Ann Allergy Asthma Immunol 135 (2025) 97–102

Contents lists available at ScienceDirect

Prevalence of mast cell activation disorders and hereditary alpha tryptasemia among patients with postural orthostatic tachycardia syndrome and Ehlers-Danlos syndrome: A systematic review

Matthew Farley, MD*; Ricardo J. Estrada-Mendizabal, MD*; Emily A. Gansert, MD†; Dayne Voelker, MD‡; Lisa A. Marks, MLS, AHIP§; Alexei Gonzalez-Estrada, MD*

* Division of Allergy, Asthma and Clinical Immunology, Department of Medicine, Mayo Clinic Arizona, Scottsdale, Arizona
† Department of Internal Medicine, Mayo Clinic, Jacksonville, Florida
‡ Division of Allergic Diseases, Department of Medicine, Mayo Clinic, Rochester, Minnesota
§ Library Services, Mayo Clinic Libraries-Arizona, Scottsdale, Arizona

ARTICLE INFO

Article history:
Received for publication January 14, 2025.
Received in revised form March 25, 2025.
Accepted for publication March 26, 2025.

ABSTRACT

Background: Postural orthostatic tachycardia syndrome (POTS) and Ehlers-Danlos syndrome (EDS) are often reported to occur concurrently with mast cell activation disorders (MCADs) and hereditary alpha tryptasemia (HAT). However, it remains unclear whether evidence supporting this relationship exists.
Objective: To determine the prevalence of MCADs and HAT in patients diagnosed with having EDS and or POTS.
Methods: We conducted a systematic search of MEDLINE (OVID), EMBASE (OVID), Scopus, and Web of Science with the assistance of an experienced medical librarian. We focused on patients with any MCAD or HAT in conjunction with a diagnosis of POTS and/or EDS.
Results: A total of 200 records were screened, 107 were excluded based on the title or abstract, 92 full texts were reviewed, and 1 record was not retrieved. No studies were identified that met our primary criterion of including patients diagnosed with any MCAD or HAT alongside POTS and/or EDS based on our prespecified diagnostic criteria.
Conclusion: Our review did not find evidence to confirm a relationship between MCADs, HAT, POTS, and EDS. However, it must be mentioned that 1 study revealed an association between mast cell activation syndrome, POTS, and EDS and came close to meeting the full diagnostic criteria for mast cell activation syndrome, unlike other studies. This indicates that further research using strict and validated diagnostic criteria is needed to clarify whether a true association between conditions exists.

Introduction

Postural orthostatic tachycardia syndrome (POTS) is an autonomic nervous system disorder characterized by an excessive heart rate increase of at least 30 beats per minute (or 40 beats per minute in adolescents) within 10 minutes of standing, in the absence of orthostatic hypotension, often accompanied by symptoms such as lightheadedness, fatigue, and palpitations.[1,2] Ehlers-Danlos syndrome (EDS) is a group of connective tissue disorders that result in hypermobile joints, skin hyperextensibility, and tissue fragility.[3] Both conditions are increasingly recognized to occur concurrently with mast cell activation disorders (MCADs), which represent a spectrum of conditions involving inappropriate mast cell activation and mediator release. MCADs include mast cell activation syndrome (MCAS; most frequently associated condition), idiopathic, monoclonal, and secondary types, including systemic mastocytosis.[4] Another condition, hereditary alpha tryptasemia (HAT), has been associated with more severe symptoms in patients with IgE and non–IgE-mediated mast cell activation, especially in patients with venom allergy, and possibly in mastocytosis.[5]

Although anecdotal and clinical observations suggest a potential relationship among POTS, EDS, and MCADs/HAT, the evidence supporting this association remains unclear. This study aimed to determine the prevalence of MCADs and HAT in patients diagnosed with having EDS and/or POTS.

Methods

A systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines and was registered in PROSPERO (identifier CRD42024550651) before study selection (June 4, 2024).

Address correspondence to: Alexei Gonzalez-Estrada, MD, Division of Allergy, Asthma, and Clinical Immunology, Department of Medicine, Mayo Clinic, Scottsdale, AZ E-mail: gonzalez.alexei@mayo.edu.

https://doi.org/10.1016/j.anai.2025.03.022

Search Strategy

We conducted a systematic search of MEDLINE (OVID), EMBASE (OVID), Scopus, and Web of Science with the assistance of an experienced medical librarian (L.A.M.). The search strategy was further refined through group discussions with the librarian based on preliminary searches.

Selection Criteria

We focused on studies including patients with any MCAD or HAT in conjunction with a diagnosis of POTS and/or EDS. The following diagnostic criteria were used for study selection: Gülen et al[6] 2021 criteria for MCAS,[6-9] the World Health Organization criteria for systemic mastocytosis,[10] genetic testing plus elevated total baseline tryptase for HAT (Table 1),[5] the American College of Cardiology diagnostic criteria for POTS (Table 2),[1] and the 2017 International Classification criteria for EDS (Table 3).[3] We considered observational studies, including case reports and conference abstracts with no date restrictions.

Data Screening

The screening consisted of 2 rounds: the first was a title and abstract screening and the second was a full-text review. This process was done independently and in duplicate by 2 subinvestigators (M.F. and R.E.). Discrepancies were resolved by group discussion.

Results

Our search identified a total of 198 records after duplicate removal, and we added 2 external studies identified through citation searching.[11,12] We excluded 107 studies based on the title or abstract. We were unable to retrieve 1 record and reviewed a total of 92 full texts. Of the 92 full texts reviewed, we excluded 83 (89%) because they failed to fulfill our prespecified diagnostic criteria,[11–90] 7 (8%) because they were reviews,[91–97] and 2 (2%) because their results revealed that the prevalence of HAT in patients with POTS and EDS, respectively, was similar to the reported prevalence in the general population.[98,99] We did not identify any studies that met our primary criterion of including patients diagnosed with any MCAD or with HAT alongside POTS and/or EDS, as defined by our prespecified diagnostic criteria (Fig 1).

