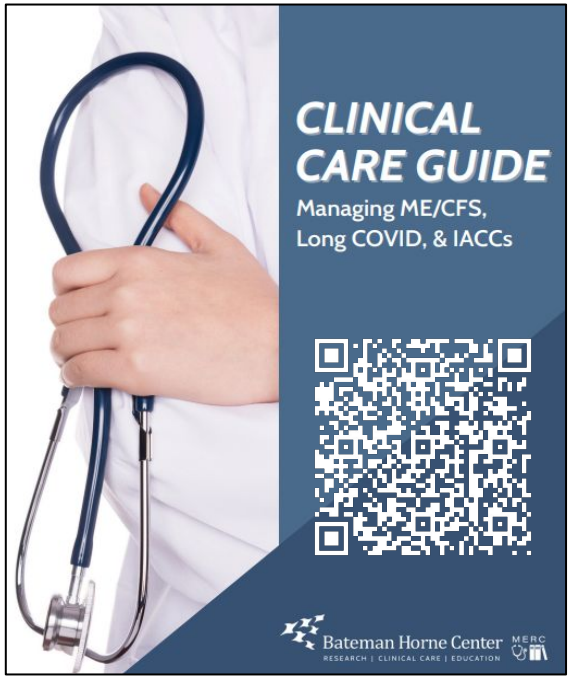
Chapter 15: Collaboration



BHC Clinical Care Guide

- Communication between providers
  - Speak the same language
  - Be specific
  - Share resources
  - Give updates

Chapter 15: Scope of Practice



BHC Clinical Care Guide

- **Occupational Therapist Role**
  - Activity of Daily Living (ADL) Specialists: Diagnose and address limitations in daily living tasks and life roles (occupations).
- **Physical Therapist Role**
  - Movement Specialists: Diagnose and manage movement dysfunction to optimize physical function and support ADLs
- **Speech Language Pathologist Role**
  - Communication Specialists: Diagnose and treat disorders of communication and cognition, as well as voice, speech, and swallow dysfunction.

Chapter 15: Scope of Practice

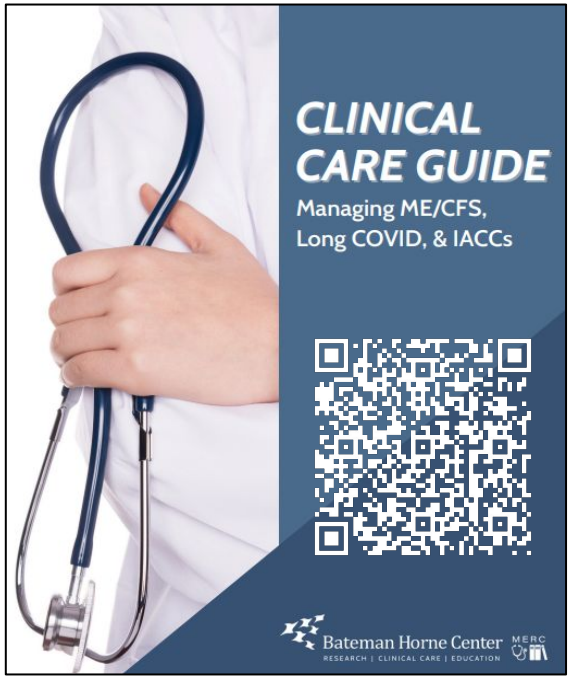
While each member of the rehab team has different roles, they all can:

- Screen for Post-Exertional Malaise (PEM)
- Support patients with Activities of Daily Living (ADLs)
- Recommend adaptive equipment and modifications to activities or environments
- Teach activity pacing and energy conservation strategies
- Educate and support caregivers and family members
- Assist with disability documentation and accommodations

Chapter 15: Benefits of Rehab for Long COVID

- **Extended Patient Interaction:** Rehab providers typically have longer and more frequent appointments, giving them greater insight into the patient's needs, limitations, and responses to treatment.
- **Specialized Focus:** With a problem-solving approach, rehab professionals focus on improving daily functioning by helping patients adapt to the challenges of living with a chronic condition.
- **Disability Support:** Rehabilitation professionals assist with disability documentation by carefully noting impairments and limitations that affect participation in daily living and work activities.
- **Comorbidity Screening:** Frequent and prolonged contact enables rehab providers to identify potential comorbid conditions that may require further medical evaluation.
- **Ongoing Monitoring:** Rehab providers can regularly update referring medical providers about the patient's status and response to treatments, supporting timely adjustments to care plans.

