Ehler’s Danlos Syndromes

More Than Hypermobility: An Interplay of Comorbidities

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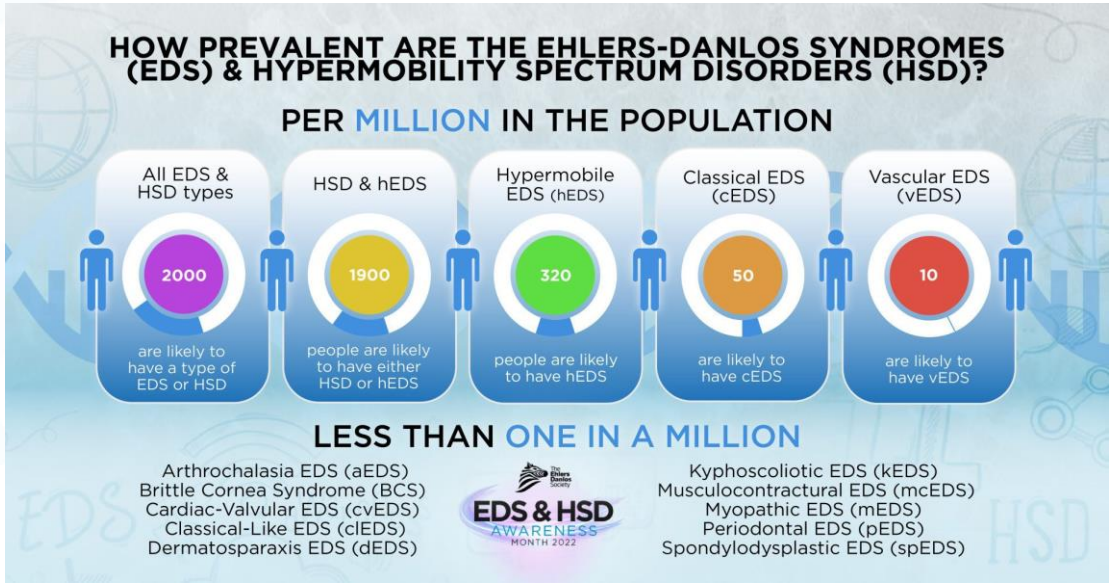
No Disclosures

Bateman Horne Center is a **Non-Profit Center of Excellence** dedicated to furthering clinical care, research, and patient and provider education regarding ME/CFS, Post-Acute Sequelae of COVID-19 (PASC), and related comorbidities (including connective tissue disorders like Ehlers Danlos Syndrome)

Aim to Explore the relationship of EDS to…

- Mast Cell Activation Syndrome
- Central Nervous System Complications
  - Craniocervical Instability/Atlantoaxial Instability
  - Occult/Acquired Tethered Cord
- Small Fiber Polyneuropathy
- Gastrointestinal Dysmotility
- Vascular Abdominal Pathologies
  - Median Arcuate Ligament Syndrome (MALS)
  - May Thurner's
  - Nutcracker
- Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Post-Acute Sequelae of COVID (PASC)



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"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/.

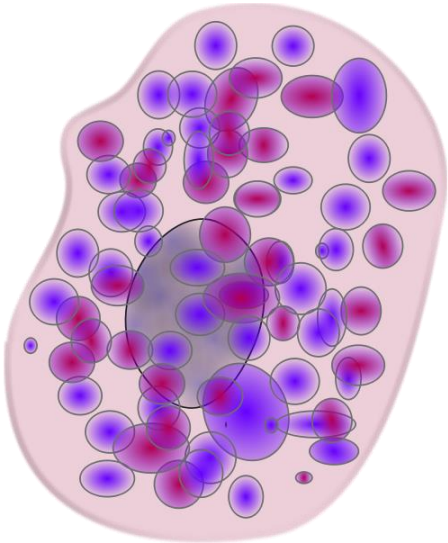
Mast Cell Activation Syndrome (MCAS)/ Mast Cell Activation Disorder (MCAD) (D89.4)

- Mast cells are a type of white blood cell that patrols most connective tissues as well as neurological, gastrointestinal, dermatological, pulmonary, and other mucosal tissues

- Mast cells are traditionally known to be involved in mediating “allergic” responses and play a critical role in protection from worm and parasite infections

- Mast cells also act as sensors for environmental and psychological stress, participate in wound healing, modulate vascular permeability, promote angiogenesis, and participate in the innate AND adaptive immune responses

- Mast cells can regulate T-cell responses, even in the absence of antigen presentation, autoimmunity, or inflammation



“Mast Cell Activation Syndrome: AAAAI.” The American Academy of Allergy, Asthma, &Immunology, www.aaaai.org/conditions-and-treatments/related conditions/mcas

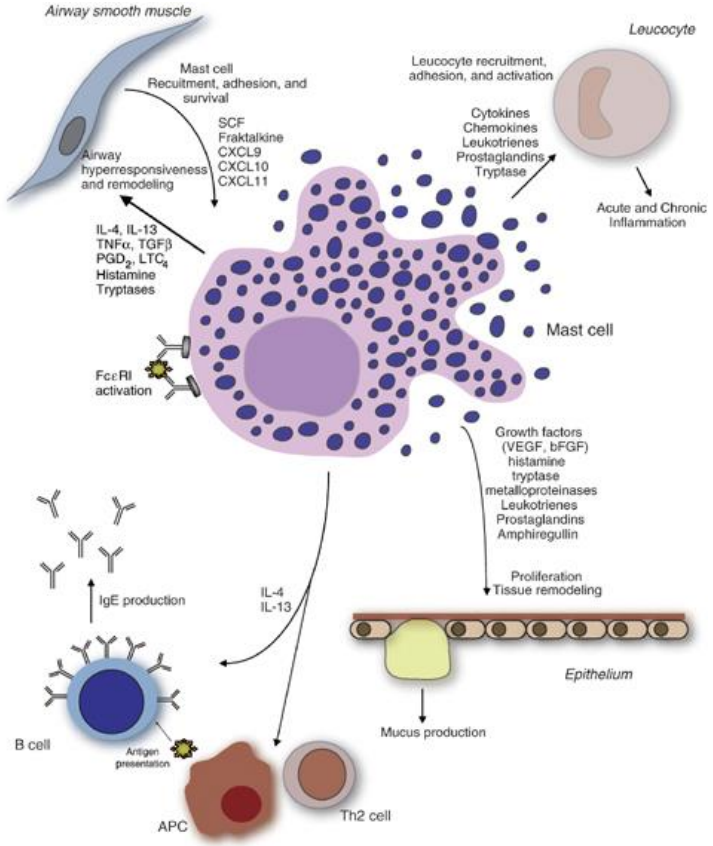
Mast Cell Activation Syndrome: A review. Frieri M., Patel R., Celestin J. Curr Allergy Asthma Rep. 2013 Feb;13(1):27-32. doi: 10.1007/s11882-012-0322-z.

Theoharides TC. Neuroendocrinology of mast cells: challenges and controversies. *Exp Dermatol*. 2017;26:751–759. This paper reviews evidence of the responsiveness of mast cells to neuroendocrine triggers and their potential role in related diseases in the absence of allergies or MCMD.

Mast Cell Activation Syndrome (MCAS)/ Mast Cell Activation Disorder (MCAD) (D89.4)

- When mast cells are “activated,” they release a collection of inflammatory mediators, cytokines, and proteases, with histamine, tryptase, and leukotrienes being the most well-known of these

- Mast cells are normally activated in the presence of a type of antibodies known as IgE antibodies, as well as several other types of immune system triggers



Clinical & Experimental Allergy, Volume: 38, Issue: 1, Pages: 4-18, First published: 21 November 2007, DOI: (10.1111/j.1365-2222.2007.02886.x)

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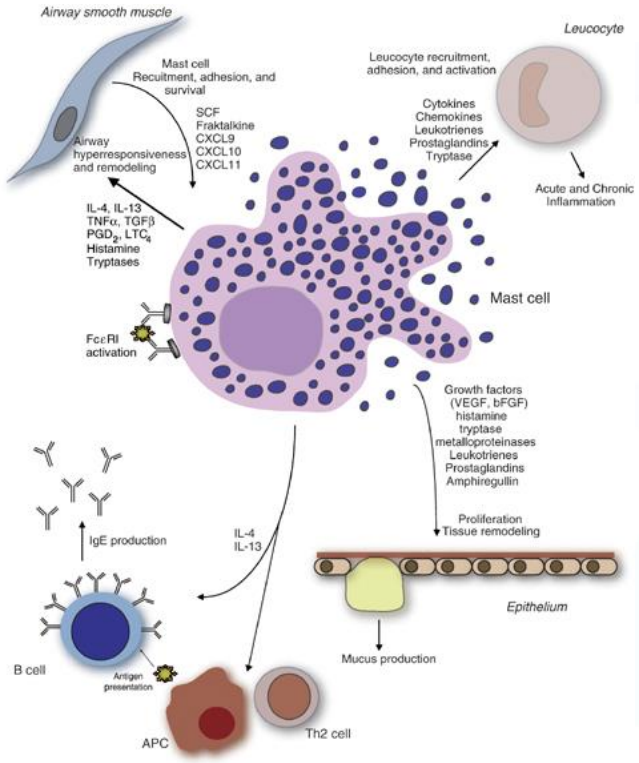

Clinical & Experimental Allergy, Volume: 38, Issue: 1, Pages: 4-18, First published: 21 November 2007, DOI: (10.1111/j.1365-2222.2007.02886.x)

In MCAS:

- Pathological accumulation of mast cells in organs and tissues or
- Aberrant release of mast cell mediators

- Mast cells can be activated by IgE-dependent reactions or, commonly, respond to non-allergic triggers (extensively diverse foreign substances) independent of IgE

- Non-allergic triggered mast cell activation may lead to inflammatory mediator release **without** traditional degranulation

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Jackson, Clayton Webster, et al. "Mastocytosis and mast cell activation disorders: Clearing the Air." *International Journal of Molecular Sciences*, vol. 22, no. 20, 2021, p. 11270, https://doi.org/10.3390/ijms222011270.

"Mast Cell Activation Syndrome: AAAAI." The American Academy of Allergy, Asthma, &Immunology, www.aaaai.org/conditions-and-treatments/related conditions/mcas

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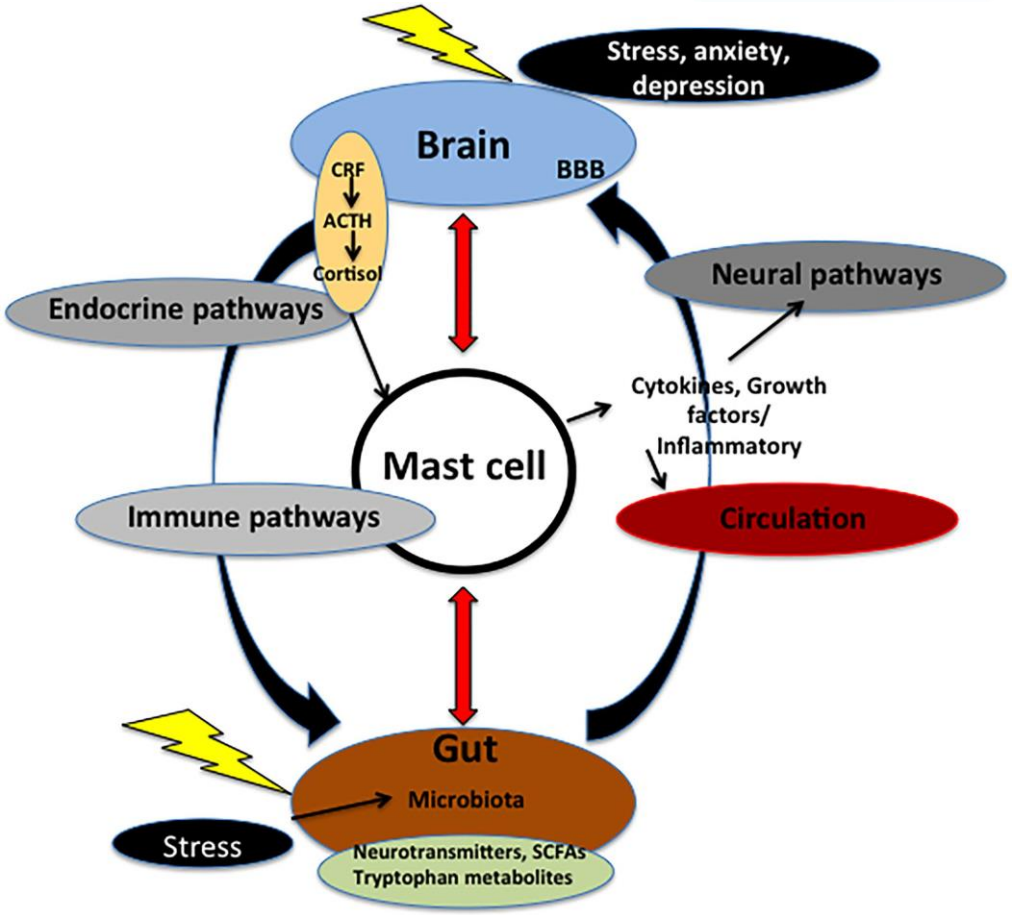
Theoharides TC, Kempuraj D, Tagen M, et al. Differential release of mast cell mediators and the pathogenesis of inflammation. *Immunol Rev*. 2007;217:65–78.

Mast Cell Activation Syndrome (MCAS)/ Mast Cell Activation Disorder (MCAD) (D89.4)



- Activated mast cells may also send distress signals, through the nervous system and immune system, to other areas of the body, alerting additional mast cells to activate as well

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Traina, Giovanna. "Mast cells in gut and brain and their potential role as an emerging therapeutic target for neural diseases." *Frontiers in Cellular Neuroscience*, vol. 13, 2019, https://doi.org/10.3389/fncel.2019.00345.

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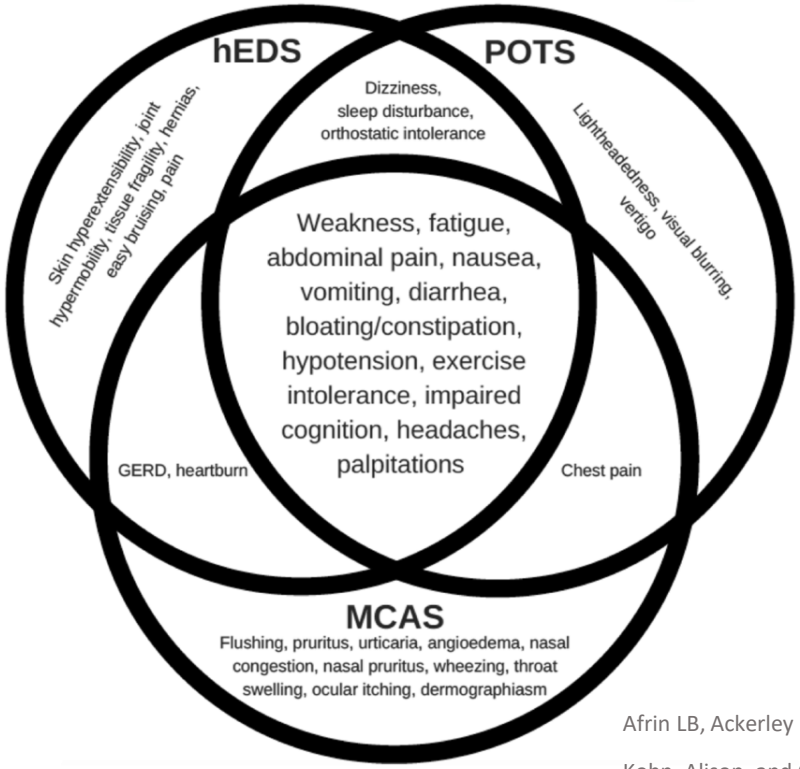

- Nearly 1 in 3 patients with MCAS had a comorbid diagnosis of hEDS in a sample of 37,665 patients diagnosed with either disorder
- In one study, 66% of patients with POTS and EDS also met symptoms for MCAS

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.

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- Abnormal laboratory testing refers to those with POTS whose laboratory workup suggested elevated MCAS-related serum and urine mediators

Table 2

Comparison of Symptoms in 44 Patients Who Underwent Laboratory Testing

Abnormal Values	POTS-like With Atypical Symptoms (n=29)	POTS Alone (n=15)	*P* Value
ESR or CRP abnormal	6/28* (21%)	3/14* (21%)	>.99
Tryptase	2/23* (9%)	0/9* (0%	>.99
Prostaglandin	16/28* (57%)	0/15 (0%)	0.0002
Histamine	17/29 (59%)	0/15 (0%)	0.0001
Histamine or methylhistamine abnormal	23/29 (79%)	0/15 (0%)	0.0001

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Kohno R, Cannom DS, Olshansky B, Xi SC, Krishnappa D, Adkisson WO, Norby FL, Fedorowski A, Benditt DG. Mast Cell Activation Disorder and Postural Orthostatic Tachycardia Syndrome: A Clinical Association. J Am Heart Assoc. 2021 Sep 7;10(17):e021002. doi: 10.1161/JAHA.121.021002. Epub 2021 Aug 16. PMID: 34398691; PMCID: PMC8649306.

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Table 3

Comparison of Symptoms in 44 Patients Who Underwent Laboratory Testing

	Abnormal Laboratory Tests (n=29)	%	Normal Laboratory Tests (n=15)	%	*P* Value
Age, y, mean±SD	34±9.5		33 ± 12.2		NS
% Female	29/29		13/15		0.111
Palpitation	25/29	86	13/15	87	1.0
Syncope	11/29	38	4/15	27	0.524
Fatigue	21/29	72	8/15	53	0.317
Lightheadedness /dizzy/brain fog	23/29	79	11/15	73	0.714
Migraines	11/29	38	3/15	20	0.314
Depression/anxiety	6/29	21	6/15	40	0.284
Fibromyalgia	4/29	14	1/15	7	0.647
Allergy	13/29	45	2/15	13	0.048
Skin rash	10/29	34	1/15	13	0.067
Gastrointestinal symptoms	18/29	62	3/15	23	0.001

POTS with "Atypical Symptoms"

NS indicates not significant.