Discussion

To our knowledge, this is the first systematic review evaluating the potential association between POTS and EDS with MCADs. We identified no adequate studies demonstrating an association between these conditions that used our prespecified diagnostic criteria.

In 2005, the first documented association was reported, highlighting a correlation between POTS and mast cell activation. A total of 177 patients were referred to an autonomic dysfunction clinic for disabling autonomic intolerance, and 8 patients (5%) were diagnosed with having both POTS and mast cell activation, defined as a flushing episode in combination with elevated urine N-methylhistamine level more than 230 μg/g creatinine. This study used validated diagnostic criteria for POTS; however, the definition of mast cell activation does not fulfill the 3 diagnostic criteria for MCAS, lacking symptoms involving 2 organ systems, episodic rise in mast cell mediators, and response to treatment.[34] Later on, Cheung et al[87] reported that MCAS

Table 1
Prespecified MC Activation Disorder Diagnostic Criteria

Diagnosis	Diagnostic criteria
MC activation syndrome[6–8]	Must fulfill all 3 of the following criteria: 1. Episodic symptoms consistent with MC degranulation, involving at least 2 organ systems (ie, cutaneous, gastrointestinal, cardiovascular, or respiratory) 2. Event-related increase in serum tryptase above individual's baseline tryptase to 20% + 2 ng/mL 3. Response of symptoms to therapy with MC-stabilizing agents, drugs directed against MC mediator production, or drugs blocking mediator release or effects of MC-derived mediators
Systemic mastocytosis[10]	Requires 1 minor and 1 major or 3 minor criteria: Major: 1. Multifocal dense infiltrates of MCs (>15 MCs in aggregate) in tryptase-stained biopsy sections of the bone marrow or other extracutaneous organs, such as the gastrointestinal tract. Minor: 1. >25% of MCs in the bone marrow or other extracutaneous organ(s) have abnormal morphology (ie, are atypical MC type 1 or are spindle–shaped MCs) in multifocal lesions in histologic examination 2. *KIT* mutation causing ligand-independent activation in extracutaneous organ(s) (in most cases bone marrow) or peripheral blood 3. *KIT*+ MCs in bone marrow have aberrant expression of CD25 (and/or less specifically CD2 or CD30) 4. Serum total tryptase > 20 ng/mL (except in patients with AHN-type disease)
Hereditary alpha tryptasemia[5]	1. Increased gene copy number of TPSAB1 encoding for alpha tryptase 2. Elevated serum tryptase level

Abbreviations: AHN, associated hematologic neoplasm; CD, cluster of differentiation; MC, mast cell; TPSAB1, *tryptase alpha/beta 1* gene; WHO, World Health Organization.
NOTE. Data are from Gülen et al,[6] Akin et al,[7] Valent et al,[8] Khoury et al,[10] and von Bubnoff et al.[5]

Table 2
Prespecified Postural Orthostatic Tachycardia Syndrome Diagnostic Criteria From the American College of Cardiology 2022

Diagnosis	Diagnostic criteria
Postural orthostatic tachycardia syndrome	Must fulfill all the following criteria: 1. Chronic symptoms of orthostatic intolerance (≥6 mo) 2. Increase in heart rate ≥ 30 bpm within 10 min of assuming an upright posture and in the absence of orthostatic hypotension (BP fall of >20/10 mm Hg) 3. Must occur in the absence of other overt causes of orthostatic tachycardia

Abbreviation: BP, blood pressure.
NOTE. Data are from Bryarly et al[1] and Mayuga et al.[2]

Table 3
Prespecified EDS Diagnostic Criteria

Diagnosis	Diagnostic criteria
Hypermobile EDS[2]	Must fulfill all 3 of the following criteria: 1 Generalized joint hypermobility a. Beighton score ≥ 6 in prepubertal children and adolescents b. Beighton score ≥ 5 from puberty up to 50 y of age c. Beighton score ≥ 4 in persons older than 50 y of age 2 ≥2 of the following features (A, B, or C) a. Feature A (5 of the following must be present) i. Unusually soft or velvety skin ii. Mild skin hyperextensibility iii. Unexplained striae distensae or rubrae at the back, groin, thighs, breasts, and/or abdomen in adolescents, men, or prepubertal girls without a history of significant gain or loss of body fat or weight iv. Bilateral piezogenic papules of the heel v. Recurrent or multiple abdominal hernias vi. Atrophic scarring involving at least 2 sites and without the formation of truly papyraceous and/or hemosideric scars as found in classical EDS vii. Pelvic floor, rectal, and/or uterine prolapse in children, men, or nulliparous women, without a history of morbid obesity or other known predisposing medical condition viii. Dental crowding and high or narrow palate ix. Arachnodactyly, as defined in ≥1 of the following: (1) positive wrist sign (Walker's sign) on both sides or (2) positive thumb sign (Steinberg's sign) on both sides x. Ratio of arm span to height > 1.05 xi. Mitral valve prolapse mild or greater based on strict echocardiography criteria xii. Aortic root dilation with Z-score > +2 b. Feature B i. Positive family history: ≥1 first-degree relatives independently meeting the current criteria for EDS c. Feature C (must have at least 1) i. Musculoskeletal pain in ≥2 limbs, recurring daily for ≥3 mo ii. Chronic, widespread pain for ≥3 mo iii. Recurrent joint dislocations or frank joint instability in the absence of trauma 3 All the following prerequisites must be met: a. Absence of unusual skin fragility, which should prompt consideration of other types of EDS b. Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. In patients with an acquired connective tissue disorder (eg, lupus or rheumatoid arthritis), additional diagnosis of hypermobile EDS requires meeting both features A and B of criterion 2. Feature C of criterion 2 (chronic pain and/or instability) cannot be counted toward a diagnosis of hypermobile EDS in this situation c. Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (eg, Bethlem myopathy), other hereditary disorders of connective tissue (eg, other types of EDS, Loeys-Dietz syndrome, or Marfan syndrome) and skeletal dysplasias (eg, osteogenesis imperfecta). Exclusion of these considerations may be based on history, physical examination, and/or molecular genetic testing, as indicated.

