

The relationship between mast cell activation syndrome, postural tachycardia syndrome, and Ehlers-Danlos syndrome

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ABSTRACT

Background: Postural tachycardia syndrome (POTS), hypermobile Ehlers-Danlos syndrome (EDS), and mast cell activation syndrome (MCAS) can occur in the same patient. In this study, we investigated the relationship among these three syndromes.

Objective: To establish the relationship of MCAS in patients diagnosed with POTS and hypermobile EDS as well as characterize the demographics of the patients affected by these syndromes.

Methods: A total of 195 medical records of patients by using a diagnostic codes data base search for disorders of autonomic dysfunction were identified. The demographics of the patients and diagnoses of POTS, EDS, or MCAS were recorded. Confidence intervals of the proportion of patients MCAS within a population of patients with POTS and EDS were compared with the proportion of patients with MCAS and without POTS and EDS. Odds ratios were also calculated within these groups.

Results: The percentage of MCAS within the group of POTS and EDS was 31% in comparison with 2% within the non-POTS and EDS group. The 95% confidence interval calculated for the MCAS in the POTS and EDS group did not overlap with 2%, which showed a statistically significant result. The odds ratio between the two groups was found to be 32.46.

Conclusion: There was a marked percentage of MCAS among the patients with diagnoses of POTS and EDS.

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Postural tachycardia syndrome (POTS) is defined as an increase in heart rate of 30 beats/min within 10 minutes of upright posture in the absence of orthostatic hypotension chronically and in the absence of other disorders or medications that are known to predispose to orthostatic tachycardia. Common cardiac symptoms include palpitations, lightheadedness, or dyspnea. Nonorthostatic symptoms could include gastrointestinal symptoms or even bladder symptoms. POTS is not considered a separate disease but rather a phenotype from different hyperadrenergic, neuropathic, or autoimmune pathophysiologic processes. In clinical practice, these different processes often overlap.¹

Adding to the complexity are many disorders associated with the different processes of POTS. One of these disorders includes Ehlers-Danlos syndrome (EDS). EDS is an umbrella term that describes inherited collagen abnormalities. Generally, patients experience skin hyperextensibility and joint hypermobility. EDS type III, or EDS hypermobility type, is the type most associated with POTS, with a relationship study that shows a prevalence of 18% in patients with POTS versus 0.02%

in the general population.² Although the specific relationship between EDS and POTS is not known, it is hypothesized to be related to connective tissue problems that lead to vascular laxity or perhaps peripheral neuropathies that lead to dysautonomia.³

Mast cell activation syndrome (MCAS) is a general term that describes symptoms that are caused by inappropriate mast cell activation or when mast cell activation is out of proportion to the normal response to outside stimuli, both in the absence of abnormal mast cell proliferation. This can cause symptoms in the skin, gastrointestinal, cardiovascular, respiratory, and neurologic systems with episodic attacks.^{4,5} It can be diagnosed with elevated tryptase levels from the individual's baseline levels during symptomatic episodes and response to medications that target mast cell activation, such as antihistamines or histamine receptor blockers. There are other markers, such as histamine, histamine metabolites, or prostaglandin D2 (PGD₂) metabolites that have been proposed, but they are less specific than tryptase.^{5–8} In clinical practice, the symptoms of MCAS often overlap with POTS and EDS, especially flushing, headaches, shortness of breath, or gastrointestinal symptoms. This leads to the question of whether there is a link among these three disorders.

POTS and EDS seem to have an association; however, the relationship of the triad of POTS, EDS, and MCAS is less certain. Several years ago, a cluster of POTS, EDS, and MCAS was described.⁹ Although the genetics for these disorders would seem convoluted, in 2016, A nature genetic study identified a tryptase-

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elevating gene that could possibly tie together the three disorders.¹⁰ A recent study that recruited patients diagnosed with MCAS discovered a high percentage of POTS and EDS among the participants.¹¹ However, the idea that POTS, EDS, and MCAS could be linked to each other has been controversial. Other articles cite outdated criteria for diagnosis, overlapping subjective symptoms, or no specific pathophysiologic mechanism that links the three disorders.^{12,13} Because of this controversy, we hope to contribute to the available body of evidence that describes the relationship of these three syndromes. Stronger evidence that ties together POTS, EDS, and MCAS would increase clinical suspicion of the other disorders when one is diagnosed, which leads to decreased time to diagnosis for these debilitating diseases.

METHODS

This was a retrospective review of 195 medical records, from 2019–2020, of patients with autonomic dysfunction. This specific group of patients was created by screening medical records of the entire neurology department for the *International Classification of Diseases, Tenth Revision* codes for disorders of autonomic dysfunction.¹⁴ The charts were then reviewed for the diagnoses of POTS, EDS, or MCAS. A subset from the initial group of 195 patients was found with the concurrent diagnoses of POTS and EDS. Some patients within this group were also found to have the triad of POTS, EDS, and MCAS.