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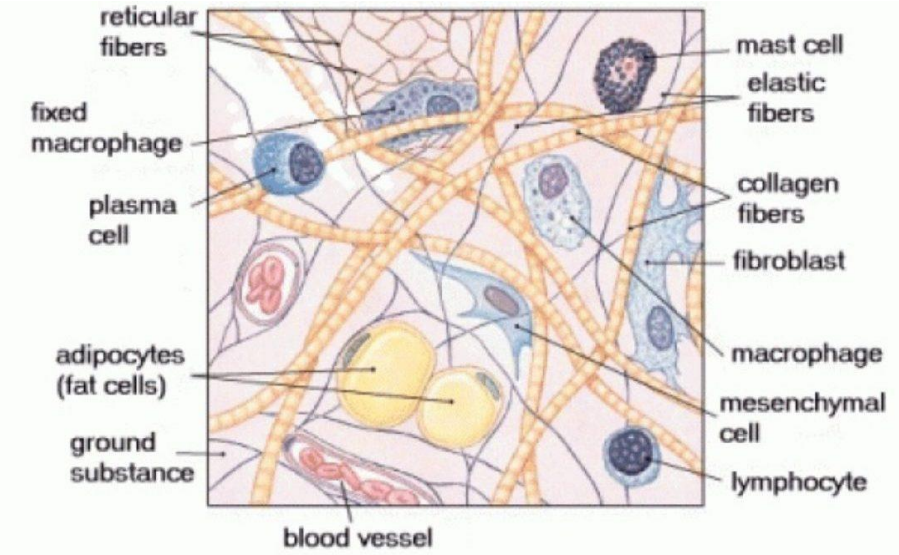
Mast Cell Activation Syndrome (MCAS)/ Mast Cell Activation Disorder (MCAD) (D89.4)

- 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
- 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
- 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



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/.

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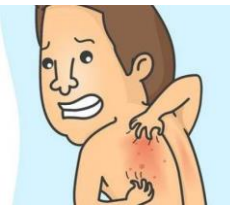
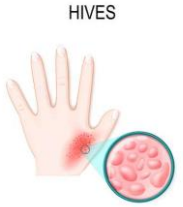
Mast Cell Activation Syndrome Symptoms

Organ and system involvement in mast cell activation syndrome. Conditions highlighted in bold are also seen in Covid-19 acute infection and/or post-infectious syndrome.

Organ/system	Symptom/finding
Constitutional	**Fatigue, fevers, chills, weight loss,** weight gain
Ears, nose and throat	**Conjunctivitis, rhinitis, sinusitis, dysosmia/anosmia, tinnitus, hearing loss, dysgeusia/ageusia, sore throat**
Neurologic	**Headaches,** migraines, **brain fog, anxiety, depression, insomnia, seizures**
Cardiovascular	**Chest pain, palpitations, hypotension**
Pulmonary	**Cough, dyspnoea, wheezing**
Urogenital	Frequency, urgency, dysuria, pelvic pain
Oesophageal	**Heartburn, dysphagia,** globus, **chest pain**
Stomach	**Dyspepsia, nausea, vomiting**
Small intestine/colon	**Bloating, food intolerance, abdominal pain, diarrhoea,** constipation
Hepatic	**Elevated transaminases,** hepatomegaly
Salivary Glands	**Swelling**
Lymphatics	**Lymphadenopathy**
Dermatologic	Flushing, pruritis, **urticaria,** haemangiomas, nodules, **rashes, alopecia**
Musculoskeletal	**Myalgias,** arthralgias, **oedema**





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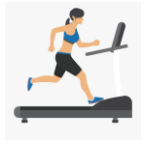
Afrin LB, Weinstock LB, Molderings GJ. Covid-19 hyperinflammation and post-Covid-19 illness may be rooted in mast cell activation syndrome. Int J Infect Dis. 2020 Nov;100:327-332. doi: 10.1016/j.ijid.2020.09.016. Epub 2020 Sep 10. PMID: 32920235; PMCID: PMC7529115.

Mast Cell Activation Syndrome Clinical Triggers

Figure 1. Some *Potential* Mast Cell Triggers[2-5]

- Heat, cold or sudden temperature changes
- Stress: emotional, physical, including *pain*, or environmental (i.e., weather changes, pollution, pollen, pet dander, etc.)



- Exercise

- Fatigue
- Food or beverages, including alcohol

- Drugs (opioids, NSAIDs, antibiotics and some local anesthetics) and contrast dyes

- Natural odors, chemical odors, perfumes and scents
- Venoms (bee, wasp, mixed vespids, spiders, fire ants, jelly fish, snakes, biting insects, such as flies, mosquitos and fleas, etc.)

- Infections (viral, bacterial or fungal)

- Mechanical irritation, friction, vibration
- Sun/sunlight

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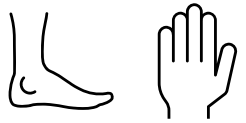
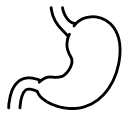
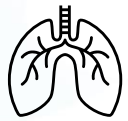
"Symptoms and Triggers of Mast Cell Activation - TMS - The Mastocytosis Society." The Mastocytosis Society, 29 July 2019, tmsforacure.org/symptoms/symptoms-and-triggers-of-mast-cell-activation/.

Diagnostic Criteria:
Mast Cell Activation Syndrome (D89.4)

1) Episodic symptoms consistent with mast cell mediator release affecting **two or more organ systems** evidenced as follows:

- Skin: urticaria (hives), angioedema (sudden swelling), flushing, dermatographia 
- Gastrointestinal: nausea, vomiting, diarrhea, abdominal cramping 
- Cardiovascular: hypotensive syncope (fainting), tachycardia 
- Respiratory: wheezing 
- Naso-ocular: conjunctival injection, pruritus(itching), nasal stuffiness 

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Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. Gerhard J Molderings et al…Afrin. Journal of Hematology & Oncology 20114:10. https://doi.org/10.1186/1756-8722-4-10©. 2011

Diagnostic Criteria:
Mast Cell Activation Syndrome (D89.4)

2) Improved symptoms after treatment with:

- H1 (antihistamines) and H2 (famotidine) histamine receptor antagonists
- Leukotriene antagonists: montelukast
- Mast cell stabilizers – cromolyn sodium, ketotifen (also an antihistamine)

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Diagnostic Criteria:

Mast Cell Activation Syndrome (D89.4)

Evidence of an elevation in a validated urinary or serum marker of mast cell activation:

- Total serum **tryptase** (very specific for mast cells)
- Elevated serum **histamine**
- Biopsy tissue (i.e. GI tissue) with staining positive for mast cells (CD 117 staining)

- 24-hour urine levels of:
  - **N-methylhistamine**
  - **11B -Prostaglandin F2α** (11B-PGF2α)
  - **Leukotriene E4 (LTE4)**

REMEMBER: Empiric trials of therapy when a clinical suspicion for MCAS can also be clinically diagnostic!

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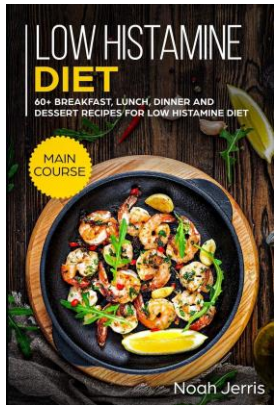
Management: Mast Cell Activation Syndrome

- Low Histamine Diet
- Diamine oxidase supplementation
- H1 Blockade (fexofenadine, loratadine, cetirizine, levocetirizine)
- H2 Blockade (famotidine, ranitidine, cimetidine)
- Benadryl (diphenhydramine)
- Leukotriene Blockade (montelukast)
- Mast Cell Stabilizers
  - Liquid cromolyn/Gastrocrom (1 mL or 20 mg up to 5 ml or 100 mg 15 minutes before meals and medications)
  - Compounded cromolyn sodium (200 mg po tid to qid)
  - Compounded ketotifen (1 mg po bid)
  - OTC Flavonoids (luteolin, quercetin)
- Anti-IgE biologics (omalizumab/Xolair)
- Steroids (for acute management)



REMEMBER: Empiric trials of therapy when a clinical suspicion for MCAS can also be clinically diagnostic!

Mast Cell Activation Syndrome-Associated Illnesses

Table 2.

Conditions Often Comorbid With Mast Cell Diseases

- Chronic inflammatory response syndrome (CIRS)
- Fibromyalgia syndrome (FMS)
- Ehlers-Danlos Syndrome (EDS)
- Gulf War Illness (GWI)
- Interstitial cystitis/bladder pain syndrome (IC/BPS)
- Irritable bowel syndrome (IBS)
- Kounis syndrome
- Multiple chemical sensitivity syndrome (MCSS)
- Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
- Post-Lyme syndrome
- Postural orthostatic tachycardia syndrome (POTS)
- Post-traumatic stress disorder (PTSD)

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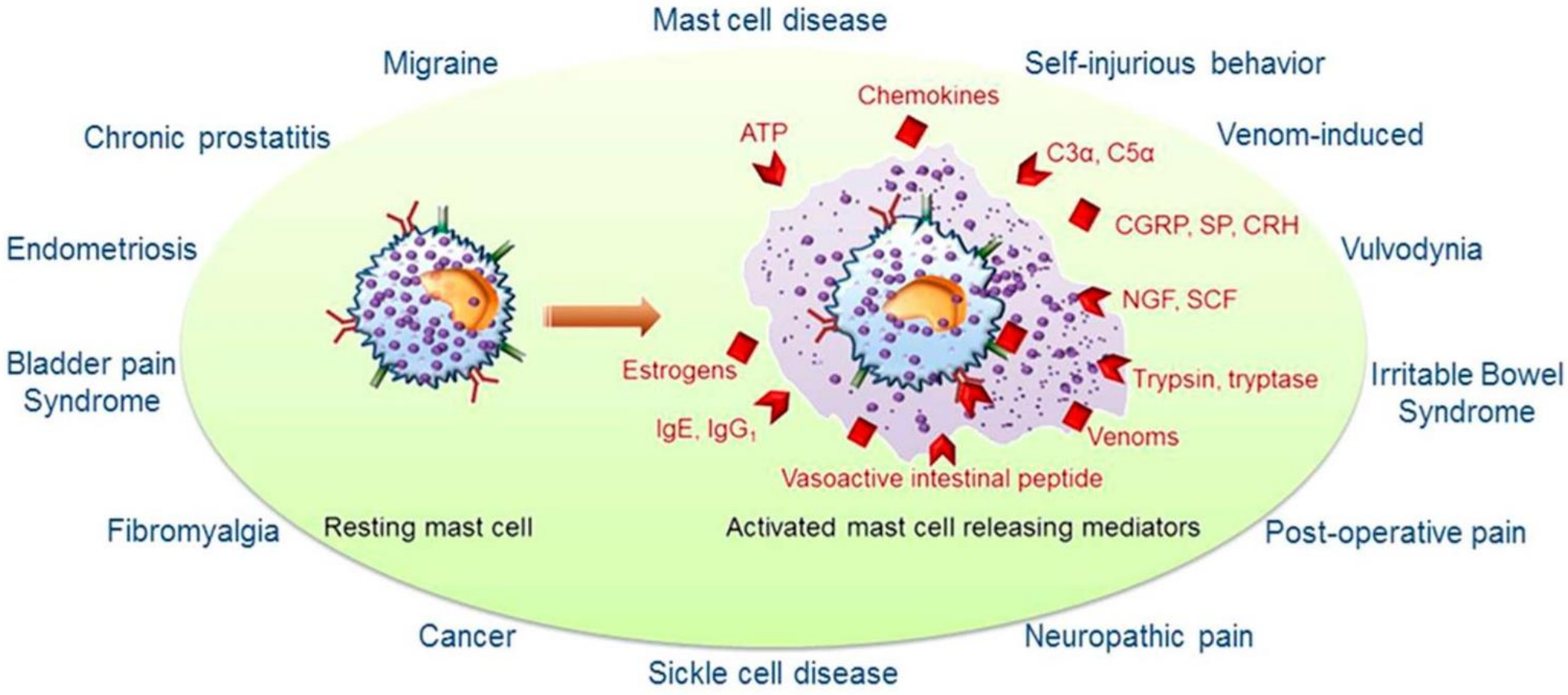
Theoharides, Theoharis C., et al. "Recent advances in our understanding of mast cell activation – or should it be mast cell mediator disorders?" *Expert Review of Clinical Immunology*, vol. 15, no. 6, 2019, pp. 639–656, https://doi.org/10.1080/1744666x.2019.1596800.

Mast cell-associated disease-specific pain syndromes, activation and common activators:



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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.

Cell Triggers of Mast Cell Degranulation:

Acetylcholine

Complement fragments

- C3α, C4α, C5α

Drugs

- Local anesthetics
- Lactam antibiotics
- Neuromuscular junction blockers
- Vancomycin

IgE

IgG_1

IgG_4

Lysophosphatidylserine

Peptides

- Adrenomedullin
- CGRP
- Endorphin
- Endothelin
- Eosinophil granule proteins
- Hemokinin-1
- Leptin
- Mastoparan
- Neurotensin
- NGF
- PTH
- Somatostatin
- SP
- Thrombin
- VIP

Physical conditions

- Cold
- Heat
- Pressure
- Stress
- Vibration

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Triggers of Mast Cells without Degranulation:

Triggers	Mediator
Peptides	
CRH	VEGF
SCF	IL-6
Cytokines	
IL-1β	IL-6
IL-33	IL-31
IL-33	CX CL8 (IL-8)
IL-33 + SP	TNF, VEGF
Heavy metals	
Aluminum	
Cadmium	
Mercury	
Herbicides	
Atrazine	
Glyphosate	
Pathogens	
Borrelia (Lyme disease)*	TNF
LPS	TNF
Poly (I:C) (viruses)	IL-6, TNF
Sporothrix (mold)*	IL-6, TNF

*Mycotoxins

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Mast Cell Mediators:

Not just...

Leukotrienes

Tryptase

Histamine

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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.

Mast Cell Mediators:

Prestored

Biogenic Amines
- Dopamine
- Histamine
- 5-Hydroxytryptamine (5-HT, serotonin)

Polyamines
- Spermidine, spermine

Cytokines
- TNF

Enzymes
- Arylsulfatases A
- Beta-hexosaminidase
- Beta-glucuronidase
- Beta-glucosaminidase
- Beta-D-galactosidase
- Carboxypeptidase A
- Cathepsins B,C, D, E, L
- Chymase
- Garnzyme B
- Kinogenases
- Phospholipases
- Renin
- Tryptase
  - Metalloproteinases (CPA3, MMP9, ADAMTSS)

Growth factors
- FGF
- NGF
- SC
- TGFβ
- VEGF

Peptides
- ACTH
- Angiogenin
- Angiopoietin
- Calcitonin gene-related peptide
- Corticotropin-releasing hormone
- Endorphins
- Endothelin
- Hemokinin-1
- Kinins (bradykinin)
- Leptin
- Melatonin
- Neurotensin

RANKL
- Somatostatin
- Substance P
- Urocortin
- Vasoactive intestinal peptide

Proteoglycans
- Chondroitin sulfate
- Heparan sulfate
- Heparin
- Hyaluronic acid
- Serglin

De novo synthesized

Chemokines
- IL-8 (CXCL8), MCP-1 (CCL2), MCP-3 (CCL7),
- MCP-4, RANTES (CCL5), Eotaxin (CCL11)

Cytokines
- IL-1β, IL-4, IL-5, IL-6, IL-15, IL-17, IL-31, IL-33, TNF

Growth Factors
- SCF, β-FGF, neurotrophin 3, NGF,
- PDGF, TGFβ, VEGF

Nitric oxide

Phospholipid metabolites
- Leukotriene B_4
- Leukotriene C_4
- Platelet activating factor
- Prostaglandin D_2

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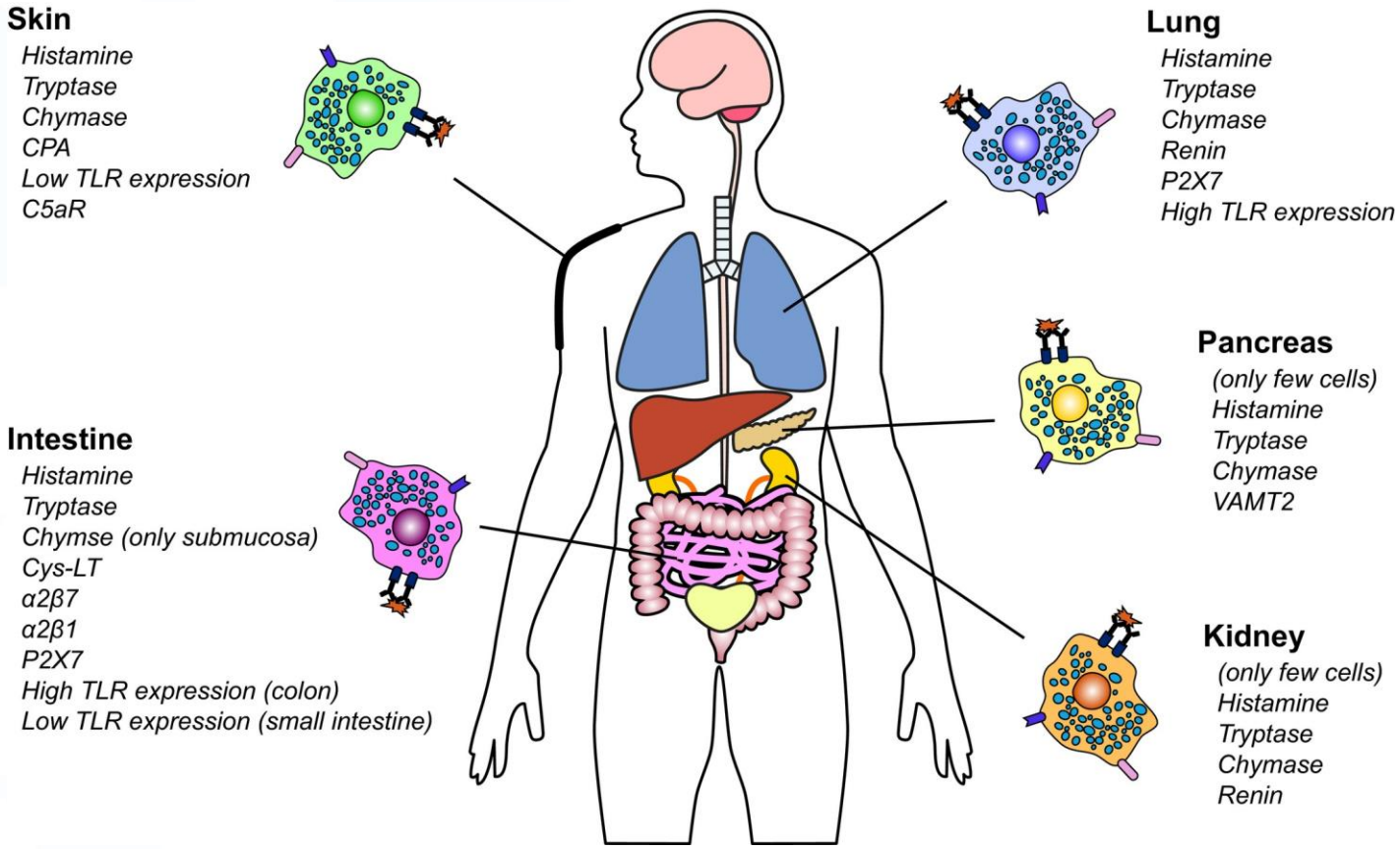
Mast Cell Activity in Different Tissues:

- Mast cells from different tissues are phenotypically different, including activating triggers, membrane receptor expression, cytokine/chemokine release



Frossi, Barbara, et al. "Is it time for a new classification of mast cells? what do we know about mast cell heterogeneity?" *Immunological Reviews*, vol. 282, no. 1, 2018, pp. 35–46, https://doi.org/10.1111/imr.12636.