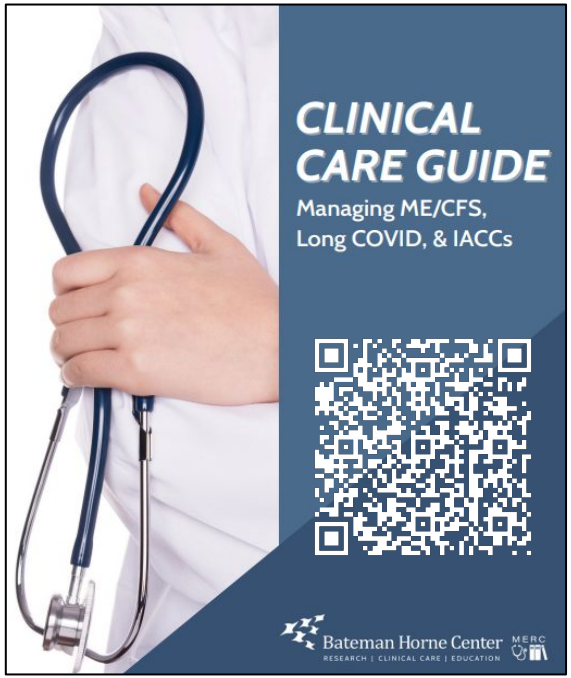
Chapter 15: Referral



BHC Clinical Care Guide

- When making referrals to rehab providers, include any comorbid conditions or other considerations.
- These can include, but are not limited to:
  - Post-Exertional Malaise
  - Orthostatic Intolerance
  - EDS or Generalized Joint Hypermobility
  - Craniocervical Instability
  - Mast Cell Hyper-reactivity or MCAS
  - Sensory Processing Disorder
  - Autism
  - History of Trauma
  - Learning Disability
- Including these details will help ensure a comprehensive and coordinated approach to the patient's treatment.

Chapter 15: Referral

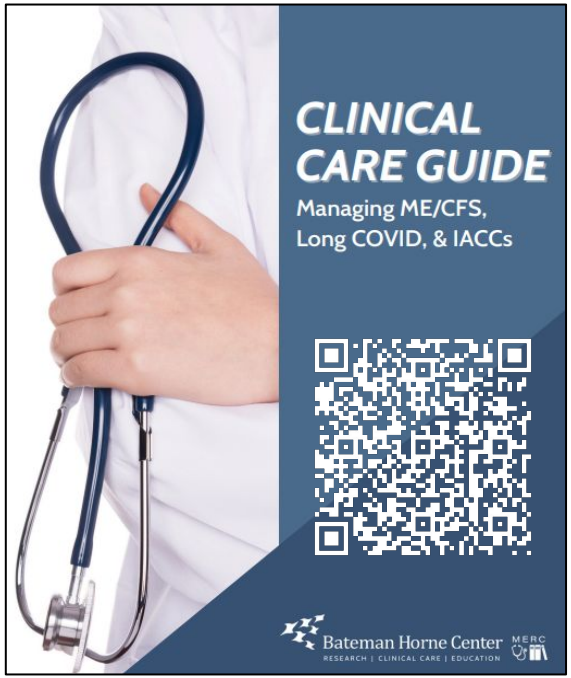


BHC Clinical Care Guide

Example Referral to Occupational Therapy:

"Refer for evaluation and treatment of functional limitations related to suspected post-exertional malaise (PEM). Please assess activities of daily living (ADLs), recommend adaptive strategies, and provide education on pacing, energy conservation, and symptom management. Screen for comorbid conditions and assist with disability documentation as needed. Offer telehealth option if able and appropriate."

Chapter 15: Referral

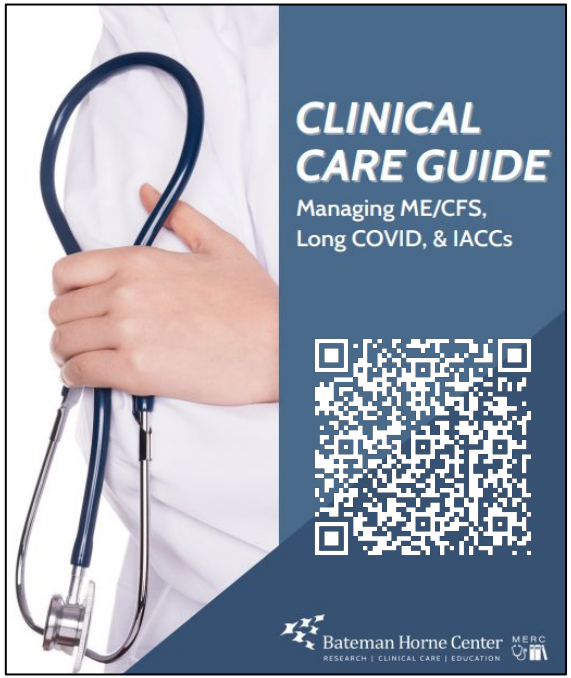


BHC Clinical Care Guide

Example Referral to Speech Therapy:

"Refer for evaluation and treatment of cognitive-communication and swallowing function in the context of suspected post-exertional malaise (PEM). Please assess for cognitive fatigue, memory, and word retrieval difficulties, teach cognitive pacing strategies, recommend communication supports, and assist with documentation for accommodations as needed. Communicate any safety concerns in the referral specific to swallow (aspiration risk, malnutrition/dehydration risk, etc.). Offer telehealth options if able and appropriate."