Abbreviation: EDS, Ehlers-Danlos Syndrome.
NOTE. Data are from Malfait et al[3] International Classification Criteria for EDS.[2]

may frequently co-segregate with POTS and EDS. Nine patients with a diagnosis of POTS and EDS were sent questionnaires for MCAS based on validated symptoms. Of the 9 patients with both POTS and EDS, 6 (66%) had validated symptoms of MCAS. There was no documentation of mast cell mediators at baseline or during episodic events, nor was there any record of the response to treatment.

Nevertheless, Shaw et al[12] conducted a cross-sectional online community-based survey for patients with a formal diagnosis of POTS, inquiring about other medical diagnoses. A diagnosis of MCAS and EDS was reported in 9% and 25% of respondents, respectively. Of the patients, 69% reported having episodic flushing. The data were patient reported without any MCAS or EDS diagnostic criteria specified. Flushing could be secondary to autonomic dysfunction, mast cell mediators, or other etiology. In 2020, Vadas et al[89] evaluated 30 patients with established MCAS diagnosis for a concomitant diagnosis of POTS and/or EDS. Of 30 patients with MCAS, 7 also had POTS and 13 had EDS or hypermobility spectrum disorder. In their cohort, 6 patients (20%) had the triad of MCAS, POTS, and EDS or hypermobility spectrum disorder. Although it was mentioned that a substantial change from baseline was found in either tryptase levels, urinary prostaglandin D_2, or N-methylhistamine, no data revealing an event-related increase in serum tryptase above the individual's baseline to 20% + 2 ng/mL were documented.

Wang et al[90] reviewed 195 charts of patients diagnosed with having autonomic dysfunction and found that 18 (9%) had a diagnosis of MCAS from a physician without the diagnostic criteria being met. Of 51 patients diagnosed with having both POTS and EDS, 16 (31%) had MCAS on their problem list. Criteria pertaining to how the physicians diagnosed these patients were unknown. In a separate study, 69 patients diagnosed with having POTS underwent testing for known mast cell activation biochemical mediators. The mediators included urinary prostaglandins, N-methylhistamine, plasma histamine, and tryptase levels. Furthermore, 44 of the 69 patients (64%) reported non-orthostatic symptoms, such as allergic complaints, rash, or gastrointestinal symptoms. Of the 44 patients, 29 (66%) exhibited at least 1 mast cell mediator abnormality at baseline, but there was no mention of these mediators during an episode nor symptom improvement with treatment.[11]

In 2021, Song et al[41] conducted a chart review of 98 patients with a diagnosis of EDS for concomitant MCAS diagnosis on their problem list. A total of 24 patients (24%) had MCAS listed as a problem, but the diagnostic criteria used to diagnose MCAS were not reported. Conversely, Vazquez et al[98] investigated the prevalence of HAT in patients with either hypermobility spectrum disorder or hypermobile EDS. Genetic testing for HAT was conducted on 210 patients, yielding a positive rate of 5%, similar to the reported prevalence in the general population.

Chollet et al[100] compared patients with HAT with healthy controls and found no statistically significant difference in the prevalence of POTS and EDS. Finally, Huang et al[99] investigated the relationship between HAT and POTS. A total of 250 patients with a POTS diagnosis, confirmed through tilt table, were screened with tryptase levels and offered HAT genetic testing. Of 250 patients, 18 (7%) had a baseline serum tryptase level more than or equal to 8 ng/mL, and genetic testing was offered to all patients with a baseline tryptase more than or equal to 6.5 ng/mL. Only a small number of patients with elevated tryptase levels agreed to undergo genetic testing; therefore, calculations were done using Poisson distribution and theory to compare the incidence of tryptase level elevation and HAT between their POTS