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Frossi B, Mion F, Sibilano R, et al. Is it time for a new classification of mast cells? What do we know about mast cell heterogeneity? *Immunol Rev*. 2018;282:35–46.

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.

Mast Cell Cytokine Mediators in hEDS/HSD

<u>Mast cells produce inflammatory changes in connective tissues, affecting multiple organ systems</u>:

a.) Localized to peripheral nerve epineurium, perineurium, and endoneurium, releasing mediators that may active nociceptive symptoms like peripheral neuropathy, headache, small fiber polyneuropathy

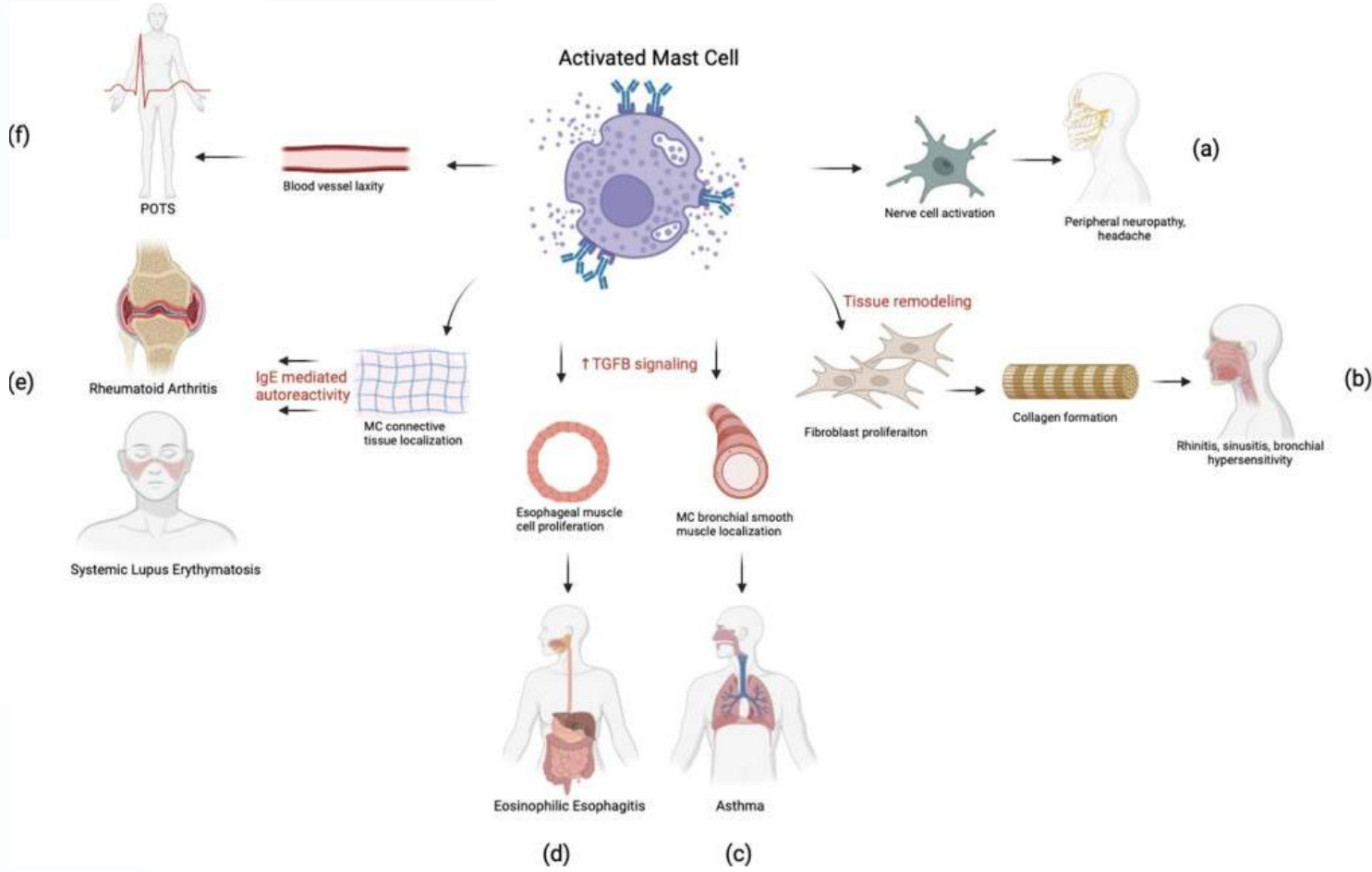
b.) MC cytokines can lead to dysfunctional fibroblast proliferation in nasal and bronchial tissue, associated rhinitis and sinusitis

c). MC-induced TGF-β upregulation in bronchial smooth muscle can modify matrix proteins of bronchial parenchyma, contribute to tissue damage and asthma

d.) TGF-β upregulation in esophageal tissue causing proliferation and smooth muscle contraction (dysphonia, dysphagia, globus, eosinophilic esophagitis)

e.) MC's in local connective tissue cause microenvironmental changes to the extracellular matrix, inducing IgE-mediated autoreactivity, which may play a role in rheumatological conditions

e.) Laxity of blood vessels with pooling of blood in the extremities (POTS, dysautonomia, ME/CFS, PASC)



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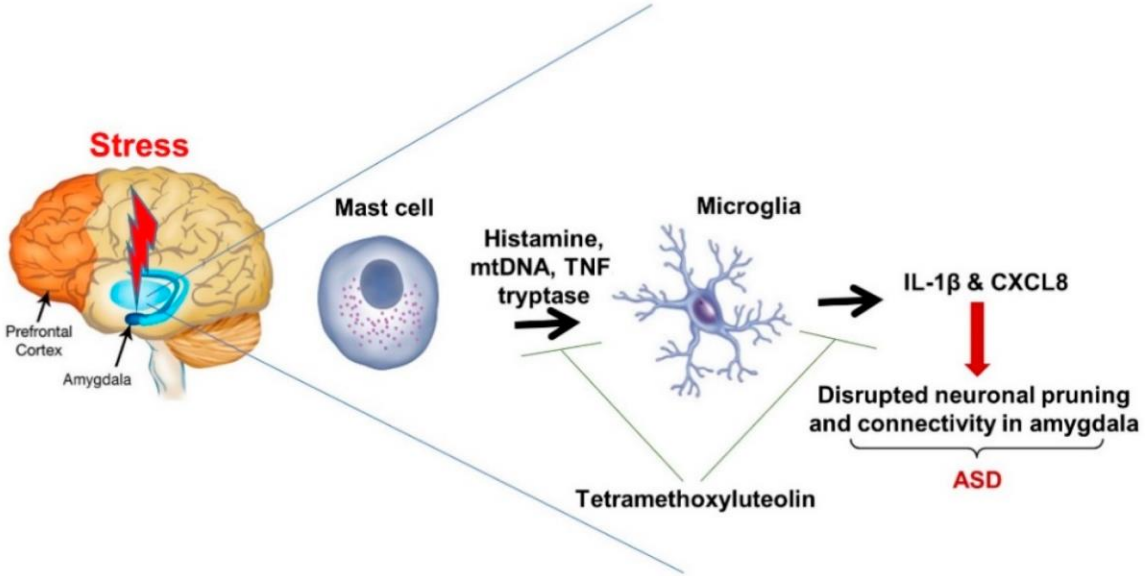
Monaco, Ashley, et al. "Association of Mast-cell-related conditions with hypermobile syndromes: A review of the literature." *Immunologic Research*, vol. 70, no. 4, 2022, pp. 419–431, https://doi.org/10.1007/s12026-022-09280-1.

Mast Cell Activation In The Brain

- Mast cells are found in the brain, particularly in the hypothalamus, thalamus, third ventricle, pituitary gland, & pineal gland
- In MCAS, mast cells are often notably activated and affected by emotional stress via effects of corticotropin-releasing hormone
- Mast cells also appear to regulate the permeability of the blood-brain-barrier and appear to be involved in neuroinflammation and brain disorders (ME/CFS, PASC, autism)



Theoharides, Theoharis C., Maria Kavalioti, et al. "Mast cells, stress, fear and autism spectrum disorder." *International Journal of Molecular Sciences*, vol. 20, no. 15, 2019, p. 3611, https://doi.org/10.3390/ijms20153611.

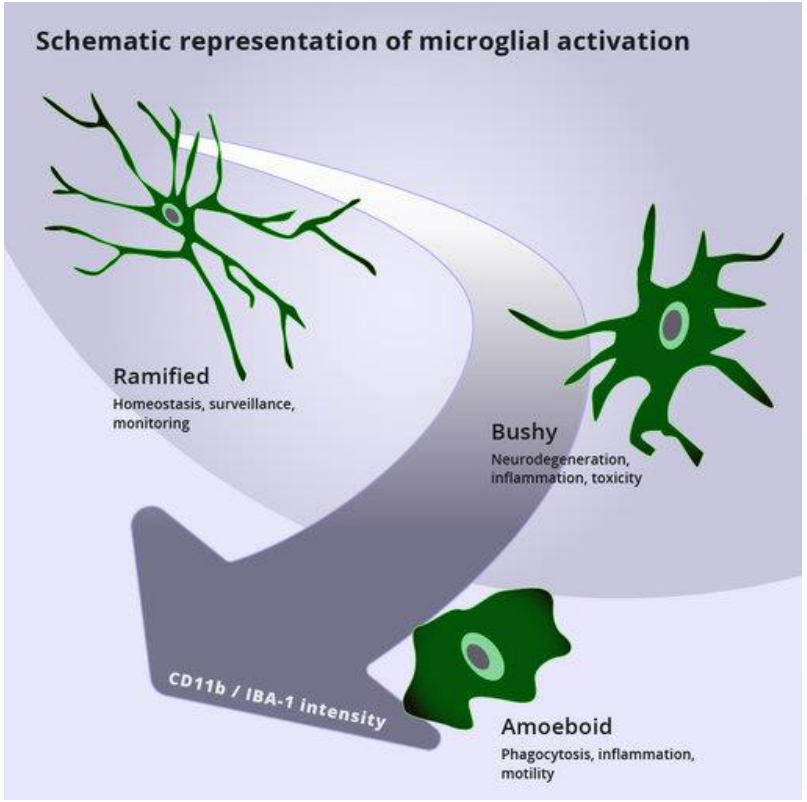
Edvinsson L, Cervos-Navarro J, Larsson LI, et al. Regional distribution of mast cells containing histamine, dopamine or 5-hydroxytryptamine in the mammalian brain. *Neurology*. 1977;27:878–884.

Theoharides TC, Donelan JM, Papadopoulou N, et al. Mast cells as targets of corticotropin-releasing factor and related peptides. *Trends Pharmacol Sci*. 2004;25:563–568.

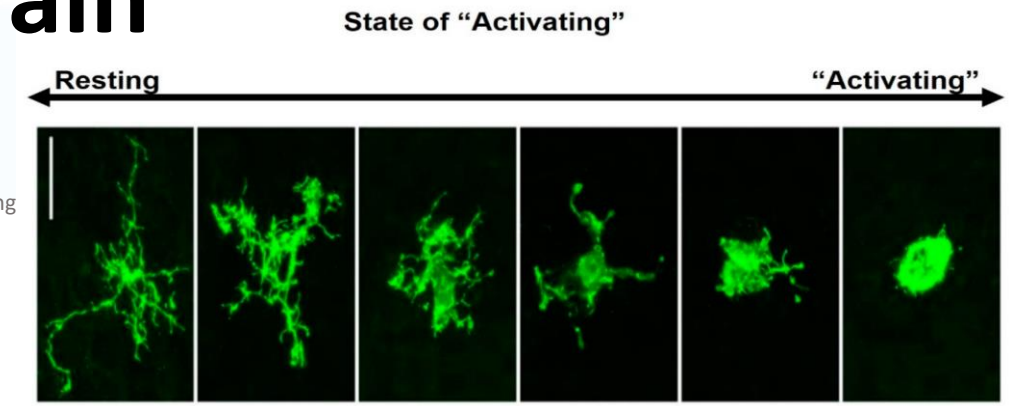
Theoharides, Theoharis C., et al. "Recent advances in our understanding of mast cell activation – or should it be mast cell mediator disorders?" *Expert Review of Clinical Immunology*, vol. 15, no. 6, 2019, pp. 639–656, https://doi.org/10.1080/1744666x.2019.1596800.

Theoharides TC. Neuroendocrinology of mast cells: challenges and controversies. *Exp Dermatol*. 2017;26:751–759. This paper reviews evidence of the responsiveness of mast cells to neuroendocrine triggers and their potential role in related diseases in the absence of allergies or MCMD.

Mast Cell Activation in the Brain



"CD11B - A Marker of Activated Microglia." *CD11b - a Marker of Activated Microglia*, sysy-histosure.com/CD11b-marker-of-activated-microglia. Accessed 30 Sept. 2023.



Rawlinson, Charlotte, et al. "Post-ischaemic immunological response in the brain: Targeting microglia in ischaemic stroke therapy." *Brain Sciences*, vol. 10, no. 3, 2020, p. 159, https://doi.org/10.3390/brainsci10030159.

- Activated mast cell mediators, such as histamine and tryptase, can also activate microglial cells in the brain
- These microglial cells, acting as part of the innate immune system, release their own proinflammatory mediators (IL-1β, IL-6, TNF)
- Microglial cell activation and neuroinflammation has been implicated in triggering neuroinflammation in multiple brain disorders, including ME/CFS and PASC

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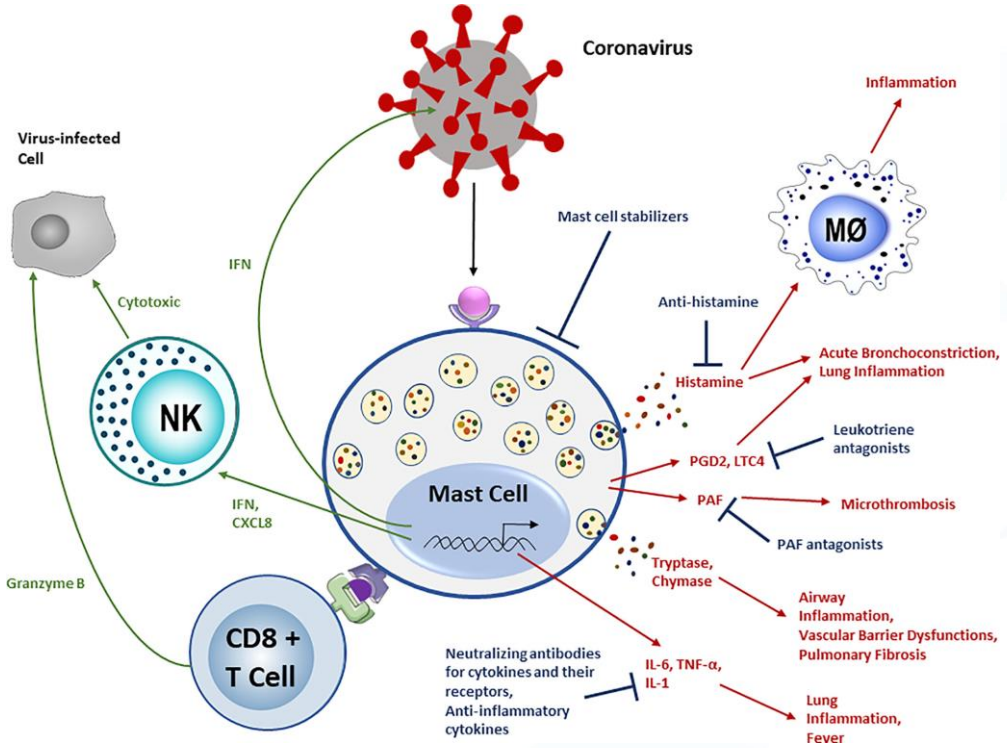
Estes ML, McAllister AK. Immune mediators in the brain and peripheral tissues in autism spectrum disorder. *Nat Rev Neurosci*. 2015;16:469–486.

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.

Zhang X, Wang Y, Dong H, et al. Induction of microglial activation by mediators released from mast cells. *Cell Physiol Biochem*. 2016;38:1520–1531.

Mast Cell Activation Syndrome & COVID-19



Lam, Hiu Yan, et al. "Mast Cells: Therapeutic targets for covid-19 and beyond." *IUBMB Life*, vol. 73, no. 11, 2021, pp. 1278–1292, https://doi.org/10.1002/iub.2552.

- Mast cells may serve as hosts for SARS-CoV-2 by expressing ACE2, an important receptor for this virus upon host cells
- Upon stimulation by SARS-CoV-2, masts cells rapidly secrete preformed granules as well as cytokines and chemokines within 6-24 hours

Mathias K, Mantha A, Mathias L, et al. POS1366 The Relationship of Mast Cell Activation Syndrome and Hypermobile Ehlers-Danlos Syndrome in Hospitalized Patients in the United States. *Ann Rheum Dis.* 2021;80:965. doi: 10.1136/annrheumdis-2020-219825.

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.

Theoharides TC. Potential association of mast cells with coronavirus disease. *Ann Allergy Asthma Immunol.* 2021;126(3):217–218. doi: 10.1016/j.anai.2020.11.003.

Valent P, Akin C, Bonadonna P, et al. Risk and management of patients with mastocytosis and MCAS in the SARS-CoV-2 (COVID-19) pandemic: expert opinions. *J Allergy Clin Immunol.* 2020;146(2):300–306. doi: 10.1916/j.jaci.2020.06.009.