Chapter 15: Referral

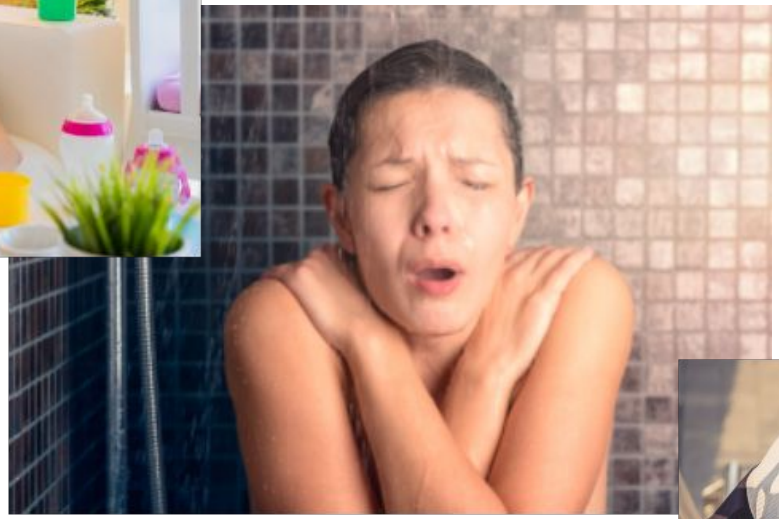


BHC Clinical Care Guide

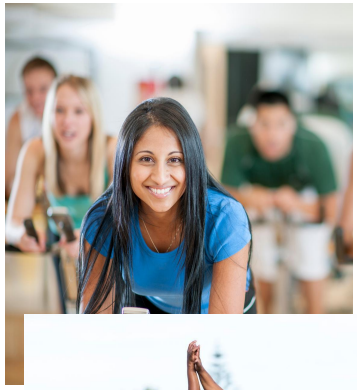
Example Referral to Physical Therapy:

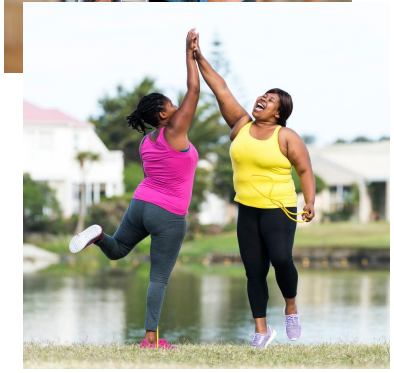
"Refer for evaluation and treatment of physical and functional limitations related to suspected post-exertional malaise (PEM). Please evaluate for safe mobility, suggest appropriate mobility aids, teach energy conservation and activity pacing techniques, and modify physical tasks to minimize exertional stress. Do not prescribe graded exercise or activity. Minimize or avoid exertion-based testing that could contribute to PEM. Offer telehealth option if able and appropriate."

Traditional Referral to PT



Exercise significantly benefits most people's health





If exercise is medicine, then dosing is important

Vina J, et al. *Br J Pharmacol*. 2012;167(1):1-12.

Exercise

- Exercise can be harmful if it results in PEM
- Graded exercise is not recommended for patients experiencing PEM
- Exercise can help with POTS and orthostatic intolerance but not if it results in PEM
- Exercise must be closely monitored during and the days after
- Exercise should be based on tolerance level
- Exercise should not be pushed at the expense of the patient being able to tolerate ADL's

Therapy for Joint Hypermobility

Patients are usually referred to therapy for symptoms:

a. Joint pain/joint instability
b. Deconditioning or fatigue
c. POTS
d. Dizziness
e. Balance problems
f. Headache

Importance of screening:

a. Screen for Post-Exertional Malaise (PEM)
b. Screen for Connective Tissue Disorders/Hypermobility Spectrum Disorders
c. Screen for Systemic Signs and Symptoms (e.g., MCAS)
d. Screen for Orthostatic Intolerance

Screening

The 5-part questionnaire for hypermobility

Just GAPE Toolkit

Systemic signs and symptoms

a. Does it take longer to heal from injuries/sickness than other people?
b. Do you bruise easily?
c. Do you have gastrointestinal symptoms? (e.g., GERD, IBS, etc.)
d. Is your skin fragile, stretchy, sensitive, or does it tear easily?
e. Do you consider yourself accident prone or clumsy?
f. Are you sensitive to lights, sounds, textures, fragrances, chemical products, medications?
g. Do you have allergies, asthma, eczema, over-reaction to bug bites?