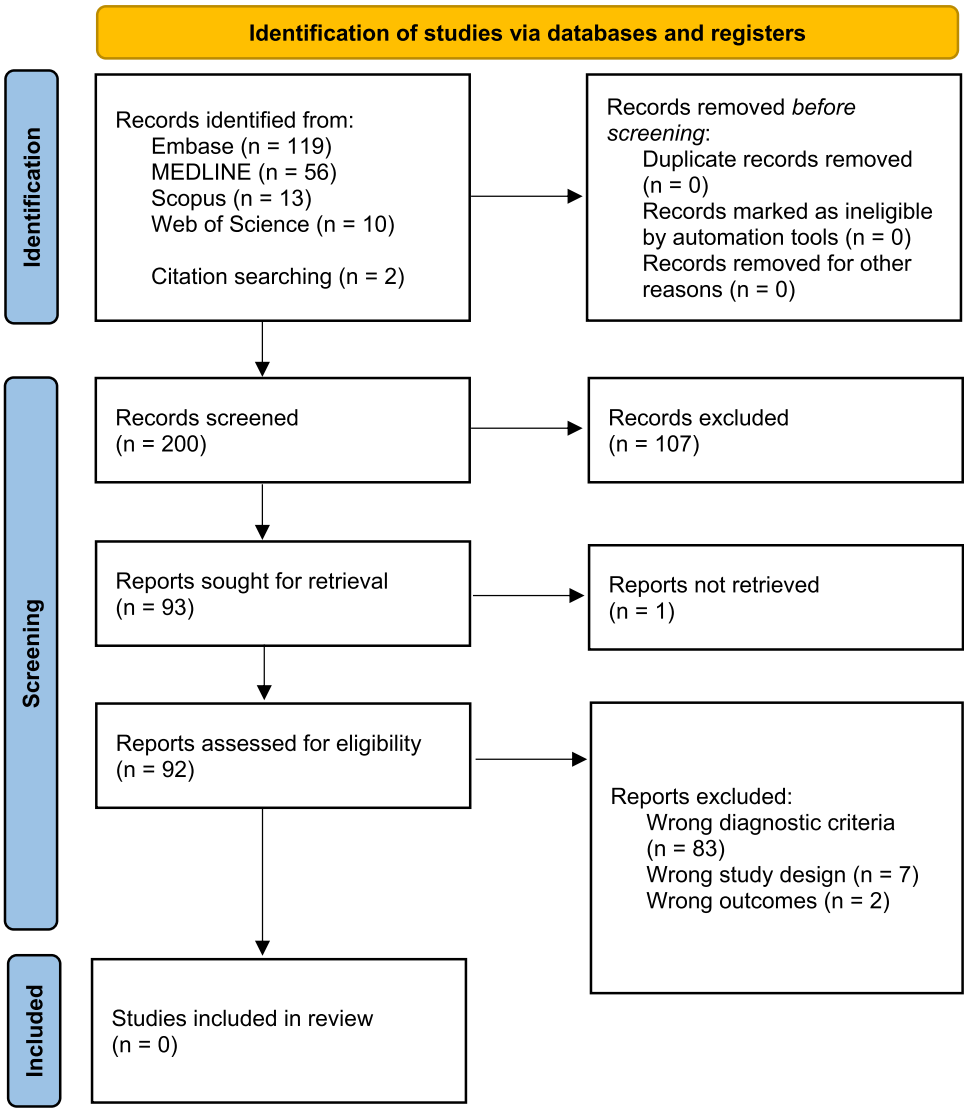

Figure 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

cohort and the general population. The maximum inferred prevalence in their cohort was 7%, similar to the reported prevalence of HAT in the general population.

A limitation of many studies reviewed is referral bias. Patients were recruited from allergy clinics and may have had independent reasons for increased mast cell mediator release. Ideally, patients should be recruited from POTS/EDS clinics. It is important to note that a "consensus-2" criteria is also being used as a proposed classification for the diagnosis of MCAS. The criteria include a much broader list of symptoms to define mast cell activation. It requires only 2 criteria to be met instead of 3.[101] The use of unvalidated and more inclusive diagnostic criteria for MCAS may result in an increased prevalence of reported cases, potentially creating misleading associations with other conditions, such as POTS and EDS. This can lead to other diagnoses being missed and patients not receiving appropriate treatment. Recently, Solomon et al[102] analyzed the California International Classification of Diseases code data for inpatient admissions to track changes in MCAS diagnosis rates over time. They observed a 12.6-fold increase in the rate of idiopathic MCAS from 2016 to 2022, likely driven by the adoption of the more inclusive criteria. In the same study, the authors used large language models to estimate the probabilities of diagnoses compatible with both consortium and alternative MCAS criteria. The results revealed that, compared with the established consortium criteria, alternative MCAS criteria yielded diagnoses that were more variable and less precise.

Our review did not find evidence to confirm the presumed association between POTS and EDS with MCADs. However, it must be mentioned that 1 study revealed an association between MCAS, POTS, and EDS and came close to meeting the full diagnostic criteria for MCAS,[89] unlike other studies. Furthermore, it is important to note that this study does not deny an association but instead reveals that there are inadequate studies on the topic. This indicates that further research using strict and validated diagnostic criteria is needed to clarify whether a true association between MCADs, POTS, and EDS exists.

Disclosures

The authors have no conflicts of interest to report.

Funding

Dr Gonzalez-Estrada receives funding from AAAAI Drug Hypersensitivity Research Grant and an Arizona Department of Health Services ABRC Award. Funders played no role in any aspect of this project.