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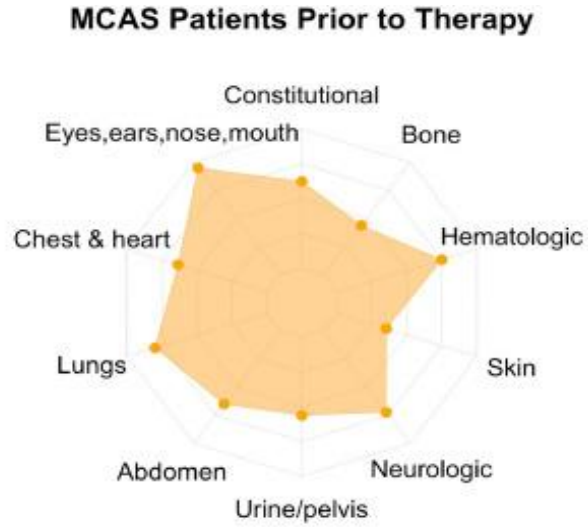
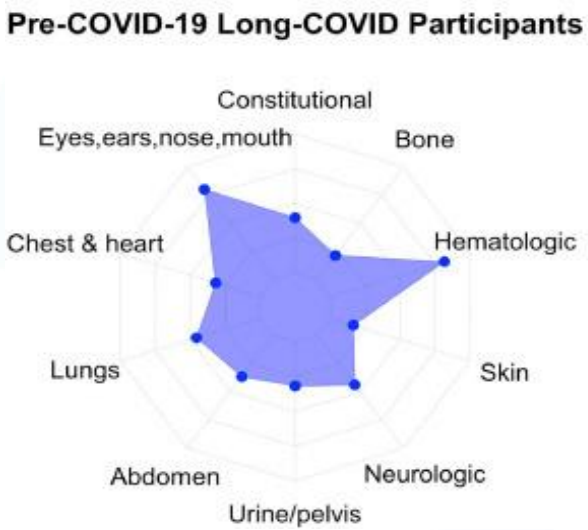
Mast Cell Activation Syndrome & COVID-19





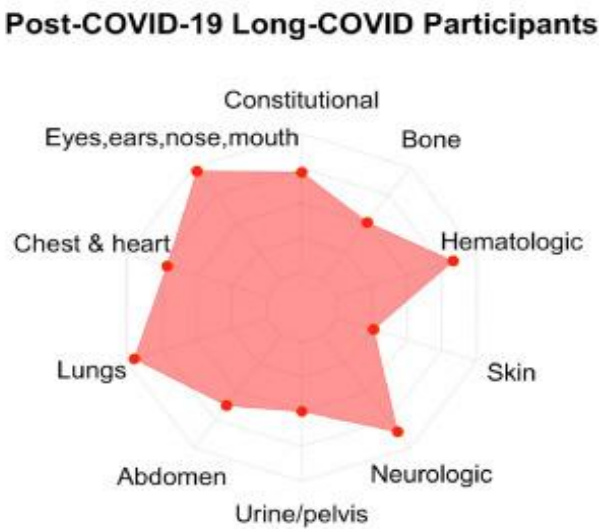


Figure 3

Spider web plots of mean mast cell mediator release syndrome scores.

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Mast cell activation symptoms are prevalent in Long-COVID. Leonard BW, Jill BB, Arthur SW et al. Int J Infect Dis. 2021 Nov. Epub 2021 Sep 23. PMID: 34563706

Mast Cell Activation Syndrome & COVID-19

- Vasoactive mediators from mast cells allow these cells to infiltrate multiple organs, including crossing the blood-brain barrier (beginning or trigger for “long-COVID”/PASC?)

- Pharmacotherapy used in mast cell related disorders has been found to be effective in reducing the severity of the both the acute viral illness caused by SARS-CoV2 as well as the incidence of Post-Acute Sequelae of COVID (PASC), also known as “long-COVID” when taken during and after acute infection

Mathias K, Mantha A, Mathias L, et al. POS1366 The Relationship of Mast Cell Activation Syndrome and Hypermobile Ehlers-Danlos Syndrome in Hospitalized Patients in the United States. *Ann Rheum Dis.* 2021;80:965. doi: 10.1136/annrheumdis-2020-219825.

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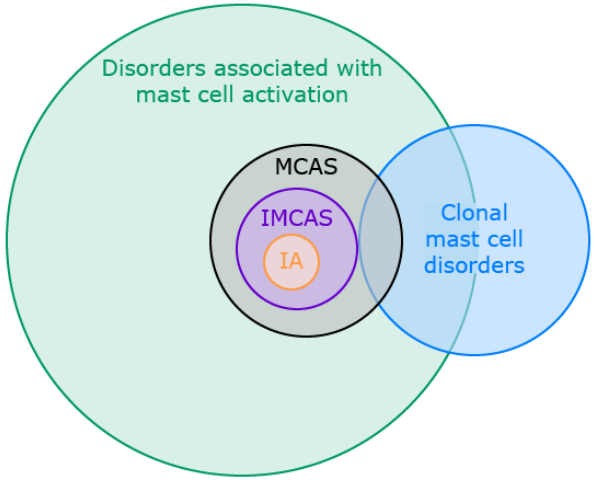
Other Clonal Mast Cell Disorders and Neoplasms

Abnormal Mast Cell Proliferation:

- Cutaneous Mastocytosis
- Systemic Mastocytosis
- Mast Cell Leukemia
- Mast Cell Sarcoma
- Mastocytosis associated with other hematological neoplasia

Mast cell disorders Venn diagram



This Venn diagram conceptualizes the relationship between different disorders that involve mast cell activation. The most general category consists of all disorders that are associated with mast cell activation, such as chronic spontaneous urticaria/angioedema, allergic reactions and anaphylaxis due to known allergens (foods, pollens, venom), and allergic asthma. MCAS is a rare and specific disorder in which patients (1) have signs and symptoms consistent with mast cell activation involving at least two organ systems, (2) have evidence of systemic mast cell-mediator release, and (3) respond to medications that counter these mediators. MCAS may be triggered by allergen-specific immunoglobulin E, physical factors, and medications. IMCAS is the same disorder without an identifiable allergen or other specific trigger. Patients with IA are a subset of those with IMCAS who fulfill the diagnostic criteria for anaphylaxis. Clonal mast cell disorders can present similarly to the other disorders of mast cell activation, but they are not idiopathic, because patients have a clonal mast cell population.

MCAS: mast cell activation syndrome; IMCAS: idiopathic mast cell activation syndrome; IA: idiopathic anaphylaxis.

Original figure modified for this publication. From: Akin C. Mast cell activation syndromes. J Allergy Clin Immunol 2017; 140:349. Illustration used with the permission of Elsevier Inc. All rights reserved.

WHO diagnostic criteria for cutaneous and systemic mastocytosis

Cutaneous mastocytosis (CM)
Skin lesions demonstrating the typical findings of urticaria pigmentosa/maculopapular cutaneous mastocytosis, diffuse cutaneous mastocytosis or solitary mastocytoma, and typical histologic infiltrates of mast cells in a multifocal or diffuse pattern in an adequate skin biopsy.* In addition, features/criteria sufficient to establish the diagnosis of systemic mastocytosis must be absent.[1-3] There are 3 variants of cutaneous mastocytosis (refer to UpToDate table on the classification of mastocytosis variants).
Systemic mastocytosis (SM)
The diagnosis of systemic mastocytosis can be made when the major criterion and at least 1 minor criterion are present, or when ≥3 minor criteria are present.
Criterion
Major criterion:
Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s).
Minor criteria:
1. In biopsy sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or >25% of all mast cells in bone marrow aspirate smears are immature or atypical. 2. Detection of an activating point mutation at codon 816 of *KIT* in the bone marrow, blood, or another extracutaneous organ. 3. Mast cells in bone marrow, blood, or another extracutaneous organ express CD25, with or without CD2, in addition to normal mast cell markers.¶ 4. Serum total tryptase is persistently >20 ng/mL, unless there is an associated myeloid neoplasm, in which case this parameter is not valid.

WHO: World Health Organization.

* This criterion applies to both the dense focal area and the diffuse mast cell infiltrates in the biopsy.

¶ CD25 is the more sensitive marker, by both flow cytometry and immunohistochemistry.

References:

1. *Hartmann K, Escribano L, Grattan C, et al. Cutaneous manifestations in patients with mastocytosis: Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. J Allergy Clin Immunol 2016; 137:35.*
2. *Valent P, Akin C, Escribano L, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. Eur J Clin Invest 2007; 37:435.*
3. *Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. Leuk Res 2001; 25:603.*

Reprinted with permission from: Horny HP, Metcalfe DD, Akin C, et al. Mastocytosis. In: WHO classification of tumours of haematopoietic and lymphoid tissues, revised 4th edition, Swerdlow SH, Campo E, Harris NL, et al (Eds), IARC, Copyright © 2017.

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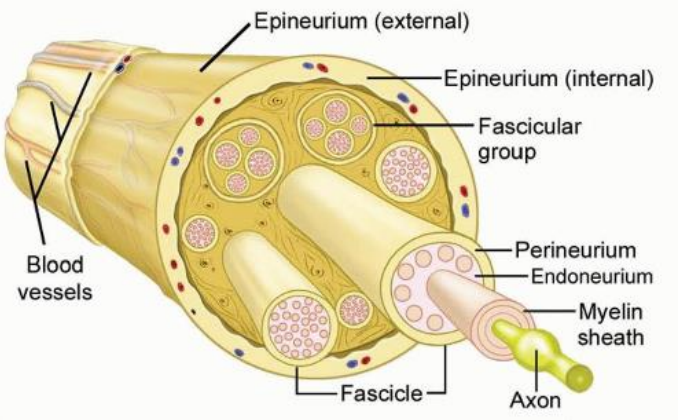
Jackson, Clayton Webster, et al. "Mastocytosis and mast cell activation disorders: Clearing the Air." *International Journal of Molecular Sciences*, vol. 22, no. 20, 2021, p. 11270, https://doi.org/10.3390/ijms222011270.

UpToDate, www.uptodate.com/contents/mast-cell-disorders-an-overview#! Accessed 30 Sept. 2023.

Neurological and Spinal Manifestations of EDS Syndromes:

- Incompetent connective tissues may result in laxity of ligaments within the axial skeleton, peripheral nerve sheaths, and even architecture of myoneural and muscular endplates
- Neurological manifestations may arise from associated weakness of the ligaments of the craniocervical junction and spine, from early disc degeneration, and from weakness of the epineurium and perineurium surrounding peripheral nerves
- Ligamentous laxity, in particular, leads to nerve structure entrapment, deformation, of biophysical deformative stresses
- These stresses may then contribute to secondary altered gene expression, cellular function, neuronal function, and phenotypic expression



Themes, UFO. "Surgical Treatment of Nerve Tumors in the Distal Upper Extremity." *Musculoskeletal Key*, 22 July 2016, musculoskeletalkey.com/surgical-treatment-of-nerve-tumors-in-the-distal-upper-extremity/.

Disclaimer:

- Authors of this study represent a working group within the International Consortium on the Ehlers-Danlos Syndromes
- Consensus Criteria and clinical practice guidelines will still require stronger epidemiological and pathophysiological evidence in the future

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Henderson, Fraser C., Claudiu Austin, et al. "Neurological and spinal manifestations of the Ehlers–danlos syndromes." *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, vol. 175, no. 1, 2017, pp. 195–211, https://doi.org/10.1002/ajmg.c.31549.

Neurological and Spinal Manifestations of EDS Syndromes:

- Headache
- Migraine
- Idiopathic Intracranial Hypertension (IIH)
- Chiari 1 Malformations
- **Craniocervical Instability (CCI)**
- **Atlantoaxial Instability (AAI)**
- Spinal Kyphosis and Instability
- **Acquired/Occult Tethered Cord Syndrome**
- Dystonias and Other Movement Disorders
- Tarlov Cyst Syndrome

Abnormal neuromuscular features

- Myalgia
- Nocturnal Muscle Cramping
- Progressive Muscle Weakness
- Hypotonia
- Poorly Developed Muscles
- Scapular Winging

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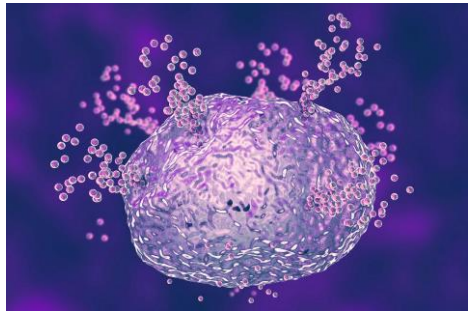
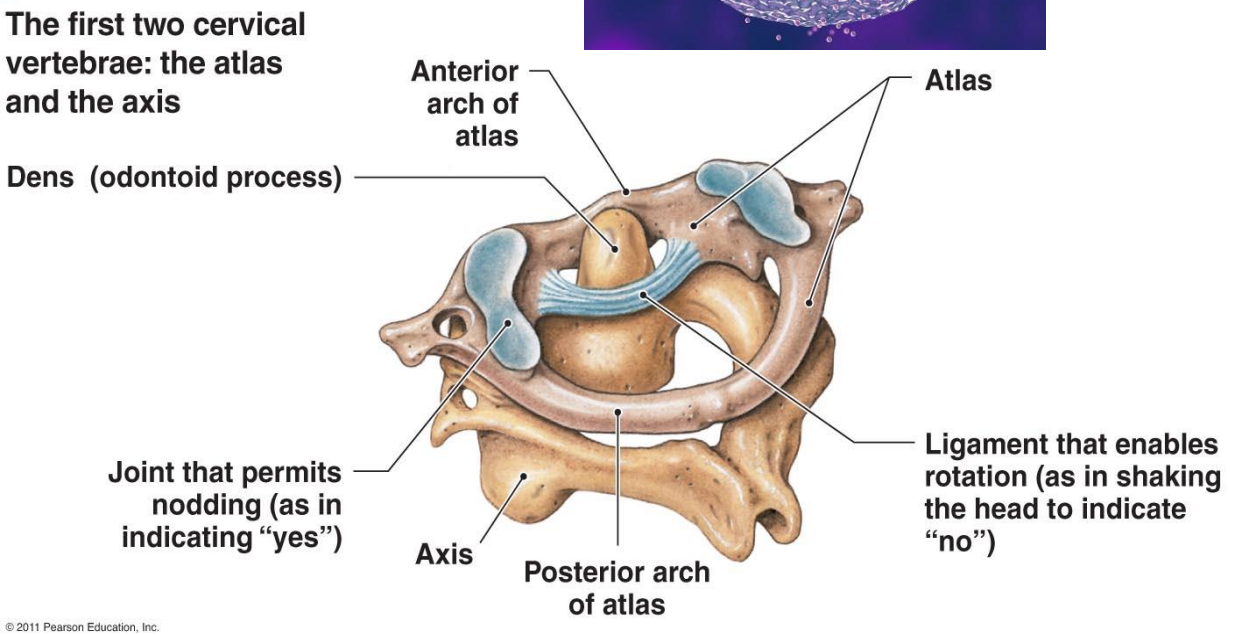
Henderson, Fraser C., Claudiu Austin, et al. "Neurological and spinal manifestations of the Ehlers–danlos syndromes." *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, vol. 175, no. 1, 2017, pp. 195–211, https://doi.org/10.1002/ajmg.c.31549.

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

- Manifestation of incompetence or hyperlaxity of ligamentous and bony elements supporting the cervical spine and the craniocervical junction (C0-C1, C1-C2), leading to increased motion at these sites
- While CCI traditionally thought to arise from neck trauma, abnormalities in expression, structure, function of the fibrillar collagen can lead to this ligamentous incompetence or hyperlaxity, leading to increased mobility at these joints
- Postulated that collagen or ligamentous incompetence may also be triggered by or accelerated by inflammation related to mast cell activation (needs more research)

"About Mast Cell Activation Syndrome (MCAS)." *Chiari Bridges*, 28 Oct. 2022, chiaribridges.org/about-mcas/.





Larsen, Kjetil. "Atlas Joint Instability: Causes, Consequences and Solutions." *MSK Neurology*, 27 Sept. 2023, mskneurology.com/atlas-joint-instability-causes-consequences-solutions/.

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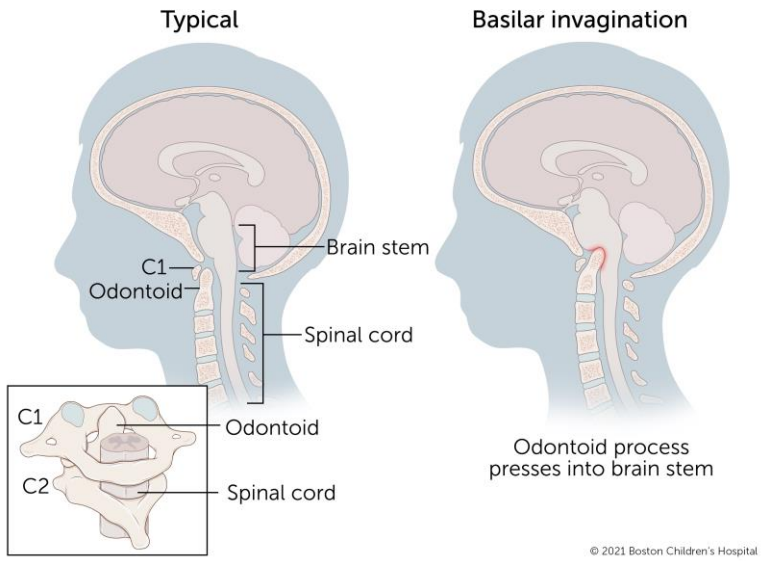
"Craniocervical Instability & Surgical Treatment." *Dr. Gilete*, 14 June 2023, drgilete.com/craniocervical-instability-ehler-danlos/.
Henderson, Fraser C., Claudiu Austin, et al. "Neurological and spinal manifestations of the Ehlers–danlos syndromes." *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, vol. 175, no. 1, 2017, pp. 195–211, https://doi.org/10.1002/ajmg.c.31549

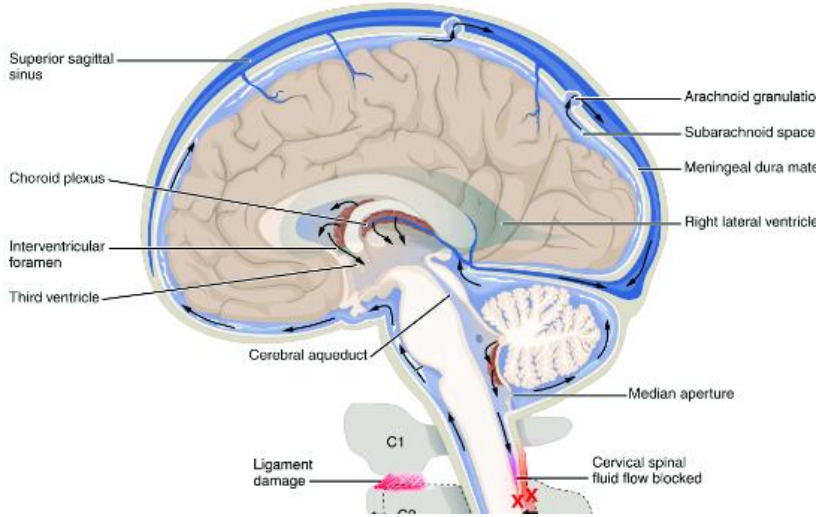
Craniocervical Instability (CCI)/Atlantoaxial Instability (AAI) (M53.2X2)



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

- Increased mobility/instability can precipitate deformation of the brainstem or upper spinal cord, including ventral brain stem compression and basilar invagination
- Increased mobility/instability can also create traction on the vertebral artery or alter venous or CSF outflow from the cranium

Caring Medical, www.caringmedical.com/prolotherapy-news/chronic-cerebrospinal-venous-insufficiency/. Accessed 1 Oct. 2023.