The diagnosis of POTS, EDS, or MCAS was determined by a thorough review of the patient's medical record, including history, assessment, and plan as well as outside patient records. Genetic and immunology records were reviewed when available. When possible, the diagnosing and treating physicians for MCAS were recorded. The patient population included both genders, and ages ranged from 19 to 67 years. The proportion of MCAS found in the POTS and EDS subset and the subset without the two diagnoses were compared by calculating a 95% confidence interval (CI). The odds ratio was also calculated between the two groups. The institutional review board of St. Elizabeth's Medical Center approved the study.

RESULTS

A retrospective review of the medical records showed a majority female population (144 women, 51 men), with a large portion of POTS ($n = 111$ [56%]), EDS ($n = 55$ [28%]), and MCAS ($n = 18$ [9.2%]) diagnoses. When the records of the participants with at least the dyad of diagnoses POTS and EDS were reviewed, the proportion of women increased (46 women, 5 men), with an average $\pm$ standard deviation age of 34.5 ± 10.3 years. The triad of diagnoses POTS, EDS, and MCAS was found to make up 31% ($n = 16$) of the group

Table 1 General study population characteristics (N = 195)

Characteristic	Results, n (%)
Gender	
Men	51 (26)
Women	144 (74)
Diagnosis	
POTS	111 (56)
EDS	55 (28)
MCAS	18 (9.2)
Combination of diagnoses	
POTS and EDS	51 (26)
POTS, EDS, and MCAS	16 (8.2)

POTS = Postural tachycardia syndrome; EDS = Ehlers-Danlos syndrome; MCAS = mast cell activation syndrome.

diagnosed with at least POTS and EDS. However, the group that did not have a diagnosis of POTS or EDS ($n = 144$) had 1.3% MCAS ($n = 2$) Tables 1 and 2. The difference between the two groups was statistically significant; the 95% CI calculated for the proportion of MCAS within the POTS and EDS group ranged from 19.1 to 45.9%. In addition, when assuming the that the diagnosis of MCAS was a positive result and the diagnosis of POTS and EDS as the exposure, there was an odds ratio of 32.46 (95% CI, 7.13–147.7).

Although there was a record of MCAS in the electronic medical record for the patients who were affected, information on the specific physicians who diagnosed and treated the illness was more limited. Of the MCAS diagnoses ($n = 18$), there were 11 records that mentioned the diagnosis by a specific physician. Four patients saw physicians at the Brigham and Womens Hospital Mastocytosis Center for their MCAS. The 11 patients with MCAS were diagnosed and seen by nine physicians in total, or ~ 1.2 patients per physician.

DISCUSSION

The comparison between the two groups of patients in our study, patients with POTS and EDS, and patients without either diagnosis showed a marked difference between the proportions of MCAS. The CI of the proportion of MCAS within the POTS and EDS population was 19.1–45.9%, much higher than the reported 2%. In addition, with an estimated odds ratio of 32.46, there seemed to be a relationship among the MCAS, POTS, and EDS diagnoses. Unfortunately, the relationship among these three diagnoses remains controversial in the literature.

Many of the symptoms experienced by the three syndromes are similar and nonspecific, which makes a pathophysiologic relationship difficult to elucidate.

Table 2 Comparison between the patients who were diagnosed with POTS and EDS, and the population of patients who did not have either diagnosis

	Participants Diagnosed with POTS and EDS, including MCAS, <i>n</i> (%) (<i>n</i> = 51)	Participants Without a Diagnosis of POTS or EDS, <i>n</i> (%) (<i>n</i> = 144)
Gender		
Men	5 (10)	45 (31)
Women	46 (90)	98 (68)
Diagnosis		
POTS and EDS, without MCAS	35 (69)	N/A
MCAS	16 (31)	2 (1.3)

POTS = Postural tachycardia syndrome; *EDS* = Ehlers-Danlos syndrome; *MCAS* = mast cell activation syndrome; *N/A* = not applicable.

Nonetheless, there have been proposed mechanisms to explain possible connections. Patients with EDS frequently have symptoms of dysautonomia that overlap with POTS symptoms,^{3,15} and studies have shown a numerical relationship between the two diseases.² It is possible that connective tissue abnormalities with EDS could cause vascular problems or peripheral neuropathies, which leads to dysautonomia.

For POTS and MCAS, one study illustrates a possible relationship between hyperadrenergic POTS and MCAS.¹⁶ The authors propose a positive feedback loop that involves mast cells, strategically located near blood vessels and peripheral neurons, releasing mediators that lead to vasodilation, sympathetic activation, norepinephrine release, and, ultimately, orthostatic intolerance. In turn, the norepinephrine release, along with neuropeptide Y release, can potentially cause mast cell degranulation.¹⁶ However, a more recent study, finding an increased percentage of the patients with MCAS within a POTS population did not correlate with a hyperadrenergic phenotype.¹⁷ Further research needs to combine these two disease processes.

A connection between EDS and MCAS has also been hypothesized, but this is controversial as well. As a connective tissue disorder, EDS could affect the migration, differentiation, and activation of mast cells.¹⁸ One study showed an increased amount of chymase-positive mast cells in the skin of patients with undifferentiated connective tissue dysplasia, although this is not equal to a diagnosis of EDS.¹⁹ Although our knowledge of the interrelationships of these three processes are still developing, our study pointed toward a numerical relationship.