References

1. Bryarly M, Phillips LT, Fu Q, Vernino S, Levine BD. Postural orthostatic tachycardia syndrome: JACC focus seminar. *J Am Coll Cardiol*. 2019;73(10):1207–1228.
2. Mayuga KA, Fedorowski A, Ricci F, Gopinathannair R, Dukes JW, Gibbons C, et al. Sinus tachycardia: a multidisciplinary expert focused review. *Circ Arrhythm Electrophysiol*. 2022;15(9):E007960.
3. Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, et al. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet C*. 2017;175(1):8–26.
4. Akin C. Mast cell activation disorders. *J Allergy Clin Immunol Pract*. 2014;2(3). 252-257:e251.
5. vonBubnoff D, Koch D, Stocker H, Ludwig RJ, Wortmann F, von Bubnoff N. The clinical features of hereditary alpha-tryptasemia—implications for interdisciplinary practice. *Dtsch Ärztebl Int*. 2024;121(8):258–264.
6. Gülen T, Akin C, Bonadonna P, Siebenhaar F, Broesby-Olsen S, Brockow K, et al. Selecting the right criteria and proper classification to diagnose mast cell activation syndromes: a critical review. *J Allergy Clin Immunol Pract*. 2021;9(11):3918–3928.
7. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. *J Allergy Clin Immunol*. 2010;126(6):1099–1104.e1094.
8. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol*. 2012;157(3):215–225.
9. Valent P, Akin C, Hartmann K, Alvarez-Twose I, Brockow K, Hermine O, et al. Updated diagnostic criteria and classification of mast cell disorders: A consensus proposal. *Hemasphere*. 2021;5(11):e646.
10. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. *Leukemia*. 2022;36(7):1703–1719.
11. Kohno R, Cannom DS, Olshansky B, Xi SC, Krishnappa D, Adkisson WO, et al. Mast cell activation disorder and postural orthostatic tachycardia syndrome: a clinical association. *J Am Heart Assoc*. 2021;10(17):e021002.
12. Shaw BH, Stiles LE, Bourne K, Green EA, Shibao CA, Okamoto LE, et al. The face of postural tachycardia syndrome - insights from a large cross-sectional online community-based survey. *J Intern Med*. 2019;286(4):438–448.
13. Szalewski RJ, Davis BP. Ehlers-Danlos syndrome is associated with Idiopathic urticaria - a retrospective study. *J Allergy Clin Immunol*. 2019;143(2):AB67.
14. Johansson M, Stahlberg M, Runold M, Nygren-Bonnier M, Nilsson J, Olshansky B, et al. Long-haul post-COVID-19 symptoms presenting as a variant of postural orthostatic tachycardia syndrome: the Swedish experience. *JACC Case Rep*. 2021;3(4):573–580.
15. Weinstock LB, Brook J, Kaleem Z, Afrin L, Molderings G. Small intestinal bacterial overgrowth is common in mast cell activation syndrome. *Am J Gastroenterol*. 2019;114(suppl):S670.
16. Alhabeeb F. Dyspnea on exertion secondary to Ehlers-Danlos syndrome presenting as a case of asthma: a case report. *Chest*. 2023;164(4):A5055.
17. Novak P, Systrom DM, Marciano SP, Knief A, Felsenstein D, Giannetti MP, et al. Mismatch between subjective and objective dysautonomia. *Sci Rep*. 2024;14(1):2513.
18. Quinn KL, Lam GY, Walsh JF, Bhereur A, Brown AD, Chow CW, et al. Cardiovascular considerations in the management of people with suspected long COVID. *Can J Cardiol*. 2023;39(6):741–753.
19. Daens S, Grossin D, Hermanns-Le T, Peeters D, Manicourt D. [Severe mast cell Activation Syndrome in a 15-year-old patient with an hypermobile Ehlers-Danlos syndrome]. *Rev Med Liège*. 2018;73(2):61–64.
20. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. *Infect Dis (Lond)*. 2021;53(10):737–754.
21. Allen SJ, Chazot PL, Dixon CJ. Can H_2 -receptor upregulation and raised histamine explain an anaphylactoid reaction on cessation of ranitidine in a 19-year-old female? A case report. *Br J Clin Pharmacol*.. 2018;84(7):1611–1616.
22. Grubb BP. Feeling shaky with palpitations: hypertension, tachycardia, dizziness, and near syncope. In: Francomano CA, Hakim AJ, Henderson LGS, Henderson FC, eds. *Symptomatic: The Symptom-Based Handbook for Ehlers-Danlos Syndromes and Hypermobility Spectrum Disorders*. Elsevier; 2024:375–379.
23. Song B, Epstein MH, Yeh PC, Nguyen DD, Ikpeama U, Harrell JS. Ehlers Danlos syndrome: who is affected and how they present. *PM R*. 2019;11(suppl 2):S45–S46.
24. Hoffman-Snyder C, Lewis J, Harris L, Dhawan P, Goodman B. Evidence of mast cell activation disorder in postural tachycardia syndrome. *Neurology*. 2015;84(suppl 14):P1–P277.
25. Wharin S, Myers B. Mast cell disorders-experience of a tertiary referral centre. *Br J Haematol*. 2018;181(suppl 1):57.
26. Greiwe J. An index case of a rare form of inducible urticaria successfully treated with omalizumab. *Ann Allergy Asthma Immunol*. 2018;121(5)(suppl):S84.
27. Zhang S, Singh U, Zimmermann N, Bernstein J. Clinical significance of mast cell counts in patients presenting with mast cell disorders. *J Allergy Clin Immunol*. 2021;147(2):AB138.
28. Velazquez-Avila Y, Valenciano-Rodriguez CR. Genodermatoses in las tunas Province, Cuba, 1989-2019. *MEDICC Rev*.. 2021;23(2):34.
29. Xiao Y, Calixte DA, Fry E, Tiesenga F. Removal of polymer clips from the gallbladder fossa in a patient with Ehlers-Danlos syndrome (EDS) to treat mast cell activation syndrome (MCAS): a case report. *Cureus*. 2023;15(1):e33704.
30. Kinsella L, Boedefeld M, Stephens J. Efficacy of epidural blood patch as a treatment for chronic orthostatic intolerance: a case series. *Clin Auton Res*. 2019;29(5):545.
31. Kim K. Abdominal vascular compression syndromes: current and future of management of abdominal vascular compression syndromes that includes median arcuate ligament syndrome, nutcracker syndrome, superior mesenteric artery syndrome, May-Thurner syndrome, and associated pelvic venous insufficiency. *J Vasc Surg*. 2023;77(4):50S.