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"Craniocervical Instability & Surgical Treatment." *Dr. Gilete*, 14 June 2023, drgilete.com/craniocervical-instability-ehler-danlos/.
Henderson, Fraser C., Claudiu Austin, et al. "Neurological and spinal manifestations of the Ehlers–danlos syndromes." *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, vol. 175, no. 1, 2017, pp. 195–211, https://doi.org/10.1002/ajmg.c.31549

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

- Increasing recognition of the formation of **axon retraction balls/bulbs** as a result of stretching or deformative stress injury upon neurons
- Similar to findings seen in diffuse axonal injury of the brain
- Stretching of neurons causes pathological calcium influx, altered gene expression, even apoptosis

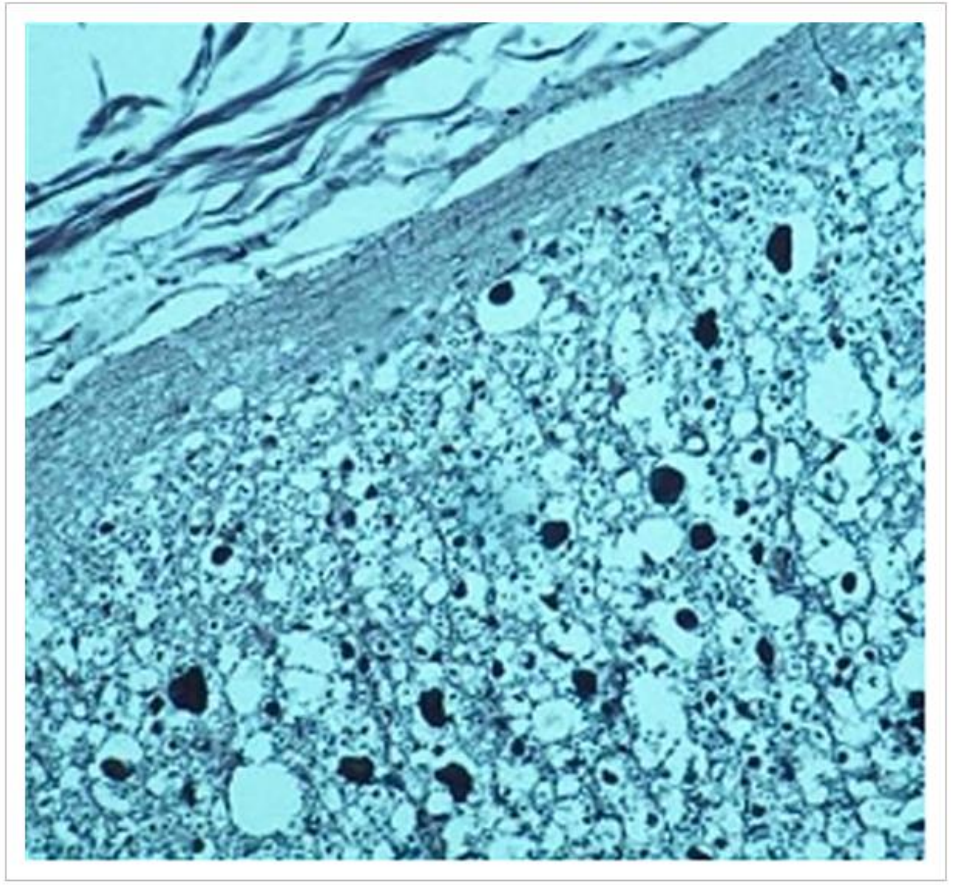

Figure 2 Open in figure viewer | PowerPoint

Axon retraction bulbs in the upper spinal cord, from cadaveric studies of subjects with basilar invagination (Microscopic photograph (×500), axial section of the dorsal column at the C2 level. Silver stain).

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American J of Med Genetics Pt C, Volume: 175, Issue: 1, Pages: 195-211, First published: 21 February 2017, DOI: (10.1002/ajmg.c.31549)
Henderson, Fraser C., Claudiu Austin, et al. "Neurological and spinal manifestations of the Ehlers–danlos syndromes." *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, vol. 175, no. 1, 2017, pp. 195–211, https://doi.org/10.1002/ajmg.c.31549

Symptoms: Cervical Medullary Syndrome (M53.2X2)

- Headaches
- Neck Pain
- Diplopia
- Dizziness/Syncope
- Vertigo
- Memory Loss
- Tinnitus/Altered Hearing
- Dysphagia
- Dysphonia/Speech Difficulties
- Altered Vision

- Numbness/Paresthesias in Arms or Legs
- Weakness in Arms or Legs
- Choking/Aspirating on Food
- Emesis
- Frequent Awakening
  Snoring
  Sleep Apnea
- Ataxia/Gait Changes
- Altered Sexual Function
- Altered Menses

"Craniocervical Instability & Surgical Treatment." *Dr. Gilete*, 14 June 2023, drgilete.com/craniocervical-instability-ehler-danlos/.
Henderson, Fraser C., Claudiu Austin, et al. "Neurological and spinal manifestations of the Ehlers–danlos syndromes." *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, vol. 175, no. 1, 2017, pp. 195–211, https://doi.org/10.1002/ajmg.c.31549

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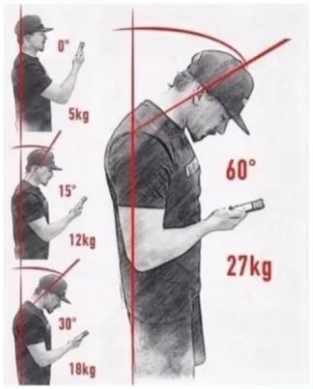
CCI/AAI Diagnosis (Functional) (M53.2X2)

Functional Assessment:

- Prolonged trial of upright cervical stabilization
- Upright Cervical traction
- Deep Water Traction



May Improve:

- Headaches
- Brain Fog
- Fatigue
- Vertigo
- Nausea
- GI Motility
- Gait/Balance/Coordination
- Extremity Weakness
- Dysphagia/Dysarthria
- Sensory Sensitivity

May Trigger:

- Nausea
- Headaches
- Muscle Spasm/Dystonia
- Post-Exertional Malaise (PEM)

Traction can elucidate occult symptoms of tethered cord syndrome:

- Urinary Symptoms
- Low Back Pain
- Lower Extremity Weakness/Pain
- Gait Disturbance
- Inability to lay down without hip/knee flexion

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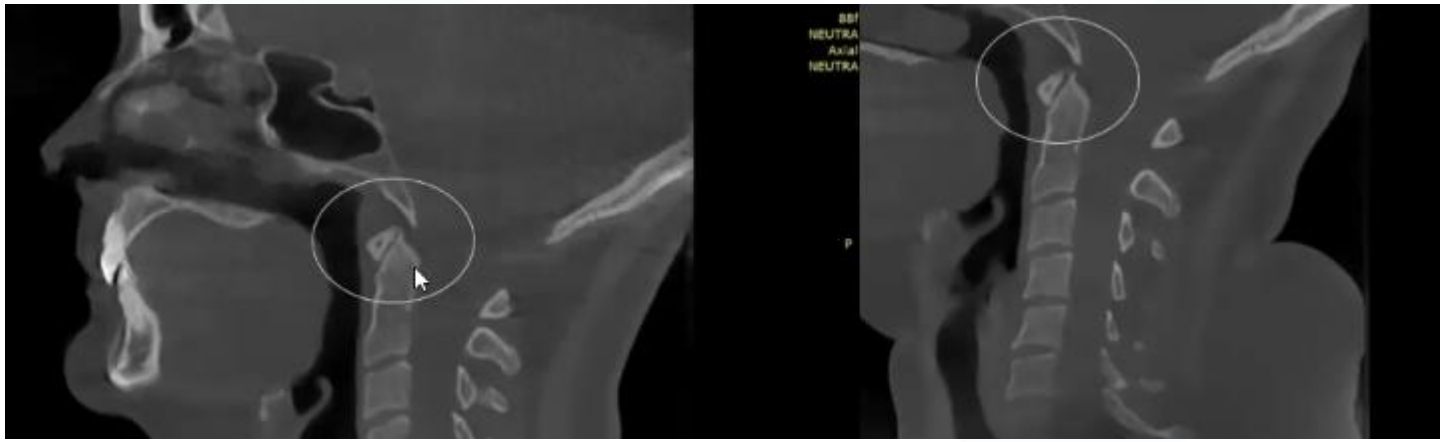
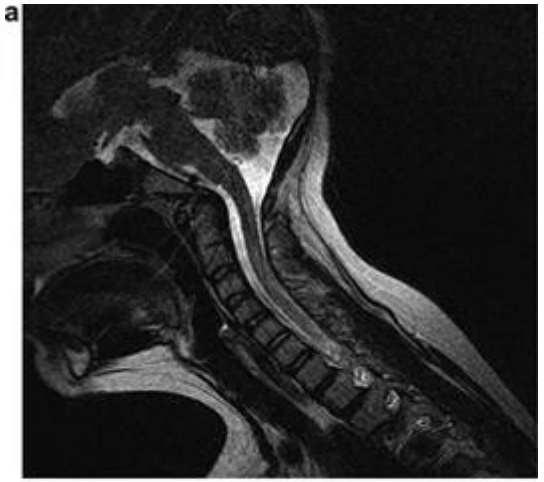
CCI/AAI Diagnosis: Imaging (M53.2X2)

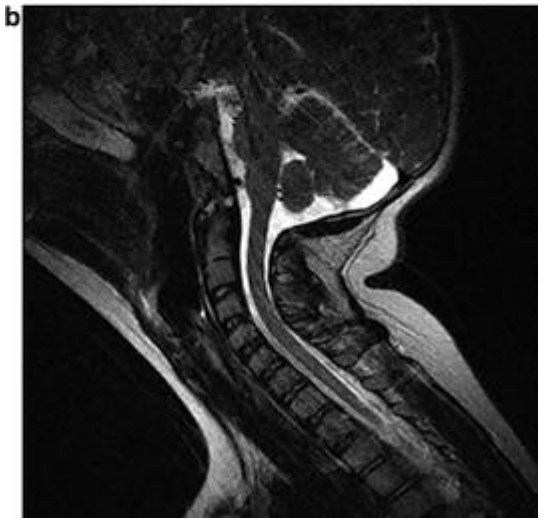
Imaging Assessment:

- Upright imaging >supine imaging, as effect of gravity upon unstable anatomy key to identifying CCI/AAI
- Dynamic flexion/extension views also critical to identifying pathological anatomy based upon positioning
- Imaging centers often unfamiliar with imaging protocols and correct positioning
- Very few radiologists/neurosurgeons trained in appropriate evaluation for these conditions





a: The craniocervical junction in flexion, showing a forward slide of the basion with respect to the odontoid (Sagittal view, T2 weighted MRI of the cervical spine in flexion).



b: In extension, the basion lies along the posterior edge of the odontoid process, demonstrating a translation of 6 mm from flexion to extension (Sagittal view, T2 weighted MRI cervical spine).

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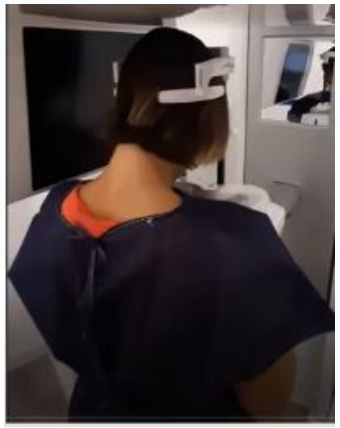
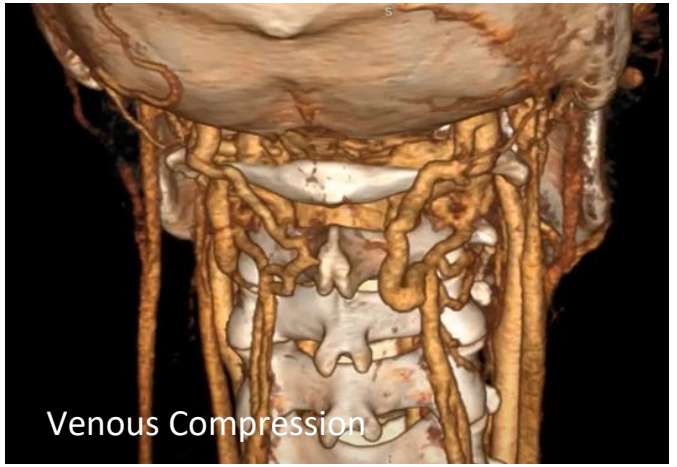
CCI/AAI Diagnosis: Imaging (M53.2X2)

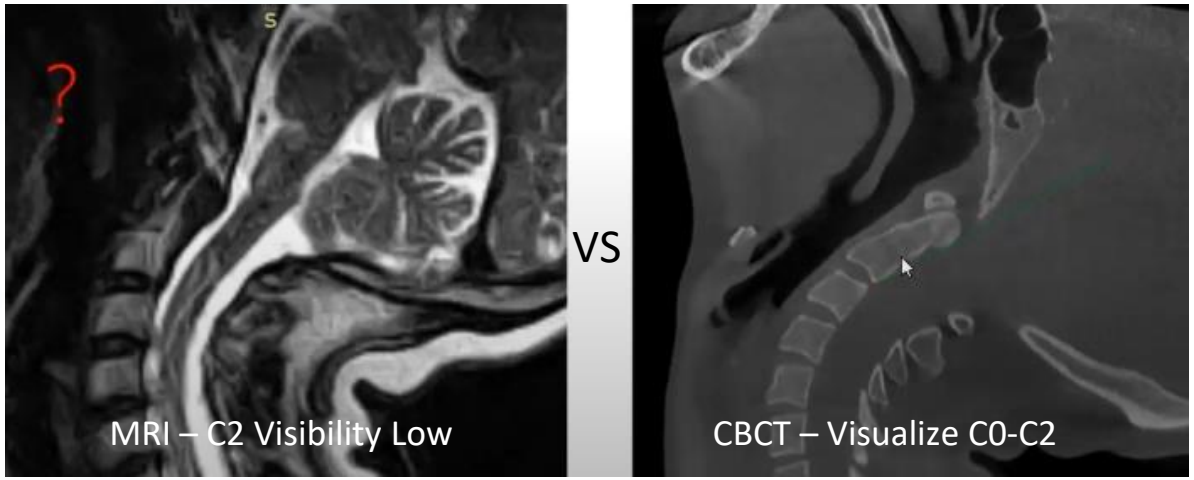
Imaging Assessment:

- Upright Brain/C-Spine MRI with flexion/extension
- 3T MRI brain/C-Spine MRI with flexion/extension
- Upright Cone Beam CT (CBCT) C-spine with flexion/extension
- Rotational CT-Scan (supine, limit to C0-C4)
- 3T MRA/MRV of head/neck
- Additional screening for tethered cord syndrome

❖ Formal ophthalmological exam to rule out papilledema and IIP is important







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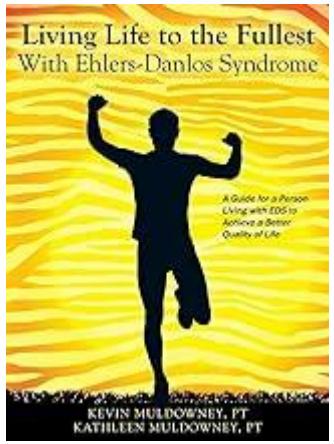
CCI/AAI Management/Treatment (M53.2X2)

Conservative Management:

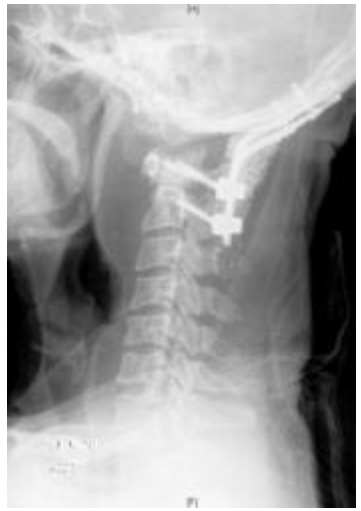
- Muldowney Protocol PT
- Specialized PT from hEDS expert
- Upright Cervical Traction/Support
- Avoid exacerbating factors (botox, muscle relaxants, activities with significant cervical motion)

Surgical (C0-C2) Fusion:

- Surgery is complex with many risks
- Post-operative care challenging
- Lack of cervical mobility can be disabling to some
- Complications can include infection, CSF leak/fistula, vertebral artery damage, hardware failure, other vertebral instability, worsening of bowel/bladder function via tethered cord exacerbation (filum terminale tethering or tightness



Surgery NOT A CURE for ME/CFS or all co-morbidities related to EDS, though it can significantly reduce symptom burden.



C1-C2 stabilization by harms arthrodesis: Indications, technique, complications and outcomes in a prospective 26-case series

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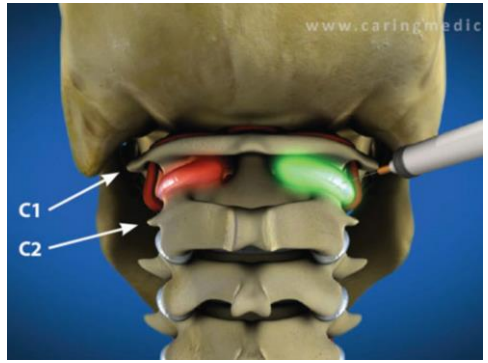
CCI/AAI Management/Treatment (M53.2X2)

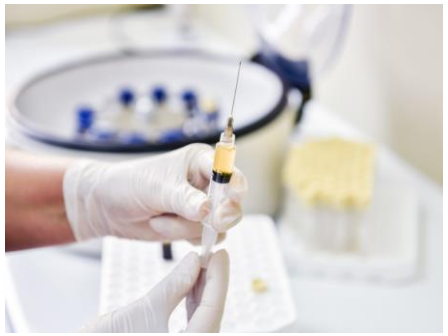
<u>Lack of Peer-Reviewed Data for Regenerative Therapies Such As</u>:

- Prolotherapy - Dextrose injections promote inflammatory response in injected ligaments that "strengthens" ligaments

- Platelet-Rich Plasma – Concentrated platelet solution injections and related growth factors thought to stimulate muscle and ligament healing

- Posterior Stem Cell Therapy/Percutaneous Implantation of the CCJ Ligaments (PICL) – Autologous stem cell injections into anterior or posterior ligaments as indicated to promote tissue integrity





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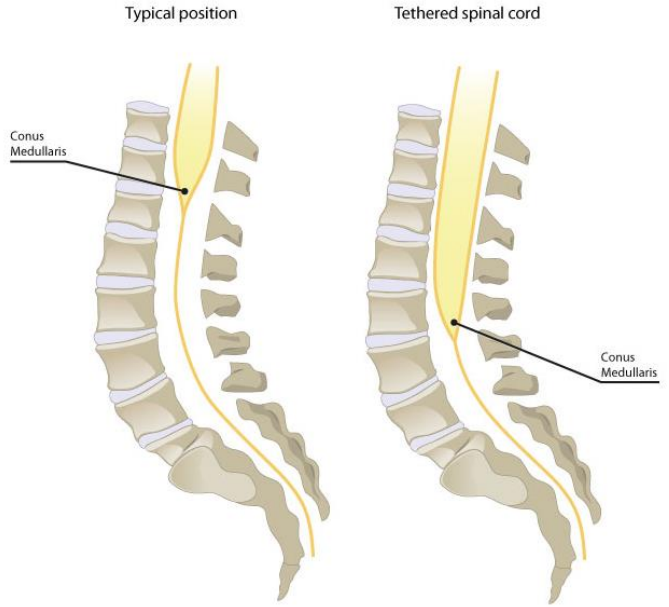
"Regenerative Medicine for Craniocervical Instability." *Craniocervical Instability Fund*, cci-fund.com/craniocervical-instability/treatment/regenerative-medicine/. Accessed 1 Oct. 2023.