Examination

1. Beighton Scale
2. Lower Limb Assessment Score
3. Upper Limb Hypermobility Scale

Examination

https://www.ehlers-danlos.com/assessing-joint-hypermobility/

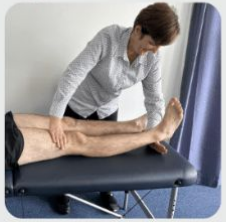
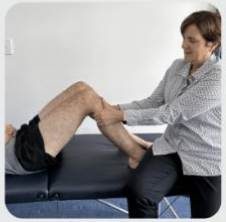
Lower Limb Assessment Score

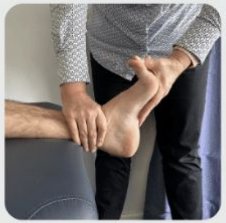
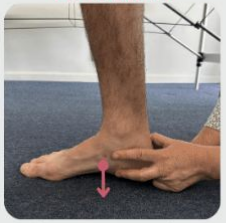
For more information www.dralisongrimaldi.com/blog

Dr. Alison Grimaldi

Lower Limb Assessment Score for Joint Hypermobility

A 12 point scoring system - a positive score is ≥7/12 each limb

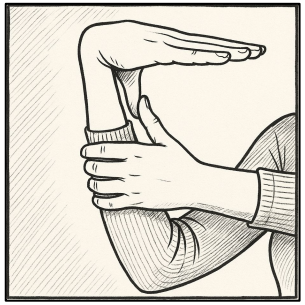
Hip Flexion	Hip Abduction	Knee Hyperextension	Knee Anterior Draw Test	Knee Rotation	Ankle Dorsiflexion
					
Mid-thigh reaches chest	Knees touch bed	Heel ≥ 3cm off bed	+ve draw/clunking	>2cm total tibial tubercle movement	>15° Dorsiflexion

Ankle Anterior Draw Test	Subtalar Joint Inversion	Midtarsal Joint Inversion	Midtarsal AB/ADD & DF/PF	1st MTP Joint Dorsiflexion	Subtalar Joint Pronation
					
+ve draw	≥ 45° inversion	≥ 45° inversion	>1cm motion	>90° extension	Relaxes to end-range pronation

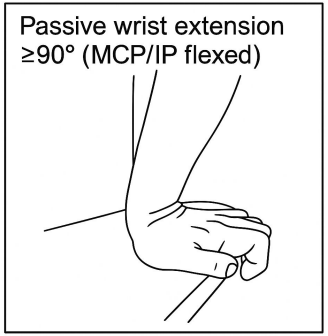
Meyer KJ, Chan C, Hopper L, Nicholson LL. Identifying lower limb specific and generalised joint hypermobility in adults: validation of the Lower Limb Assessment Score. BMC Musculoskelet Disord. 2017 Dec 6;18(1):514.

Upper Limb Hypermobility Scale

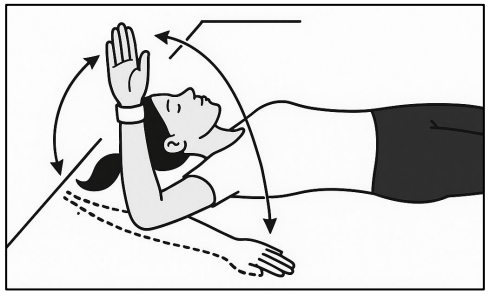
Thumb to forearm



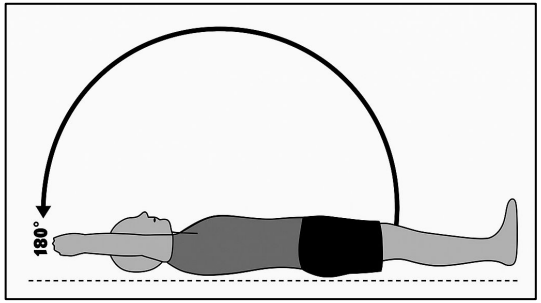
Passive wrist extension ≥90° (MCP/IP flexed)