There were several limitations to our study. One limitation of the study included the diagnosis of MCAS and EDS because many of the patients were referred from outside the hospital system to us for autonomic dysfunction. This made it difficult to confirm the validated criteria for the MCAS or EDS diagnoses.

However, the majority of our patients with MCAS were diagnosed and followed up by a board-certified allergist/immunologist or a mast cell specialist, with a large proportion coming from the Mastocytosis Center at Brigham and Women's Hospital. The majority of our patients with EDS were diagnosed by a geneticist with significant experience with EDS, and all of the patients with POTS had autonomic evaluation and testing to confirm the diagnosis. In addition, the reason why the proportion of MCAS within the POTS and EDS group was not compared with the general population was due to the limitations on current knowledge. To date, there are a wide range of estimates of the prevalence of MCAS within the general population, with results of a study reported as "rare,"²⁰ and another study reported upward of 17%.²¹

CONCLUSIONS

Our study pointed toward a high number of likely MCAS diagnoses in patients with concurrent POTS and EDS; therefore, MCAS should be strongly considered if a patient presents with the previous two diseases.

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REFERENCES

1. Garland EM, Celedonio JE, Raj SR. Postural tachycardia syndrome: beyond orthostatic intolerance. *Curr Neurol Neurosci Rep.* 2015; 15:60.
2. Wallman D, Weinberg J, Hohler AD. Ehlers-Danlos syndrome and postural tachycardia syndrome: a relationship study. *J Neurol Sci.* 2014; 340:99-102.

3. Gazit Y, Nahir AM, Grahame R, et al. Dysautonomia in the joint hypermobility syndrome. *Am J Med.* 2003; 115:33–40.
4. Frieri M. Mast cell activation syndrome. *Clin Rev Allergy Immunol.* 2018; 54:353–365.
5. Theoharides TC, Valent P, Akin C. Mast cells, mastocytosis, and related disorders. *N Engl J Med.* 2015; 373:163–172.
6. Theoharides TC, Tsilioni I, Ren H. Recent advances in our understanding of mast cell activation—or should it be mast cell mediator disorders? *Expert Rev Clin Immunol.* 2019; 15:639–656.
7. Khalid MB, Lieberman P. Mast cell disorders and idiopathic anaphylaxis: evaluation and management. *Allergy Asthma Proc.* 2020; 41:90–98.
8. Valent P, Akin C, Bonadonna P, et al. Proposed diagnostic algorithm for patients with suspected mast cell activation syndrome. *J Allergy Clin Immunol Pract.* 2019; 7:1125–1133.e1.
9. 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; 135:AB65.
10. Lyons JJ, Yu X, Hughes JD, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat Genet.* 2016; 48:1564–1569.
11. Vadas P, Guzman J, McGillis L, et al. Cosegregation of postural orthostatic tachycardia syndrome, hypermobile Ehlers-Danlos syndrome, and mast cell activation syndrome. *Ann Allergy Asthma Immunol.* 2020; 125:719–720.
12. Kohn A, Chang C. The relationship between hypermobile Ehlers-Danlos syndrome (hEDS), postural orthostatic tachycardia syndrome (POTS), and mast cell activation syndrome (MCAS). *Clin Rev Allergy Immunol.* 2020; 58:1–25.
13. Valent P, Akin C. Doctor, I think I am suffering from MCAS: differential diagnosis and separating facts from fiction. *J Allergy Clin Immunol Pract.* 2019; 7:1109–1114.
14. World Health Organization. (2004). ICD-10 : international statistical classification of diseases and related health problems : tenth revision, 2nd ed. World Health Organization. <https://apps.who.int/iris/handle/10665/42980>.
15. De Wandele I, Calders P, Peersman W, et al. Autonomic symptom burden in the hypermobility type of Ehlers-Danlos syndrome: a comparative study with two other EDS types, fibromyalgia, and healthy controls. *Semin Arthritis Rheum.* 2014; 44:353–361.
16. Shibao C, Arzubiaga C, Roberts LJ II, et al. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. *Hypertension.* 2005; 45:385–390.
17. Hoffman-Snyder C, Lewis J, Harris L, et al. Evidence of mast cell activation disorder in postural tachycardia syndrome (P1.277.). *Neurology.* 2015; 84.
18. Seneviratne SL, Maitland A, Afrin L. Mast cell disorders in Ehlers-Danlos syndrome. *Am J Med Genet Part C Semin Med Genet.* 2017; 175:226–236.
19. Luzgina NG, Potapova OV, Shkurupiy VA. Structural and functional peculiarities of mast cells in undifferentiated connective tissue dysplasia. *Bull Exp Biol Med.* 2011; 150:676–678.
20. Akin C. Mast cell activation syndromes. *J Allergy Clin Immunol.* 2017; 140:349–355.
21. Molderings GJ, Haenisch B, Bogdanow M, et al. Familial occurrence of systemic mast cell activation disease. *PLoS One.* 2013; 8:e76241. □

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