Acquired/Occult Tethered Cord Syndrome (G95.89)

- Anatomical restriction of the normal movement of the spinal cord via the filum terminale “tightening” or “tethering” abnormally
- A healthy filum is a fibrous, collagenous, and elastic band connecting the conus medullaris to the dural sac at the s2 level
- Filum appears to be morphologically altered with fatty tissue, dysplastic axons (“nerve twigs”), fat and vascular lacunes, or even “congested” veins
- Pathology thought to be from forcible flexion stretching of the spinal cord against the filum causing tissue damage and repair, inflammation (MCAS?), and/or altered gene expression



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/.

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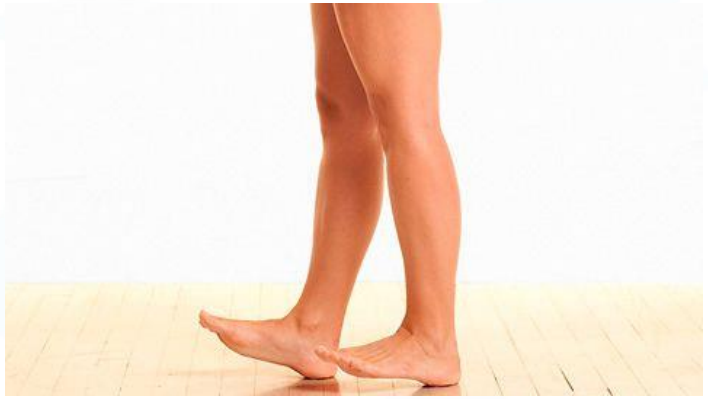
Tethered Cord Syndrome: Symptoms (G95.89)

Classic Triad:

- Neurogenic Bladder
- Lower Extremity Weakness and Sensory Loss
- Lower Back Pain



- Unsteady gait
- Loss of lower extremity sensation
- Pain (often migratory) in lower extremities
- Urinary frequency/urgency
- Frequent UTI's
- Dysuria
- Urinary retention
- Gastrointestinal problems/dysfunction
- Lower back pain
- Pulling sensation (brain, upper spine, sacral)
- Suboccipital pain/pressure
- Toe Walking/Inability to Heel-Walk

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"Craniocervical Instability & Surgical Treatment." *Dr. Gilete*, 14 June 2023, drgilete.com/craniocervical-instability-ehler-danlos/.
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Acquired/Occult Tethered Cord Syndrome (G95.89)

Table 1. Transmission Electron Microscopy Findings of the Filum Terminale

	hEDS-TCS (n= 78)	TCS (n= 10)	Chi-Square with Bonferroni Correction
Congenital collagen abnormalities			
Fibril disorganization	69.6%	10.0%	$P < 0.001$
Variation in fibril diameter in cross section	40.5%	11.1%	$P < 0.001$
Acquired collagen microdamage			
Kinking fibrils	63.3%	30.0%	$P < 0.05$
Loss of D-period banding	68.4%	30.0%	$P < 0.01$

The filum ultrastructure of the EDS-TCS and typical TCS cases was evaluated in longitudinal and cross sections. Markers of EDS collagen structural abnormalities such as fibril disorganization and variation in fibril diameter in cross section were assessed as well as markers of collagen microdamage such as kinking fibrils and loss of D-period banding.

hEDS, hypermobile Ehlers-Danlos syndrome; TCS, tethered cord syndrome.

- hEDS patients frequently present with symptoms of tethered cord syndrome without the “traditional” finding of a low-lying conus medullaris
- Morphological and biomechanical testing of the filum terminale in 78 hEDS patients indicated limited elastic properties, exposing the conus medullaris to non-physiologic stretch forces. Findings compared to 38 cases of low-lying conus TC without hEDS.
- Perhaps hEDS patients may benefit from filum terminale excision even in the absence of a radiographic low-lying conus medullaris

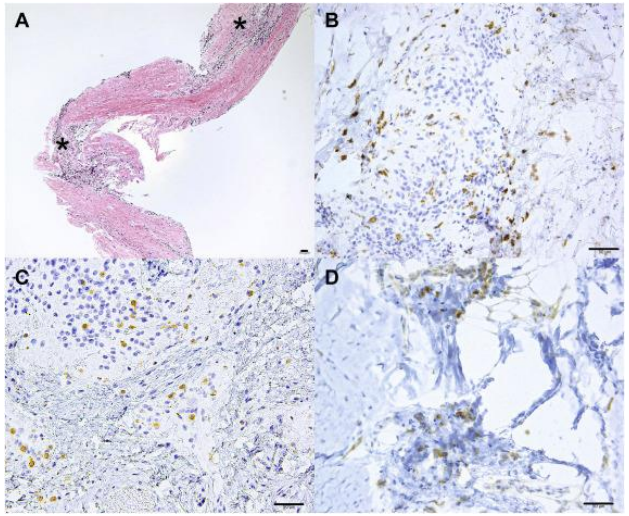

Figure 2. (**A**) Representative hematoxylin-eosin stain of the filum terminale at lower magnification showing regions of dense cellularity *(asterisks).* Areas examined in hypermobile Ehlers-Danlos syndrome specimens with immunohistochemistry confirmed local inflammation. Common leucocyte marker CD45 (**B**), markers of microglial (CD68, **C**), and immunologically activated mast cells (CD117, **D**) were applied.

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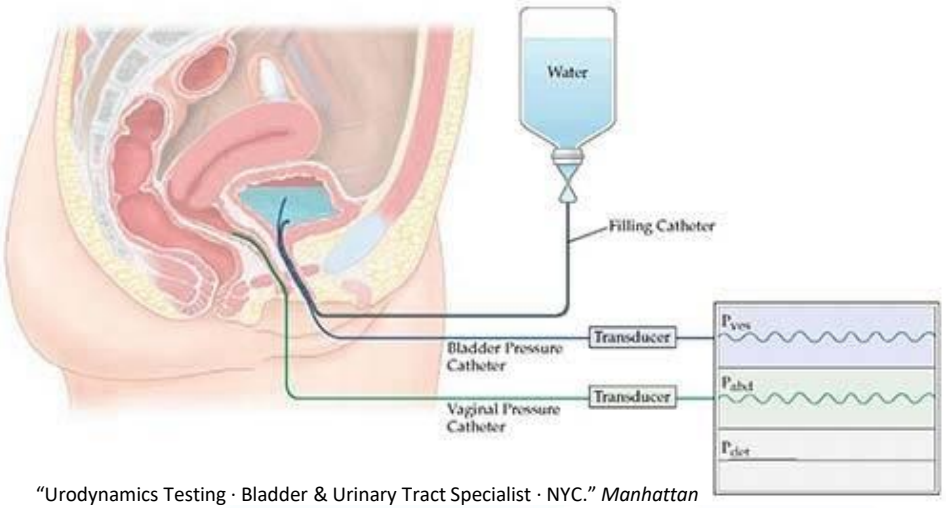
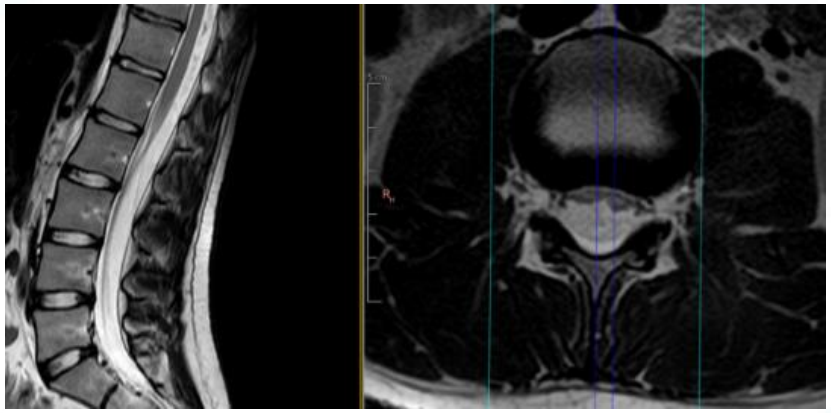
Tethered Cord Syndrome: Diagnostics (G95.89)



"Urodynamics Testing · Bladder & Urinary Tract Specialist · NYC." *Manhattan Gynecologists & Best Rated OBGYN Specialists in NYC*, 23 Sept. 2023, www.obgynecologistnyc.com/procedures/urodynamics/.



- **Urodynamic Testing** to evaluate for neurogenic bladder manifestations
- **Somatosensory and Motor Evoked Potentials**
- **3T Prone/Supine L-spine MRI** (specific protocol not done at most imaging centers)

Remember: normal supine MRI usually not adequate for evaluation. Few currently doing appropriate evaluations.

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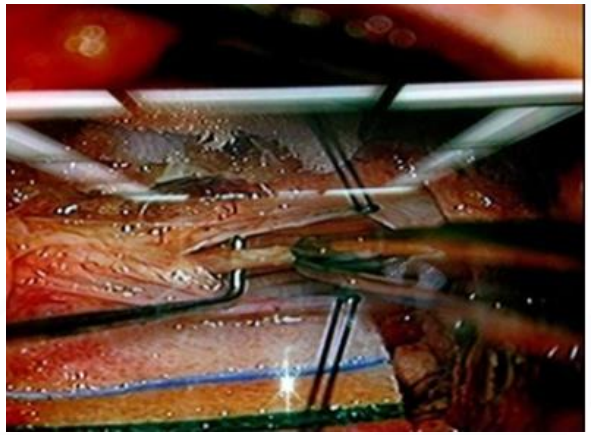
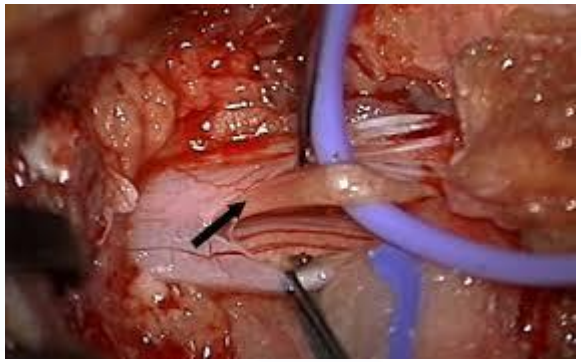
Tethered Cord Syndrome: Treatment (G95.89)

- Surgical detethering is a viable option for those presenting with moderate to severe symptoms and radiographic findings

- Some cases can retether again over time
  - Continued abnormal forces from CCI/AAI?
  - MCAS or other inflammation?
  - Surgical “Gore-Tex” to help prevent retethering





Agarwalla, Pankaj K., et al. “Tethered cord syndrome.” *Neurosurgery Clinics of North America*, vol. 18, no. 3, 2007, pp. 531–547, https://doi.org/10.1016/j.nec.2007.04.001.

- The filum terminale could be part of a sensorimotor system involved in spinal alignment, sensing non-physiological stretch forces from excessive spinal movements

- As such, the filum terminale could be acting as a stabilization syndrome in some cases of CCI/AAI

- Surgical detethering could thus expose or exacerbate existing CCI/AAI, but could also allow for improved clinical response to cervical traction

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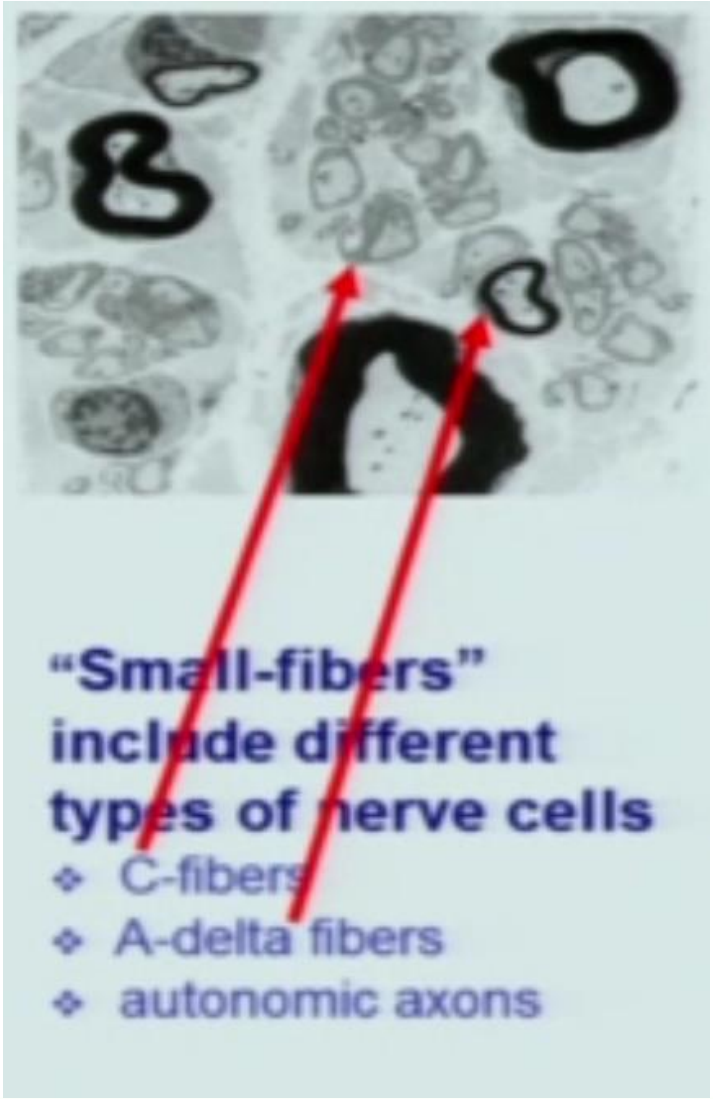
Small Fiber Polyneuropathy (SFPN) (G62.89)

<u>Small Fiber Nerves</u>:

- Small unmyelinated sensory afferent C-fibers
- Thinly myelinated A-delta fibers
- Post-ganglionic, sympathetic autonomic axons

These nerves are small diameter fibers that innervate most organs and tissues.



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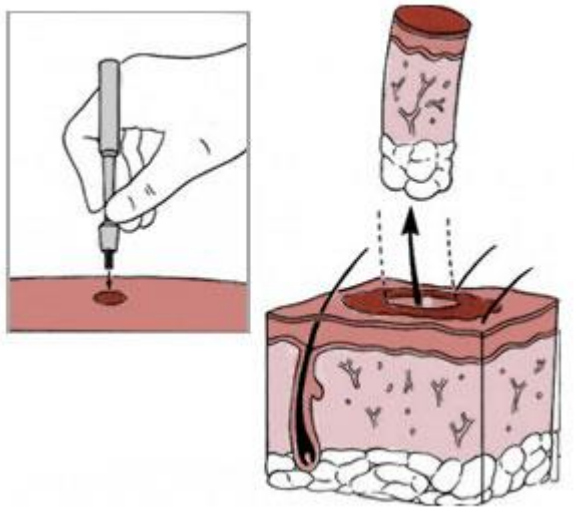
Oaklander AL, Nolano M. Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy: A Review. *JAMA Neurol.* 2019;76(10):1240–1251. doi:10.1001/jamaneurol.2019.2917

Small Fiber Polyneuropathy (SFPN) (G62.89)

Gold-standard for diagnosis is a 3 mm punch biopsy of the lower leg, as all epidermal nerve fibers are small fibers.

EMG/NCS and formal neurologic exams are not sensitive for the detection of small fiber polyneuropathy.



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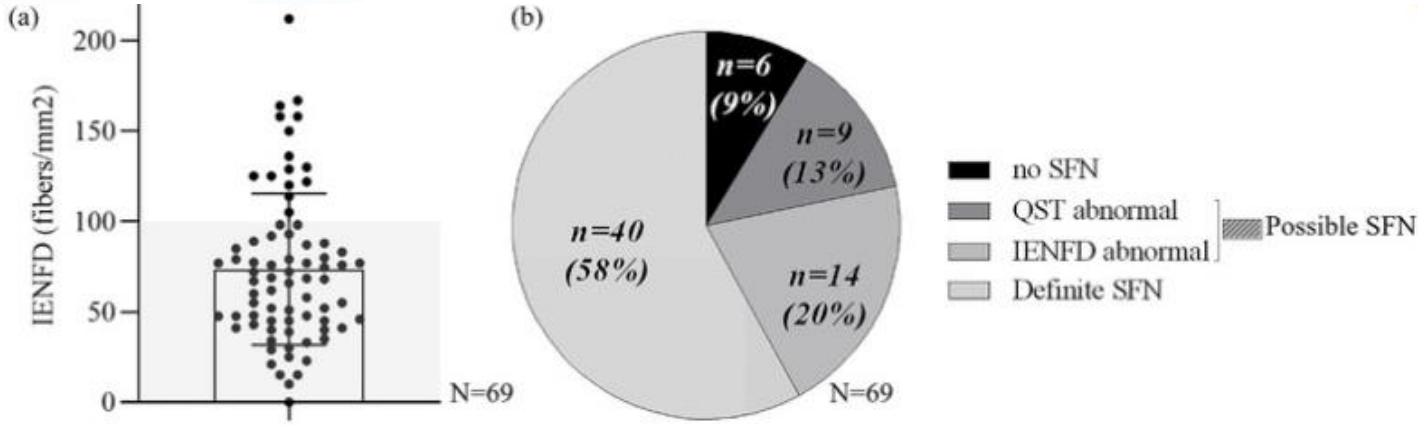
Small Fiber Polyneuropathy (SFPN) (G62.89)

- 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 for 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)

- 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

“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.