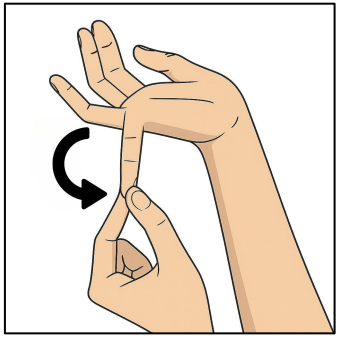
Shoulder rotation >180° at 90°abduction



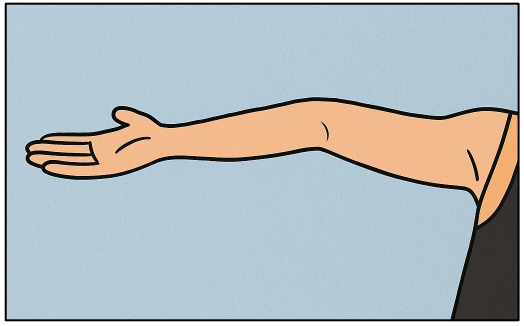
Supine shoulder flexion 180°



2-5 digit extension > 90°

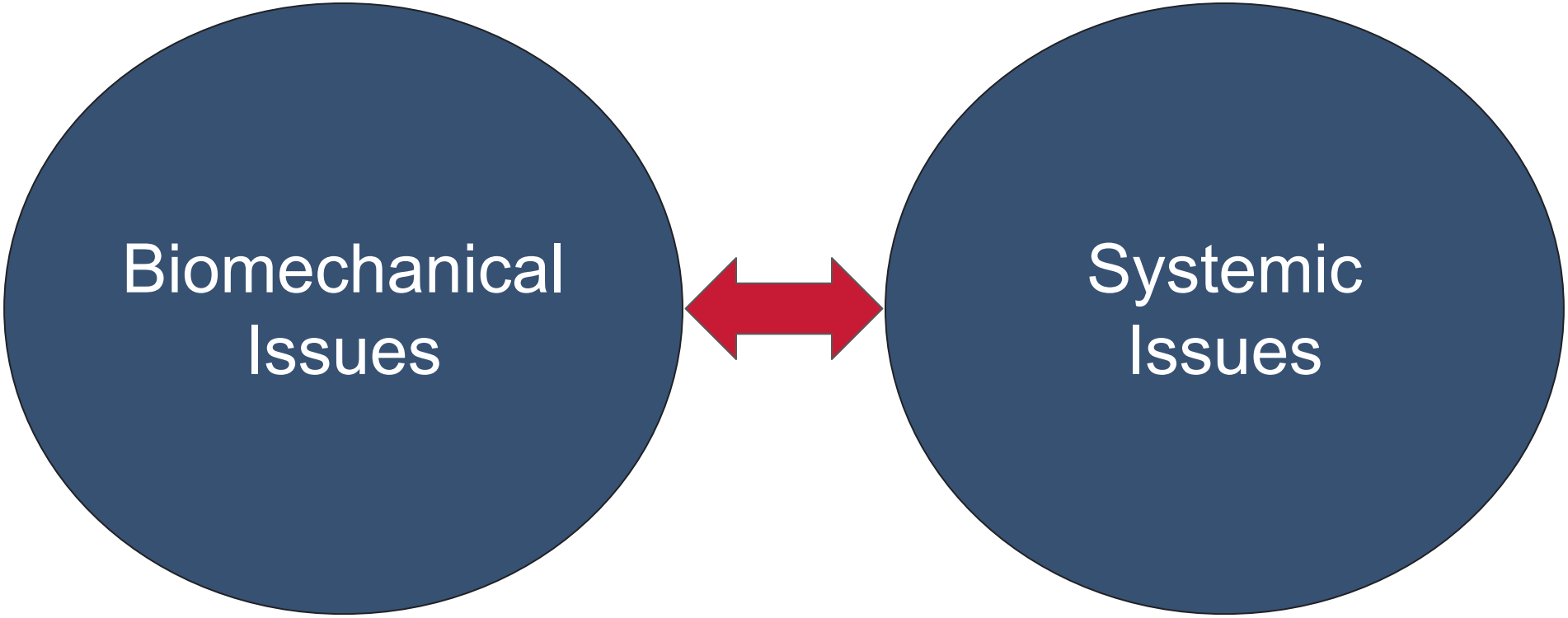


Elbow extension >10°



Other parts of the test

- Elbow Valgus/Varus
- Radioulnar Joint Supination/Pronation
- Sulcus Sign
- Distal Radioulnar Joint (DRUJ) play
- Wrist Radial/Ulnar Deviation
- Handspan: Hand Length