32. Srivastava PP, Walsh S, Vadas P. Clinical features and response to treatment in patients with skin biopsies showing congenital connective tissue disorders. *J Allergy Clin Immunol*. 2020;145(2):AB236.
33. Alomari M, Shatnawei A, Raheem SA, Olayan M, Abdulbaki R, Senussi NH. Severe gastrointestinal dysmotility in patients with Ehlers-Danlos syndrome: case series-1 center experience. *Am J Gastroenterol*. 2017;112(suppl 1):S1358.
34. Shibao C, Arzubiaga C, Roberts LJ, Raj S, Black B, Harris P, et al. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. *Hypertension*. 2005;45(3):385–390.
35. Shusterman A, Abbas KF, Patel M, Sussman G. Mast cell activation syndrome (MCAS): symptom prevalence and characteristic of patients with this presumed diagnosis. *Allergy, Asthma and Clinical Immunology*. 2019;16. *Conference*;Vol..
36. O'Brien J, De Loughrey G, McAuliffe N. Elective caesarean section in a patient with mast cell activation syndrome. *Int J Obstet Anesth*. 2022;50(suppl 1):99.
37. Jackson T, Rosenfeld W, Ferguson L, Maitland A, Bolognese P. Chiari malformation (CM) and/or tethered cord, idiopathic mast cell activation syndrome (MCAS), Ehlers-Danlos syndrome (EDS), and postural orthostatic tachycardia syndrome (POTS): a new pediatric disease cluster. *Pediatrics*. 2018;144:467.. (2_MeetingAbstract).
38. Huang KZ, Dellon ES. Increased prevalence of autonomic dysfunction due to postural orthostatic tachycardia syndrome in patients with eosinophilic gastrointestinal disorders. *J.*. 2019;28(1):47–51.
39. Neri SA, Sgroi C, Timpanaro I, Callea M, Bonaccorso M, Morana IM. Mast cell activation syndrome or other? *Ital J Med*. 2022;16(suppl 1):27.
40. Upadhyaya A, Topan R, Pandya S, Williams S, Zarate-Lopez N, Aziz Q, et al. Medication usage in hypermobile Ehlers-Danlos syndrome/hypermobile spectrum disorder patients with concomitant disorders of Gutbrain interactions. *Gut*. 2023;72(suppl 2):A189–A190.
41. Song B, Yeh P, Harrell J. Systemic manifestations of Ehlers-Danlos syndrome. *Bayl Univ Med Cent Proc*. 2020;34(1):49–53.
42. Brock I, Prendergast W, Maitland A. Mast cell activation disease and immunoglobulin deficiency in patients with hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorder. *Am J Med Genet C*. 2021;187(4):473–481.
43. Bourne K, Stiles L, Shaw BH, Shibao CA, Okamoto LE, Garland EM, et al. Ehlers-Danlos syndrome and mast cell activation syndrome in postural tachycardia syndrome: contributions to a sicker phenotype? *Clin Auton Res*. 2018;28(5):502.
44. Bourne K, Shaw B, Ng J, Stiles L, Green EA, Shibao C, et al. Mast cell activation syndrome in postural tachycardia syndrome: a sicker phenotype? *Heart Rhythm*. 2018;15(5)(suppl 1):S82–S83.
45. Arndt KK, Viswanathan RK, Mathur SK. Clinical characteristics of patients in allergy clinic with presumed diagnosis of mast cell activation syndrome (MCAS). *J Allergy Clin Immunol*. 2018;141(2)(suppl 1):AB50.
46. Pace LA, Feng BJ, Hemp J, Velinder M. Familial hypermobile Ehlers-Danlos syndrome and comorbid dysautonomia may have a genetic neuroimmunologic origin. *J Womens Health*. 2019;28(11):1590–1591.
47. Chang AR, Vadas P. Prevalence of symptoms of mast cell activation in patients with postural orthostatic tachycardia syndrome and hypermobile Ehlers-Danlos syndrome. *J Allergy Clin Immunol*. 2019;143(2):AB182.
48. Petracek LS, Broussard CA, Swope RL, Rowe PC. A case study of successful application of the principles of ME/CFS care to an individual with long COVID. *Healthcare*. 2023;11(6):865.
49. Petracek LS, Suskauer SJ, Vickers RF, Patel NR, Violand RL, Swope RL, et al. Adolescent and young adult ME/CFS after confirmed or probable COVID-19. *Front Med*. 2021;8:668944.
50. Lee D, Mueller E. Mast cell activation features in ehlers-danlos/joint hypermobility patients: A retrospective analysis in light of an emerging disease cluster. *Arthritis and Rheumatology. Acad R/ARHP. Conference;Vol. 69: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting*; 2017.
51. Szari S, Quinn J. Multiple co-morbid conditions in patient with mast cell activation syndrome. *Ann Allergy Asthma Immunol*. 2017;119(5)(suppl 1):S85–S86.
52. Belbezier A, Boccon-Gibod I, Bouillet L. Efficacy of omalizumab in a series of 23 patients suffering from mast cell activating disorders. *Rev Med Intern*. 2019;40(suppl 2):A188–A189.
53. Maitland A. Itchy rash and general malaise: multiple seemingly disparate symptoms, referable to mast cell activation syndrome (MCAS), a subtype of mast cell activation disease (MCAD). In: Francomano CA, Hakim AJ, Henderson LGS, Henderson FC, eds. *Symptomatic: The Symptom-Based Handbook for Ehlers-Danlos Syndromes and Hypermobility Spectrum Disorders*. Elsevier; 2024:59–66.
54. Topan R, Pandya S, Williams S, KR J, Zarate-Lopez N, Aziz Q, et al. Quantifying the burden of food related allergic reactions in hypermobile Ehlers Danlos syndrome. *U Eur Gastroenterol J*. 2022;10(suppl 8):499–500.
55. Gamper L, Simpson J, Moeda S, Segal TY. When symptoms dictate a young person's life-and the importance of building trust and teamwork in rehabilitation of patients with complex conditions. *Arch Dis Child*. 2019;104(suppl 2):A249.
56. Schofield JR, Afrin LB. Recognition and management of medication excipient reactivity in patients with mast cell activation syndrome. *Am J Med Sci*. 2019;357(6):507–511.
57. Chau AS, Jongco AM. Immunodeficiencies in Ehlers-Danlos syndrome: a case series of three patients. *J Clin Immunol*. 2017;37(2):231–232.
58. Mathias K, Mantha A, Mathias L, Arkfeld D. The relationship of mast cell activation syndrome and hypermobile Ehlers-Danlos syndrome in hospitalized patients in the united states. *Ann Rheum Dis*. 2021;80(suppl 1):965.