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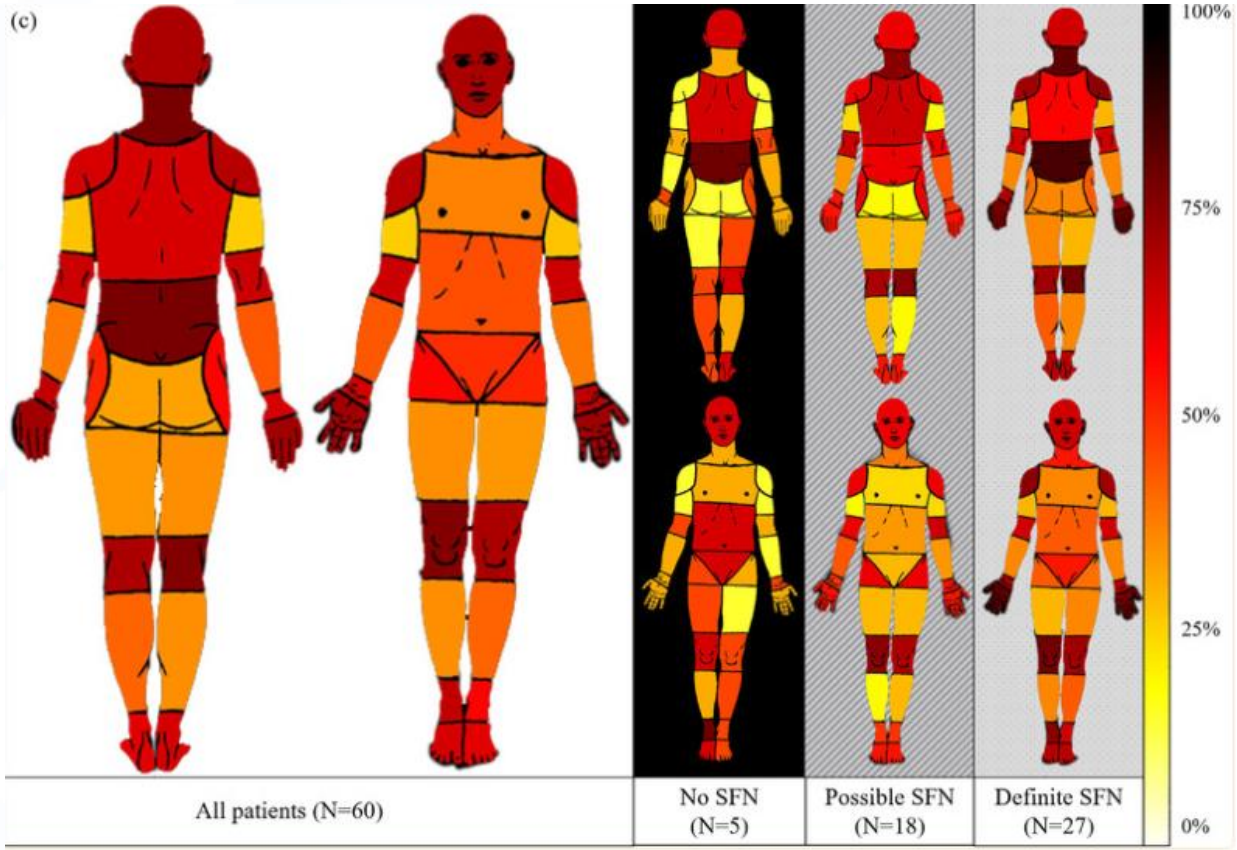
- Additional 23/69 (33%) of patients met one of the two criteria, leaving only 9% without signal for SFPN



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.

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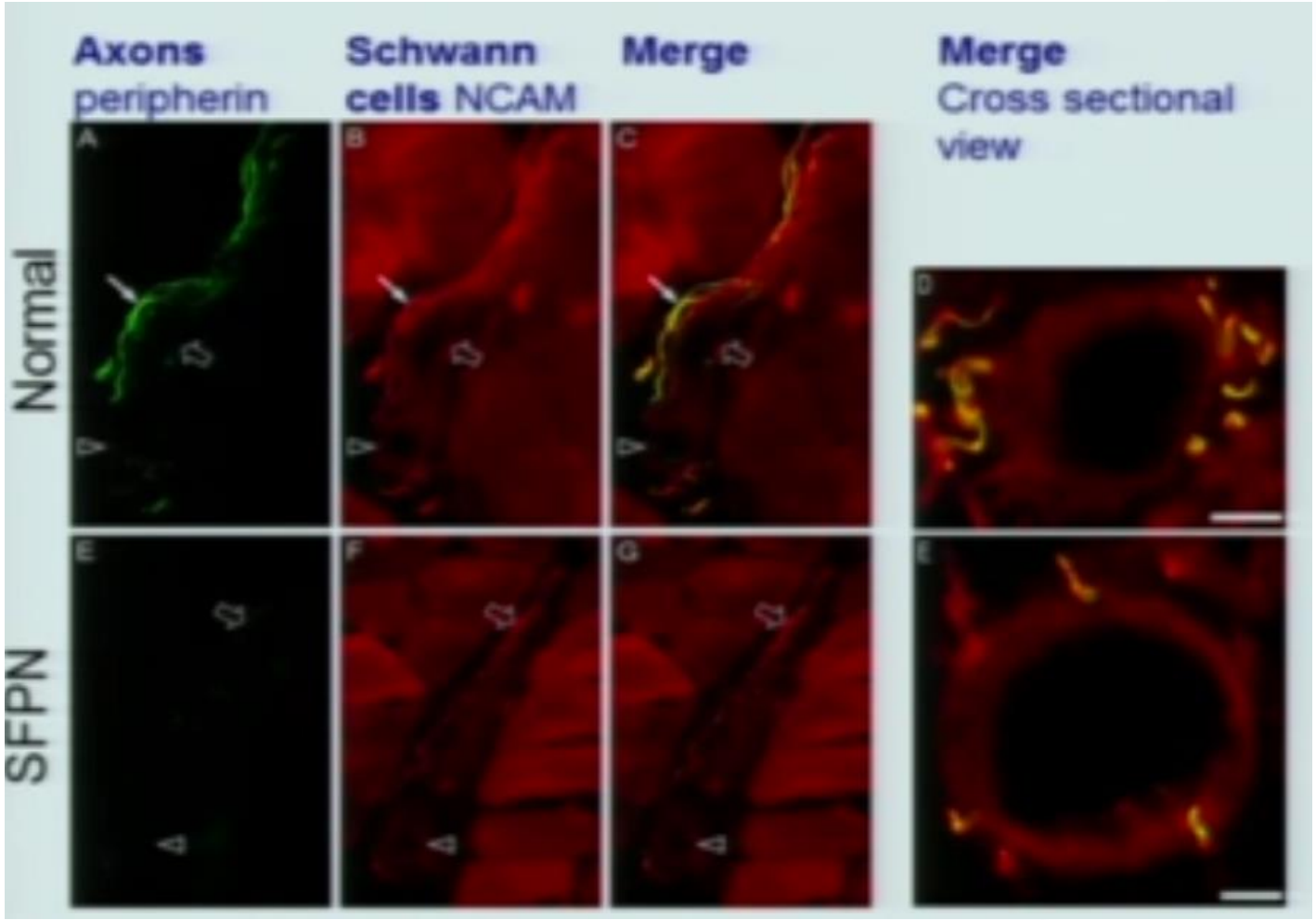
“Fernandez, Aurore, et al. “Small fiber neuropathy in hypermobile Ehlers Danlos syndrome/hypermobility spectrum disorder.” *Journal of Internal Medicine*, vol. 292, no. 6, 2022, pp. 957–960, https://doi.org/10.1111/joim.13539.

Small Fiber Polyneuropathy (SFPN) (G62.89)



Loss of axon innervation of myovascular structures in small fiber neuropathies

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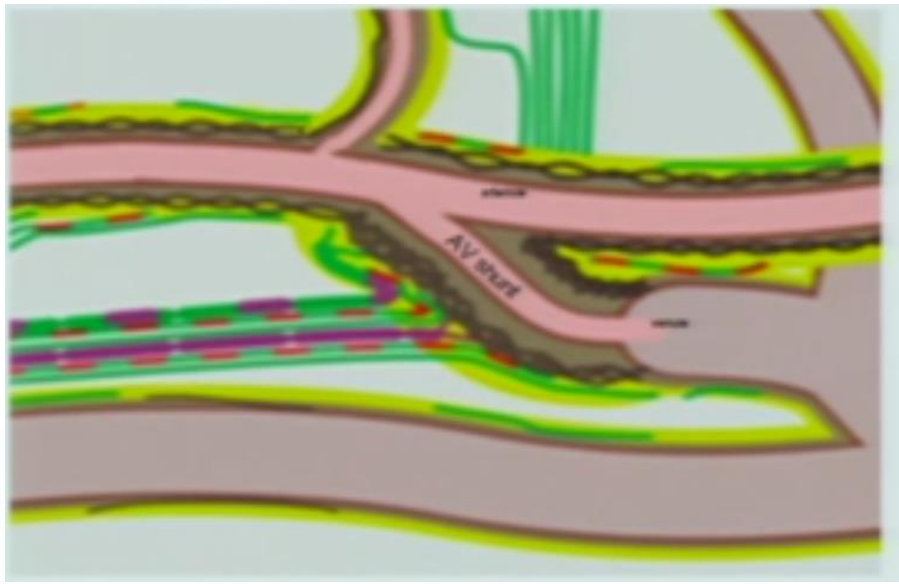
Dori, A., Lopate, G., Keeling, R. and Pestronk, A. (2015), Myovascular innervation: Axon loss in small-fiber neuropathies. Muscle Nerve, 51: 514-521. doi:10.1002/mus.24356

Small Fiber Polyneuropathy (SFPN) (G62.89)

- Loss of myovascular innervation can result in vessel patency that leads to arteriovenous shunting of blood.
- Capillary beds can be entirely bypassed in this distal "left to right" shunt.



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Phillip J. Albrecht, PhD, Quanzhi Hou, MD PhD, Charles E. Argoff, MD, James R. Storey, MD, James P. Wymer, MD PhD, Frank L. Rice, PhD, Excessive Peptidergic Sensory Innervation of Cutaneous Arteriole–Venule Shunts (AVS) in the Palmar Glabrous Skin of Fibromyalgia Patients: Implications for Widespread Deep Tissue Pain and Fatigue, *Pain Medicine*, Volume 14, Issue 6, June 2013, Pages 895–915

Small Fiber Polyneuropathy (SFPN) (G62.89)

Autonomic Functions of Small Fiber Nerves:

- Heart rate response to **deep breathing**
- Heart rate and blood pressure response to **Valsalva**
- Heart rate and blood pressure response to **tilt**
- Sudomotor **(sweat)** response
- **Gastrointestinal** functions

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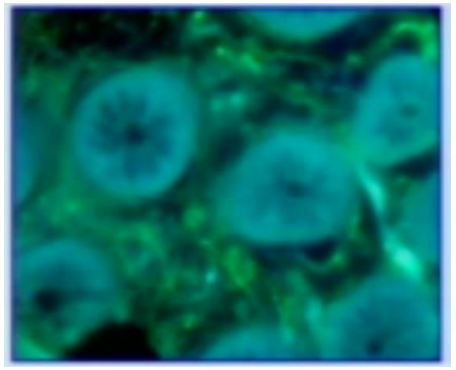
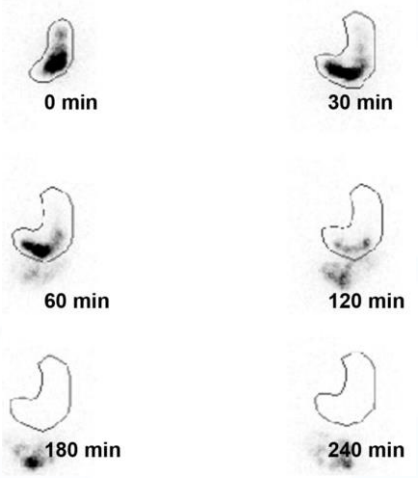
Oaklander AL, Nolano M. Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy: A Review. *JAMA Neurol.* 2019;76(10):1240–1251. doi:10.1001/jamaneurol.2019.2917

Small Fiber Polyneuropathy (SFPN) (G62.89)





The gut is densely innervated by small fibers as well, and loss of these fibers can result in wide ranging abdominal and digestive symptoms including:

GI Symptoms of SFPN:

- GI Dysmotility
  - Esophageal Dysmotility
  - Gastric-emptying scintigraphs show slowed emptying of the stomach
  - Sitz marker studies show alterations of colon transit time
- Post-prandial nausea and vomiting
- GERD
- Weight Loss/Anorexia/Cachexia
- Diarrhea
- Constipation
- Irritable Bowel Syndrome (IBS)

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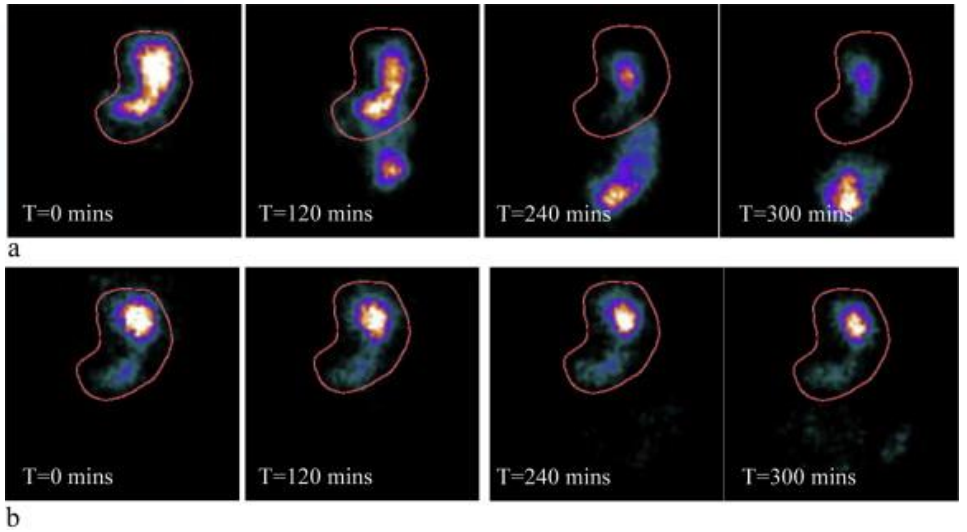
Oaklander AL, Nolano M. Scientific Advances in and Clinical Approaches to Small-Fiber Polyneuropathy: A Review. *JAMA Neurol.* 2019;76(10):1240–1251. doi:10.1001/jamaneurol.2019.2917

Gastrointestinal Dysmotility

- 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



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

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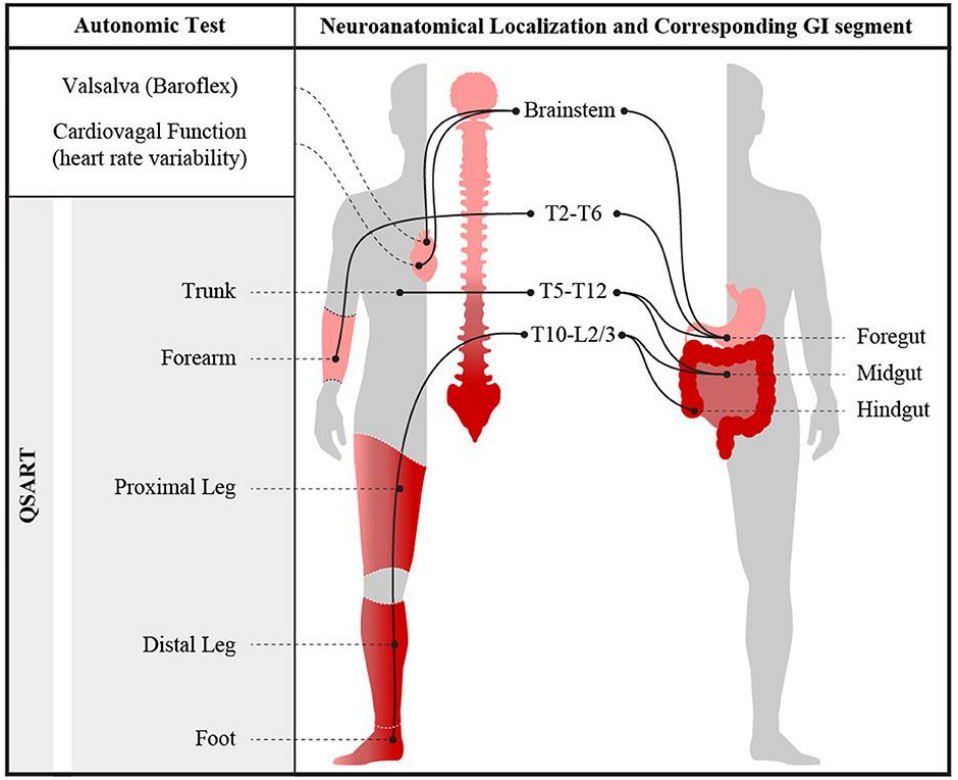
Nelson, A. D., Mouchli, M. A., Valentin, N., Deyle, D., Pichurin, P., Acosta, A. and Camilleri, M, Ehlers Danlos syndrome and gastrointestinal manifestations: a 20-year experience at Mayo Clinic. Neurogastroenterology & Motil 2015; 27: 1657–1666.

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.

Gastrointestinal Dysmotility

- Wireless motility capsule testing (Smartpill) was performed on 20 individuals with idiopathic autonomic neuropathy and unexplained gastrointestinal symptoms to evaluate entire gastrointestinal transit time and contractility
- Transit times were predominantly abnormal and delayed in the foregut (50%)
- Contractility abnormalities were far more prominent in the hindgut and were present in 85% of patients
- Detected neuroanatomical overlap between the presence of autonomic reflex abnormalities and transit-time and contractility abnormalities



WMC transit time parameters

Gastrointestinal segment	Normal transit time (h)
Gastric emptying time (GET)	2.5–4.5
Small bowel transit time (SBTT)	2.5–6.0
Colonic transit time (CTT)	10–59
Whole gut transit time (WGTT)	15–73

Transit times considered abnormal if falling outside of the 5th-95% percentiles of published normal transit times

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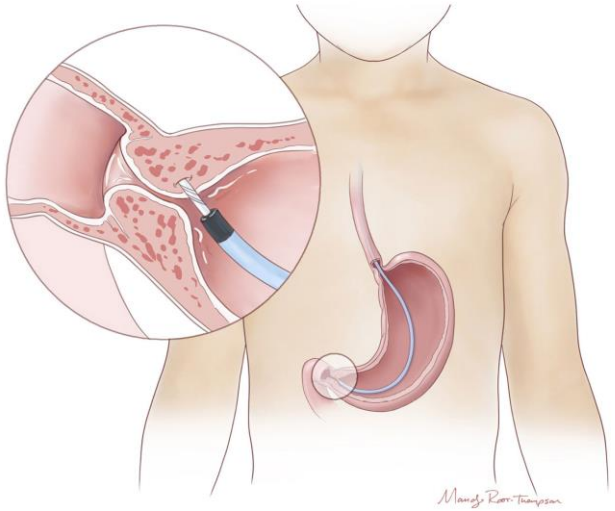
Langford, Jordan S., et al. "Quantitative gastrointestinal function and corresponding symptom profiles in Autonomic neuropathy." *Frontiers in Neurology*, vol. 13, 2022, https://doi.org/10.3389/fneur.2022.1027348.