Biomechanical

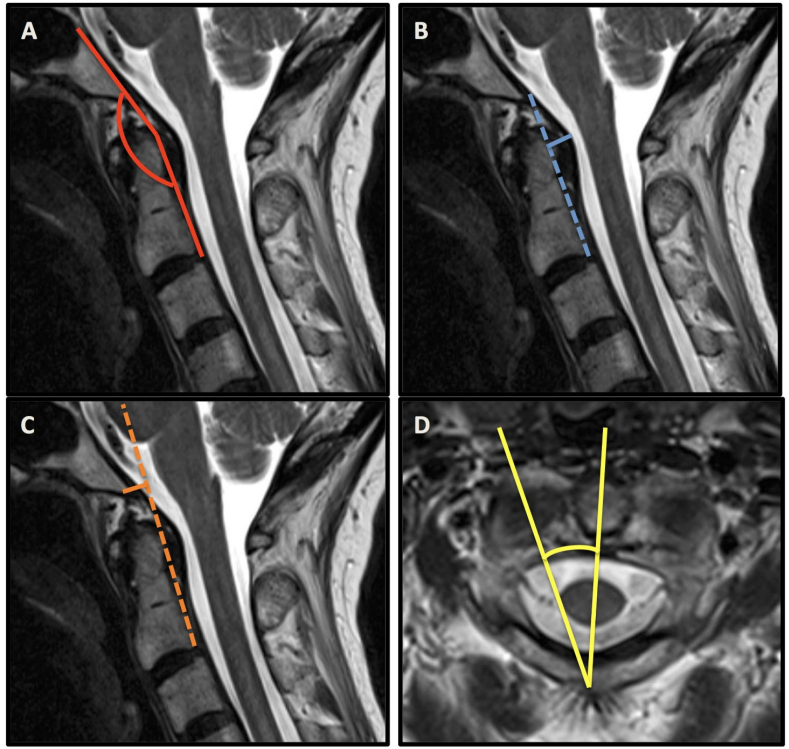
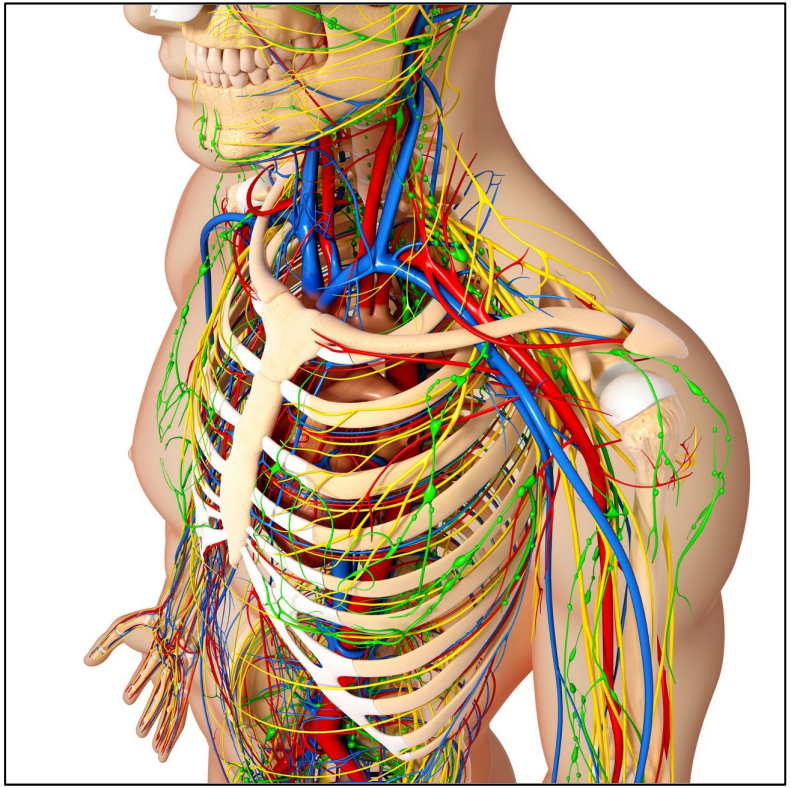


Figure 2. Sagittal MRI sequences containing the clivo-axial angle (CXA) (A), the Harris measurement (B), the Grabb–Mapstone–Oakes measurement (C). Axial MRI sequence illustrating the angular displacement of C1 to C2 (D).

Lohkamp L-N, et al. *Global Spine Journal*. 2022;12(8):1862-1871.

Systemic



Clinical Reasoning

Where to start?

Good subjective history taking

Trial and pivot

Pneumatic compression example

Considerations

1. Before addressing joint pain or instability, physical therapists should determine if systemic issues are impeding the patient's ability to stabilize their joints.

2. Neuro-immune exhaustion and neurological issues may contribute to:
   a. Increased joint instability
   b. Increased pain/discomfort
   c. Decreased sensory tolerance
   d. Poor motor recruitment, control, and learning
   e. Reduced endurance
   f. Delayed healing and recovery after exertion
   g. Increased inflammation
   h. Autonomic dysregulation
   i. Other symptoms

Henderson FC Sr, et al. *Am J Med Genet C Semin Med Genet*. 2017;175(1):195-211.

Ganesh R, Munipalli B. *Front Neurol.* 2024;15:1455498.

Hakim A, et al. *Am J Med Genet C Semin Med Genet*. 2017;175(1):175-180.