59. Karnik AN, Gadkari S, Ruark J. (207) Factitious disorder in pregnancy: when should you confront the patient? *J Acad Consult-Liaison Psychiatry*. 2023;64 (suppl):S103.
60. Paul M, Engler D. Complex, persistent, multi-generational presentation of hereditary alpha tryptasemia syndrome requiring high dose omalizumab. *Ann Allergy Asthma Immunol*. 2019;123(5)(suppl):S90.
61. Ruhoy I, Brock I, Maitland A. Mast cell activation syndrome, mannose binding lectin, Ehlers-Danlos syndrome, and neuropsychiatric symptoms. *Neurology*. 2022;98(suppl 18):740.
62. Huang J, Del Valle JC, White A. The prevalence of hereditary alpha-tryptasemia in patients diagnosed with POTS via tilt table testing. *J Allergy Clin Immunol*. 2021;147(2):AB135.
63. Jahanbani F, Sing JC, Maynard RD, Jahanbani S, Dafoe J, Dafoe W, et al. Longitudinal cytokine and multi-modal health data of an extremely severe ME/CFS patient with HSD reveals insights into immunopathology, and disease severity. *Front Immunol*. 2024;15:1369295.
64. Caballero B, Austin A. An unusual case of hot flashes in an athlete. *Clin J Sport Med*. 2022;32(2):e203–e204.
65. Shah N, Trimble A. Excessive dynamic airway collapse in a young woman with hypermobility-type Ehlers-Danlos syndrome. *Conference*;Vol. 199 *American Journal of Respiratory and Critical Care Medicine*. 2019.
66. Schofield JR. Persistent antiphospholipid antibodies, mast cell activation syndrome, postural orthostatic tachycardia syndrome and post-COVID syndrome: 1 year on. *Eur J Case Rep Intern Med*. 2021;8(3):002378.
67. Louisias M, Silverman S, Maitland A. Prevalence of allergic disorders and mast cell activation syndrome in patients with Ehlers Danlos syndrome. *Ann Allergy Asthma Immunol*. 2013;1:A12–A13.
68. Reeves L, Ginoza L, Gjurgevich A. Considerations for treatment of comorbid headaches and mast cell activation syndrome: a multidisciplinary team approach. *Headache*. 2021;61(suppl 1):160.
69. Afrin LB, Dempsey TT, Weinstock LB. Post-HPV-vaccination mast cell activation syndrome: possible vaccine-triggered escalation of undiagnosed pre-existing mast cell disease? *Vaccines (Basel)*. 2022;10(1):16.
70. Cheung I, Holoff J, Guzman J, Londono RM, Walsh S, Vadas P. A new disease cluster: postural tachycardia syndrome, hypermobile Ehlers-Danlos syndrome/ hypermobility spectrum disorder and mast cell activation syndrome. *Clin Auton Res*. 2019;29(5):543.
71. Midtlien JP, Curry BP, Chang E, Kiritsis NR, Aldridge JB, Fargen KM. Characterizing a new clinical phenotype: the co-existence of cerebral venous outflow and connective tissue disorders. *Front Neurol*. 2024;14:1305972.
72. Quinn AM. Complex presentations, identification and treatment of mast cell activation syndrome and associated conditions: a case report. *Integr Med (Encinitas)*. 2023;22:36–41.
73. Li S, Chen M, Greenberger P. Lifelong vibratory urticaria in a patient with postural orthostatic tachycardia syndrome and chronic abdominal pain. *Ann Allergy Asthma Immunol*. 2021;127(5)(suppl):S85.
74. Zha K, Brook J, McLaughlin A, Blitshteyn S. Gluten-free diet in postural orthostatic tachycardia syndrome (POTS). *Chronic Illn*. 2023;19(2):409–417.
75. Luskin K, Kahn B, White A. An innovative treatment approach to hereditary alpha-tryptasemia and interstitial cystitis. *Ann Allergy Asthma Immunol*. 2019;123(5):S131–S132.
76. Kacar M, Denman S, Savic S. Selective response to omalizumab in a patient with concomitant ncMCAS and POTS: what does it teach us about the underlying disease? *J Investig Allergol Clin Immunol*. 2018;28(4):261–263.
77. Tremain-Hill T, So K, Ballal M, Pearce CB. Case Series of Severe Gastrointestinal Dysmotility in Ehlers-Danlos Syndrome (Eds). Discussion of Nutritional Management Roadmap. A BN. *Clin Nutr*. 2019;38(suppl 1):S77–S79.
78. Weinstock LB, Brook JB, Myers TL, Goodman B. Successful treatment of postural orthostatic tachycardia and mast cell activation syndromes using naltrexone, immunoglobulin and antibiotic treatment. *BMJ Case Rep*. 2018;11:11.
79. Weinstock LB, Nelson RM, Blitshteyn S. Neuropsychiatric manifestations of mast cell activation syndrome and response to mast-cell-directed treatment: a case series. *J Pers Med*. 2023;13:31.
80. Robblee J, Vanderpluym J, Mendez N, Potter J, Slonaker J, Grimsrud K, et al. Postural tachycardia syndrome (POTS) in migraine patients & their response to erenumab. *Cephalalgia*. 2019;39(1):268–269.