Gastrointestinal Dysmotility: Treatments

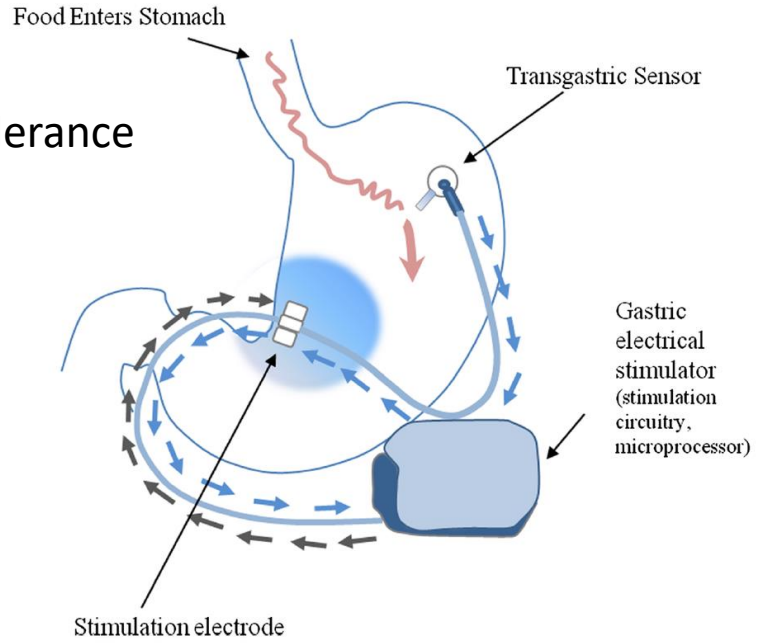
- Pyridostigmine
- Prucalopride (Motegrity)
- Metoclopramide (2.5-5 mg po bid)
- Pyloric Sphincter Botox/Myotomy
- Gastric Pacing
- Treat underlying MCAS
- Treat Dysautonomia/Orthostatic Intolerance
  - Midodrine/Droxidopa

Brind'Amour, Katie, et al. "Katie Brind'Amour, PhD, MS, Ches." *Pediatrics Nationwide*, Katie Brind'Amour, PhD, MS, CHES https://pediatricsnationwide.org/wp-content/uploads/2021/03/Katie-B-portrait.gif, 22 Mar. 2021, pediatricsnationwide.org/2019/10/10/a-new-therapeutic-era-in-pediatric-functional-and-motility-disorders/.



PYLORIS BOTOX®

Botox injections into the pyloric or anal [not pictured] sphincters may help alleviate GI disorders such as gastroparesis and internal anal sphincter achalasia. It is a low-risk procedure often offered for children with severe symptoms prior to exploring surgery.



"Gastric Pacemakers." *Questions and Answers in MRI*, mriquestions.com/gastric-pacemakers.html. Accessed 30 Sept. 2023.

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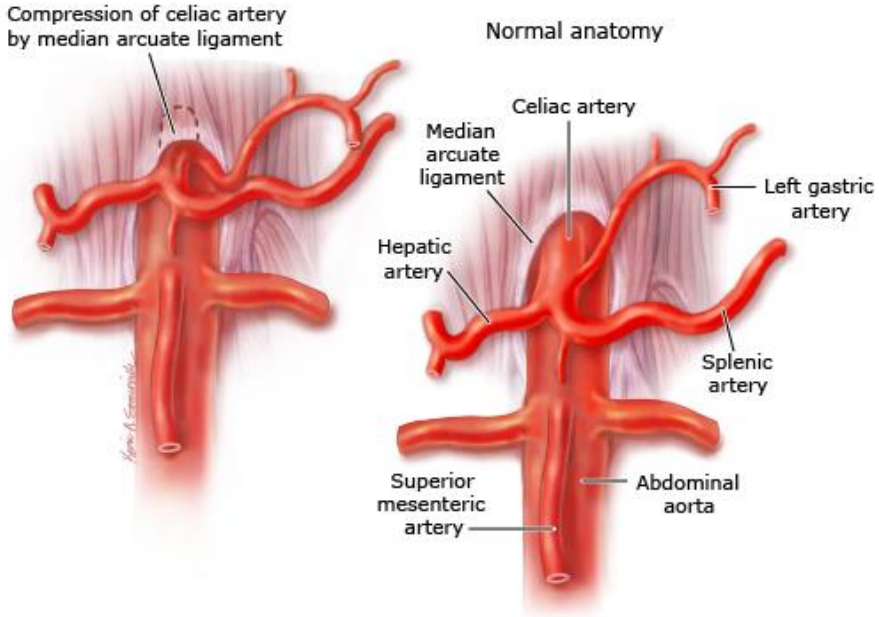
Median Arcuate Ligament Syndrome (MALS)/ Celiac Artery Compression Syndrome (I77.4)

- Eleven patients with MALS who underwent corrective surgery between 2013-2018 were evaluated for other “uncommon” disorders in a retrospective study
- 7/11 found to have radiographic evidence for “delayed gastric emptying”
- 4/11 found to have radiographic abnormalities in the visceral vasculature
- 3/11 found to have POTS
- 2/11 found to have EDS
- Authors suggested there may be a possible pathophysiological relationship

Huynh, Desmond T., et al. “Median arcuate ligament syndrome and its associated conditions.” *The American Surgeon*, vol. 85, no. 10, 2019, pp. 1162–1165, https://doi.org/10.1177/000313481908501019.

Median Arcuate Ligament Syndrome (MALS)/ Celiac Artery Compression Syndrome (I77.4)

- Defined by recurrent abdominal pain related to compression of the celiac artery by the median arcuate ligament
- Symptoms could be mediated by ischemia or other neuropathic mechanisms
- Characterized by a trial of postprandial abdominal pain, weight loss, (sometimes) abdominal bruit
- More common in females
- Often presents in the fourth decade of life



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

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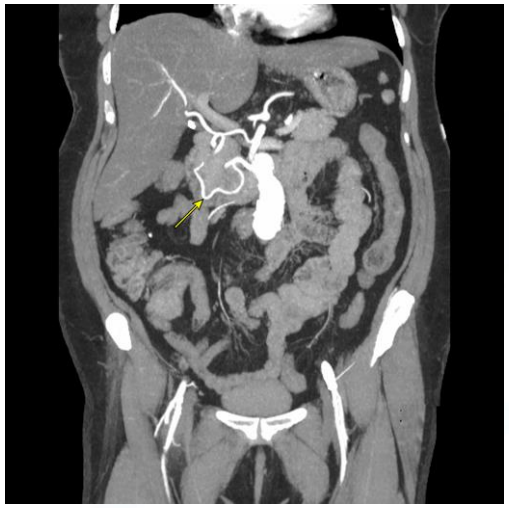
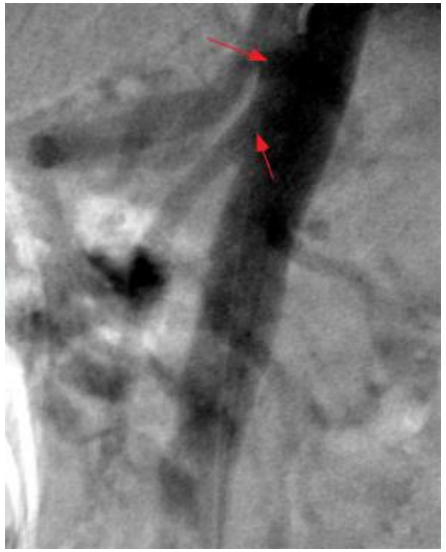
Sherry, Scovell, et al. "Celiac Artery Compression Syndrome." *UpToDate*, www.uptodate.com/contents/celiac-artery-compression-syndrome?search=celiac+artery+compression+syndrome&source=search_result&selectedTitle=1~17&usage_type=default&display_rank=1#H1023978010. Accessed 30 Sept. 2023.

Median Arcuate Ligament Syndrome (MALS)/ Celiac Artery Compression Syndrome (I77.4)



A coronal reconstruction of a CT shows a large pancreaticoduodenal artery (arrow) arising from the SMA and acting as collateral blood supply to the celiac artery, which has a stenosis at its origin.

A lateral arteriogram with widely patent origins of the celiac artery (most superior vessel) and SMA (inferior vessel). This image was taken upon end-inspiration in a patient suspected of having celiac axis syndrome.



- Initial imaging often done with mesenteric duplex ultrasound
- Diagnosis confirmed when elevated celiac artery velocities that normalize with deep inspiration are measured
- Follow-up CT angiogram may then show “J-hook” conformation of the celiac artery
- Surgical options include release of the median arcuate ligament
- May also elect to preform neurolysis of the celiac nerve plexus
- 70-80% surgical success rate in reducing abdominal pain, though continued abdominal symptoms may be representative of the presence of other functional gastrointestinal complications

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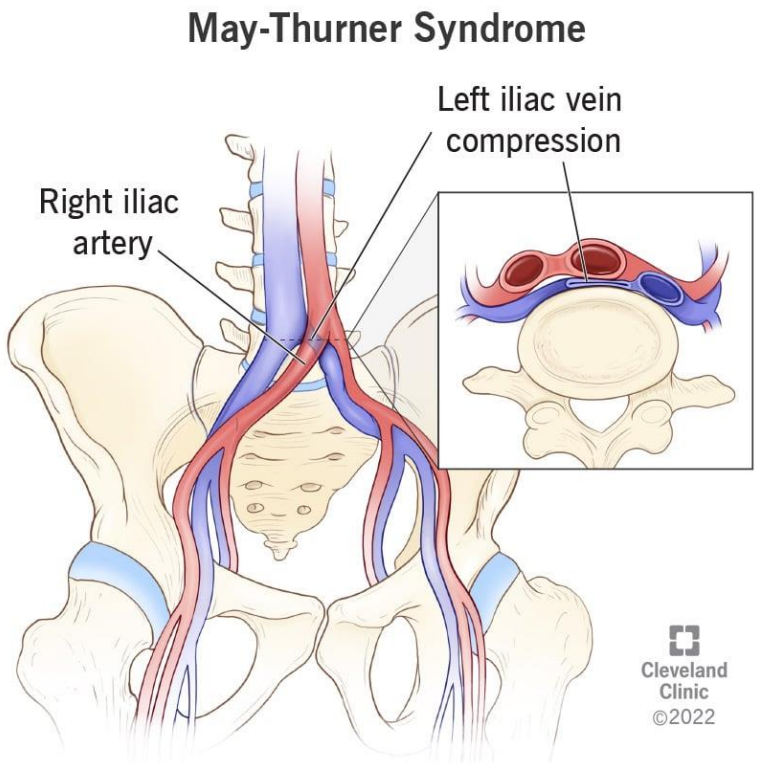
Skelly, Christopher L., and Grace Z. Mak. “Median arcuate ligament syndrome – current state of management.” *Seminars in Pediatric Surgery*, vol. 30, no. 6, 2021, p. 151129, https://doi.org/10.1016/j.sempedsurg.2021.151129.

Sherry, Scovell, et al. “Celiac Artery Compression Syndrome.” *UpToDate*, www.uptodate.com/contents/celiac-artery-compression-syndrome?search=celiac+artery+compression+syndrome&source=search_result&selectedTitle=1~17&usage_type=default&display_rank=1#H1023978010. Accessed 30 Sept. 2023.

May-Thurner Syndrome (I87.1)



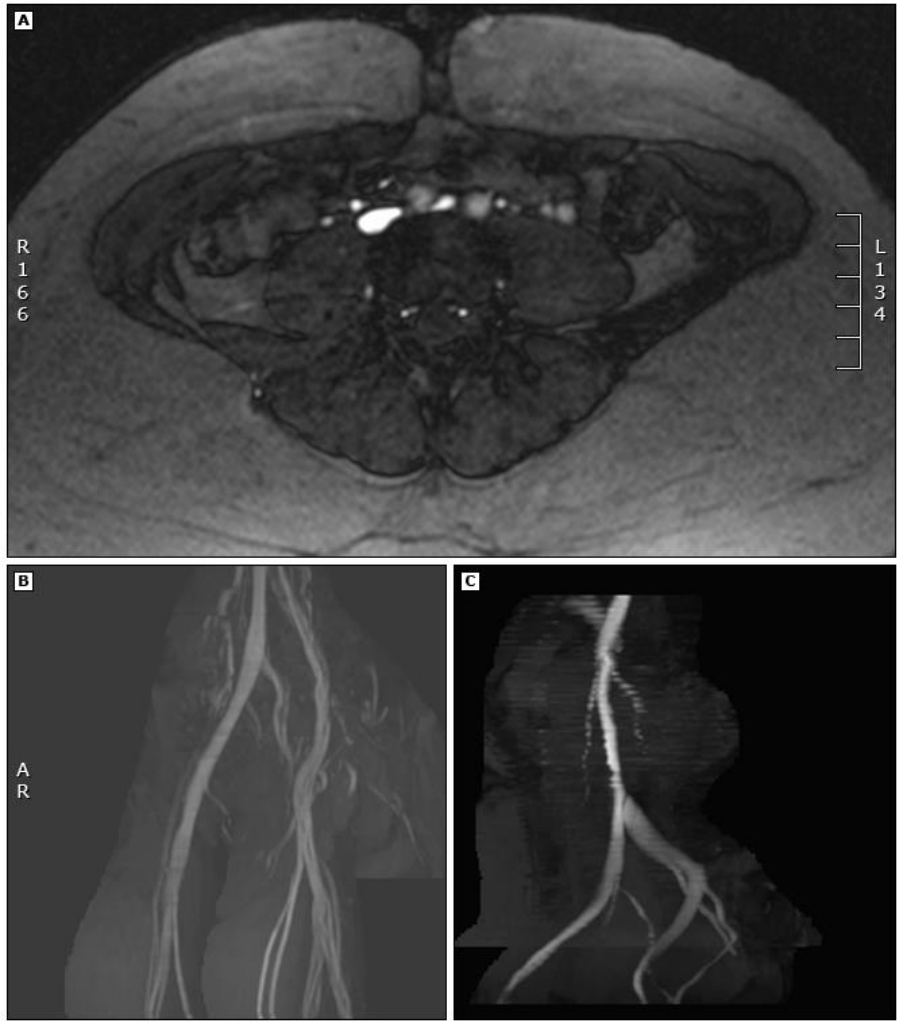
- Defined by extrinsic venous compression by the arterial system against bony structures in the iliocaval venous territory (most commonly of the left common iliac vein by the right common iliac artery)
- Partial obstruction can often be asymptomatic, but progression can lead to DVT formation
- Estimated prevalence of 2-5% of patients, more common in females presenting in the second-third decade of life
- Symptomatic patients present with extremity pain, swelling, venous claudication, or signs of venous insufficiency (most common in the left lower extremity)

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

Mousa, Albier Y, et al. "May-Thurner Syndrome." *UpToDate*, www.uptodate.com/contents/may-thurner-syndrome?search=may+thurner+syndrome+adult&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed 30 Sept. 2023.

May-Thurner Syndrome (I87.1)

- Diagnostic considerations can include CT or MR Venography, but the gold-standard is Intravascular Ultrasound (IVUS)
- Conservative management with compression stockings for mild symptoms
- More symptomatic patients most commonly treated with angioplasty and stenting; could also require thrombolysis of clots and post-operative anticoagulation in some cases



Magnetic resonance angiography demonstrates extrinsic compression of the left iliac vein by the right iliac artery in both axial (A) and sagittal (B,C) projections. In the axial view (A), note the normally enhanced iliac vein on the right anteromedial to the psoas muscle.

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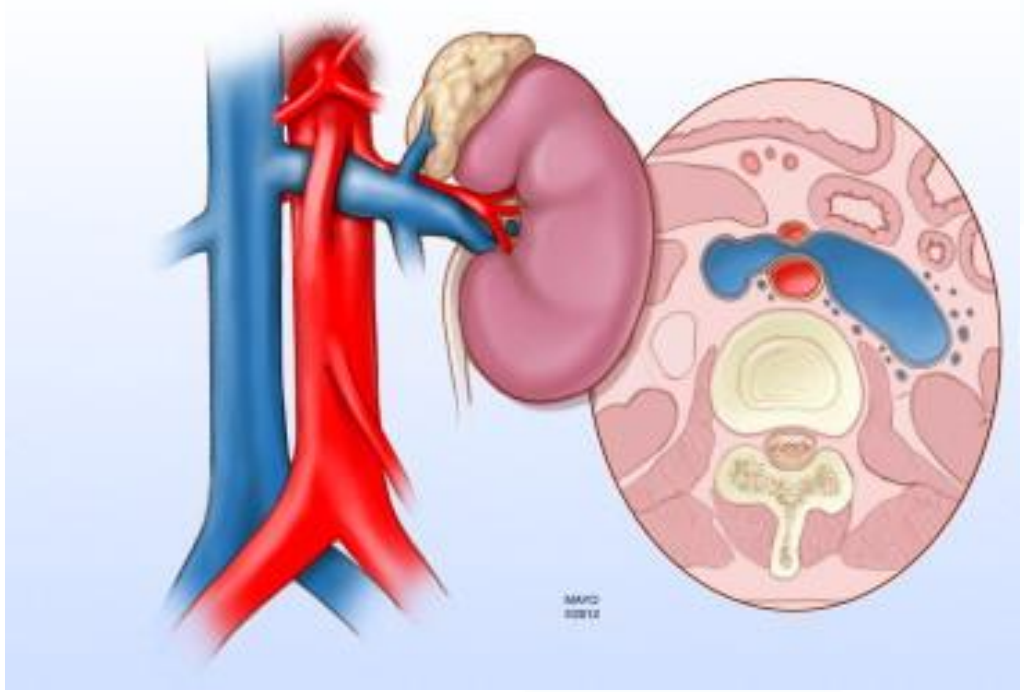
Mousa, Albier Y, et al. "May-Thurner Syndrome." *UpToDate*, www.uptodate.com/contents/may-thurner-syndrome?search=may+thurner+syndrome+adult&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed 30 Sept. 2023.

Nutcracker Syndrome (Q27.8)



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.

- Refers to compression of the left renal vein between the aorta and the proximal superior mesenteric artery
- Symptoms can include hematuria, orthostatic proteinuria, and left flank pain
- Diagnosis suspected when CT or MRI showing intrarenal and perirenal varices, enhancement of left gonadal vein collateral
- Diagnosis confirmed with doppler ultrasound showing left renal vein compression and elevated flow velocities
- Treatments can include left renal vein stent placement, transposition of the SMA or left renal vein, or left kidney auto-transplant

Perazella, Mark A, et al. "Etiology and Evaluation of Hematuria in Adults." *UpToDate*, www.uptodate.com/contents/etiology-and-evaluation-of-hematuria-in-adults?search=nutcracker+syndrome&sectionRank=1&usage_type=default&anchor=H25&source=machineLearning&selectedTitle=1~21&display_rank=1#. Accessed 30 Sept. 2023.

2015 IOM Criteria for Diagnosis of ME/CFS (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome) (G93.32)

- There is no single sensitive and specific biomarker for the diagnosis of ME/CFS
- These are the core clinical criteria to rule in a diagnosis of ME/CFS, though MANY additional comorbid symptoms and conditions can be present
- Post-Exertional Malaise (PEM) is widely considered **pathognomonic** for ME/CFS

Diagnosis requires that the patient have the following three symptoms

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities, that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, and
2. Post-exertional malaise,* and
3. Unrefreshing sleep*

At least one of the two following manifestations is also required:

1. Cognitive impairment* or
2. Orthostatic intolerance

* Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS (SEID)[a] should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity

[a] The recommendation for the term systemic exertion intolerance disease (SEID) was not adopted.

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Thank You