Goals of Therapy for Hypermobility

1. Improve quality of life
2. Improve participation in ADL's, work, school, recreation
3. Build resilience & self-management
4. Reduce additional damage
5. Reduce symptoms
6. Improve strength and stability of the joints
7. Increase interoception and proprioception
8. Improve motor recruitment and control
9. Improve cardiovascular function
10. Increase autonomic function

Engelbert RH, et al. *Am J Med Genet C Semin Med Genet*. 2017;175(1):158-167

Therapy for Joint Hypermobility with PEM

Identify systemic issues and refer when appropriate

Stabilize environment (reduce stimulation in clinic, reduce paperwork, virtual appt)

Stabilize emotions (listen, believe, validate, reassure, create a plan, educate)

Stabilize nervous system (autonomic quieting, positioning, lower threat/stressors)

Stabilize systemic issues (PEM, MCAS, OI, pain)

Stabilize joints

Considerations

- Sensory stimulation (light, sound, environment, textures)
- Positioning (upright tolerance, strain on joints)
- Rapid positional changes (full body and cervical)
- Compression (improves OI and provides external feedback)
- Hydration
- Autonomic quieting (awareness of breathing throughout the session)
- Relaxation/mindfulness to calm nervous system
- Frequent rest breaks
- Overstretching ligaments during exercise
- Overheating during activity
- Brain fog (simpler, slower, multiple formats)
- Interoception (external feedback, biofeedback)
- Proprioception (need external cues vs verbal)
- Delayed healing/recovery
- Easy bruising
- Skin fragility (caution with manual therapy, taping, exercises, braces)
- Poor oxygen utilization (limit aerobic activity)
- Lymphatic issues (poor drainage)
- Protect the nervous system (avoid nerve tension, TCS)
- MCAS (adhesive, friction, vibration, heat/cold)
- Chemical sensitivities (fragrances, topical agents)
- Testing that provokes symptoms (strength testing, joint movements, mobilizations)
- Bowel/bladder issues (pelvic floor therapy)
- Joint subluxations (caution with joint mobilizations and relaxing the muscles too much)
- Spine instability
- Used to exercise for coping (adjust expectations)
- Vascular compressions
- Movement sequencing more difficult
- Multi-step movements or instructions harder
- Ergonomics (positional supports, avoid end-ranges)
- Prolonged plan of care
- Psychological barriers to self-care
- Financial barriers
- Healthcare access and literacy barriers

Refer to therapists who understand the complexities

Avoid

- Neuroimmune exhaustion (PEM)
- Overstimulation
- Frequent position changes
- Prolonged upright activities
- Positions or movements that overstretch the joints
- Repetitive strain on the joints
- Overheating during activity/exercise
- High impact activities or movements
- Overloading the tissues (fatigue for stairs later)
- Prolonged positioning (postural strain, pressure wounds)
- Reinforcing compensations or poor movement patterns

Therapy Plan

Education

Activity Modifications

Lifestyle Changes

Exercises (strength and control vs cardio; Muldowney - belly button down first)

Manual Therapy (external feedback, lymphatic massage, joint support)

Rest & Autonomic Quieting (Mindfulness, breathing, sensory modalities)

Caregiver Support

Disability/Accommodation Support

Assistive Devices

Joint Supports

Rigid Bracing vs Joint Supports

- Rigid braces/splints when necessary for:
  - Acute injury
  - Support during activity
  - Reducing load on tissues
  - Smaller joints (fingers, toes)
  - Prolonged positioning
- Joint supports for:
  - Prolonged positioning (sleep)
  - Activity
  - Compression
  - Proprioception

Support

Sacroloc

vs.

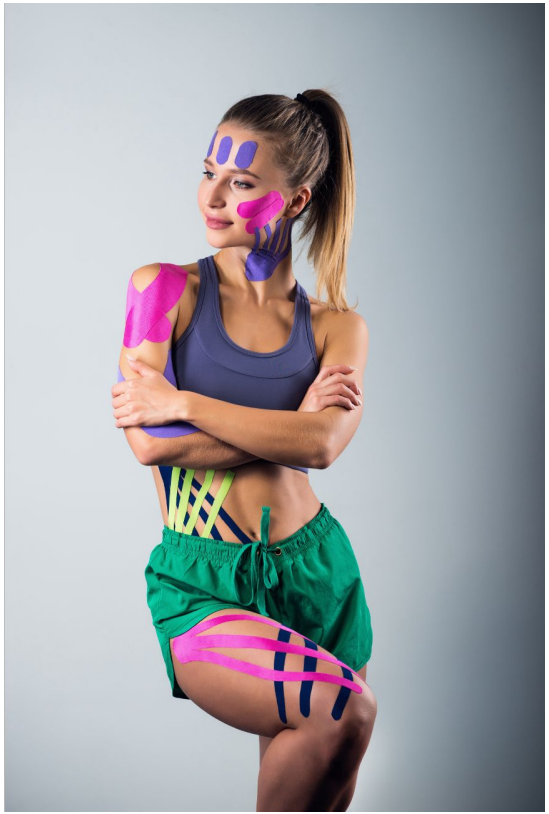
Rigid

Coxatrain

Taping

Taping for support vs feedback

- Adhesive reaction (cromolyn sodium, others)
- Tape after treating the joint
- McConnell vs Kinesio