81. Teodorescu DL, Kote A, Reaso JN, Rosenberg C, Liu X, Kwan AC, et al. Postural orthostatic tachycardia syndrome after COVID-19 vaccination. *Heart Rhythm*. 2024;21(1):74–81.
82. Walsh M, Walsh M, Salomone J, Davis B. Ehlers-Danlos syndrome is associated with mast cell activation syndrome and chronic urticaria. *Ann Allergy Asthma Immunol*. 2022;129. S34-S34.
83. Dubuske IV, Koudoro FH, Dubuske L. Association of stiff person syndrome with anti GAD antibodies with immune dysregulation and symptoms of mast cell activation syndrome. *Allergy Eur J Allergy Clin Immunol*. 2018;73(suppl 105):764.
84. Gonzalez-Alvarez F, Estanol B, Gonzalez-Hermosillo JA, Gomez-Perez FJ, Tamez-Torres KM, Pena E, et al. Complete remission with histamine blocker in a patient with intractable hyperadrenergic postural orthostatic tachycardia syndrome secondary to long coronavirus disease syndrome. *J Hypertens*. 2024;42(5):928–932.
85. Alharbi M, Burstin H. Small fiber neuropathy pots and Gottron sign is COVID19 the culprit. *J Gen Intern Med*. 2021;36(suppl 1):S269.
86. Topan R, Pandya S, Williams S, Ruffle JK, Zarate-Lopez N, Aziz Q, et al. Comprehensive assessment of nutrition and dietary influences in hypermobile Ehlers-Danlos syndrome-a cross-sectional study. *Am J Gastroenterol*. 2024;119(4):727–738.
87. Cheung I, Vadas P. A new disease cluster: mast cell activation syndrome, postural orthostatic tachycardia syndrome, and Ehlers-Danlos syndrome. *J Allergy Clin Immunol*. 2015;1:AB65.
88. Sprunger AC, Nguyen CT. Mast cellactivation syndrome: likely diagnosis in an adolescent and her family with elevated tryptase and postural tachycardia syndrome [pots]. *Ann Allergy Asthma Immunol*. 2012;5:A87.
89. Vadas P, Guzman J, McGillis L, Mittal N, Walsh S. Cosegregation of postural orthostatic tachycardia syndrome, hypermobile Ehlers-Danlos syndrome, and mast cell activation syndrome. *Ann Allergy Asthma Immunol*. 2020;125(6):719–720.
90. Wang E, Ganti T, Vaou E, Hohler A. The relationship between mast cell activation syndrome, postural tachycardia syndrome, and Ehlers-Danlos syndrome. *Allergy Asthma Proc*. 2021;42(3):243–246.
91. Wong S, Hasan S, Parducci C, Riley BA. The gastrointestinal effects amongst Ehlers-Danlos syndrome, mast cell activation syndrome and postural orthostatic tachycardia syndrome. *AIMS Allergy Immunol*. 2022;6:19–24.
92. Bonamichi-Santos R, Yoshimi-Kanamori K, Giavina-Bianchi P, Aun MV. Association of postural tachycardia syndrome and Ehlers-Danlos syndrome with mast cell activation disorders. *Immunol Allergy Clin North Am*. 2018;38(3):497–504.
93. Bromser-Kloeden T. Navigating environmental academia in a disabled body: an embodied autoethnography of ableism and advocacy. *Disabil Soc*. 2025;40(1):213–218.
94. Smith GB, Shribman AJ. Anaesthesia and severe skin disease. *Anaesthesia*. 1984;39(5):443–455.
95. Afrin LB. Some cases of hypermobile Ehlers-Danlos syndrome may be rooted in mast cell activation syndrome. *Am J Med Genet C*. 2021;187(4):466–472.
96. Mathias CJ, Owens AP, Iodice V. The postural tachycardia syndrome (POTS). *Auton Nerv Syst Sleep Order Disorder*. 2021:229–237.
97. Tu Y, Abell TL, Raj SR, Mar PL. Mechanisms and management of gastrointestinal symptoms in postural orthostatic tachycardia syndrome. *Neurogastroenterol Motil*. 2020;32(12):e14031.
98. Vazquez M, Chovanec J, Kim J, DiMaggio T, Milner JD, Francomano CA, et al. Hereditary alpha-tryptasemia modifies clinical phenotypes among individuals with congenital hypermobility disorders. *HGG Adv*. 2022;3(2):100094.
99. Huang J, Imam K, Criado JR, Luskin KT, Liu Y, Puglisi LH, et al. Hereditary alpha-tryptasemia in patients with postural orthostatic tachycardia syndrome. *J Allergy Clin Immunol Pract*. 2024;12(2):528–529.e1.
100. Chollet MB, Akin C. Hereditary alpha tryptasemia is not associated with specific clinical phenotypes. *J Allergy Clin Immunol*. 2022;149:728–735.e2.
101. Afrin LB, Ackerley MB, Bluestein LS, Brewer JH, Brook JB, Buchanan AD, et al. Diagnosis of mast cell activation syndrome: a global "consensus-2". *Diagnosis (Berl)*. 2021;8(2):137–152.
102. Solomon BD, Khatri P. Clustering of clinical symptoms using large language models reveals low diagnostic specificity of proposed alternatives to consensus mast cell activation syndrome criteria. *J Allergy Clin Immunol*. 2025;155(1):213–218.e4.