Pain/Symptom Management

- Education
- Autonomic quieting/vagus nerve stimulation
- Breathing
- Manual therapy
- Appropriate exercise
- Cold or heat packs
- Compression garments and/or pneumatic compression
- Transcutaneous electrical stimulation (TENS)
- Topical rubs
- Nutrition and supplements
- Sensory modalities (e.g., compression, smell, touch)
- Green light exposure
- Photobiomodulation
- Supplemental oxygen

Engelbert RH, et al. *Am J Med Genet C Semin Med Genet*. 2017;175(1):158-167

Strengthening for Joint Hypermobility

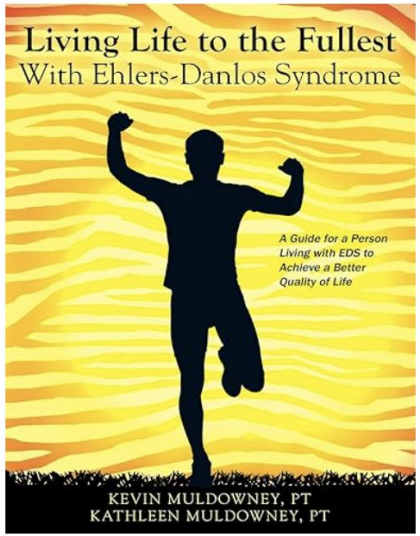
Resources

[EDS New Zealand Course](#)

[Bendy Bodies Guides](#)

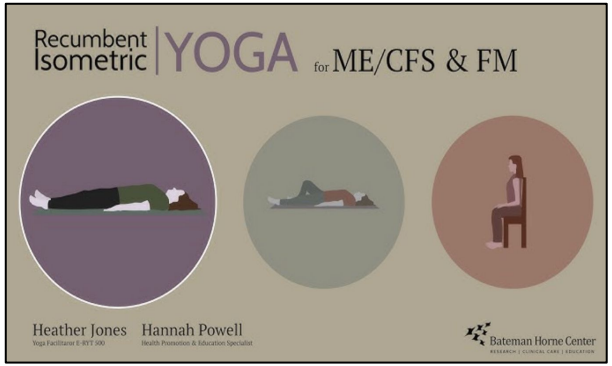
THE BENDY BODIES PODCAST

[Muldowney Protocol](#)



[Jeannie Di Bon YouTube](#)

[Bateman Horne Center YouTube](#)



Bateman Horne Center Rehab Professionals

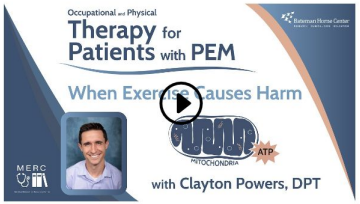
Short Education Videos

These education videos aim to equip rehabilitation professionals on how to assess and safely manage patients with PEM/PESE.

Series Intro

Why PEM Matters

PEM: The Basics



When Exercise Causes Harm

Pacing for PEM/PESE

Understanding PEM/PESE

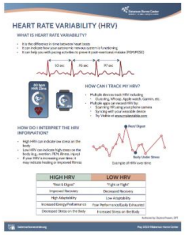
Credit to the collective knowledge and collaborative effort shared by ME/CFS informed rehab professionals and that of the Physical Therapist/Occupational Therapist Resources for Treating ME/CFS Facebook Group.

Screening Tools

- Functional Capacity Questionnaire (FUNCAP55)
- Assessing Functional Capacity in ME/CFS Questionnaire (FUNCAP27)
- Screening for PEM/PESE (BHC)
- DePaul Questionnaire (DSQ-PEM)
- Post-Exertional Malaise Timecourse for ME/CFS (Workwell)
- The Composite Autonomic Symptom Score (COMPASS-31)

Pacing Resources

- Pacing for PEM/PESE (BHC)
- Pacing Upright Activity (BHC)
- Pacing & Management Guide (MEAction)
- Energy Conservation Tips (BHC)
- Top Energy Saving Tips (Workwell)
- Crash Survival Guidebook
- ME/CFS Activity Management with a Heart Rate Monitor (Workwell)
- Heart Rate Variability (HRV) (BHC)



Rehab Professionals Page

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