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Association of Postural Tachycardia Syndrome and Ehlers-Danlos Syndrome with Mast Cell Activation Disorders

Rafael Bonamichi-Santos, MD[a,*], Kelly Yoshimi-Kanamori, MD[a], Pedro Giavina-Bianchi, MD, PhD[a], Marcelo Vivolo Aun, MD, PhD[a,b]

KEYWORDS

• Ehlers-Danlos syndrome • Postural tachycardia syndrome • Dysautonomia
• Mast cell activation disorders • Mastocytosis

KEY POINTS

- Mast cell activation disorders (MCADs) consist of episodic symptoms due to mast cell (MC) mediator release, even anaphylaxis, and diagnosis includes high levels of serum tryptase.
- Ehlers-Danlos syndrome (EDS) and postural tachycardia syndrome (POTS) frequently coexist in a single patient.
- Preliminary data suggest that patients with EDS and/or POTS can present symptoms compatible to MCADs, which could represent a specific phenotype.
- In terms of genetics, it seems there is a role for tryptase in the pathogenesis of MCADs, EDS, and POTS association.
- Studies with larger samples evaluating clinics, genetics, and histopathology are needed to determine if there really is a particular new disease cluster.

INTRODUCTION

Mast cells (MCs) are derived from myeloblasts, which are pluripotent hemopoietic progenitors in the bone marrow.[1] MC growth, differentiation, survival, migration, and functions are modulated by a transmembrane tyrosine kinase receptor (KIT) (also known as CD117) and its interaction with plasma stem cell factor.[1] Local tissue factors, such as interleukin (IL)-3, IL-4, IL-9, and IL-33, and transforming growth

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[a] Clinical Immunology and Allergy Division, University of São Paulo, Av. Dr. Arnaldo, 455, Cerqueira César, São Paulo, São Paulo CEP 01246-903, Brazil; [b] Faculdade Israelita de Ciências da Saúde Albert Einstein, São Paulo, São Paulo, Brazil
* Corresponding author. Clinical Immunology and Allergy Division, University of São Paulo, Rua Florida 1901, 111BS, São Paulo, São Paulo 04565-001, Brazil.
E-mail address: rafaelbonamichi@hotmail.com

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factor β1, have been shown to influence the number and mediator content of MCs, leading to specific phenotypes.[2] MCs in the connective tissue, skin, and peritoneal cavity contain tryptase in their granules and express IL-5 and IL-6. MCs in the respiratory mucosa and gut contain tryptase and chymase and express IL-4.[3]

MC activation is triggered by the following: binding of KIT and stem cell factor; binding of bacterial peptidoglycan to complement receptors; corticotropin-releasing factor receptor 1 and corticotropin-releasing hormone; binding of Fc epsilon receptor I and specific antibodies, such as IgE, to antigens; binding of Fc gamma receptor I and specific antibodies, such as IgG, to worms; binding of Toll-like receptors to lipopolysaccharide and mold; binding of vasoactive intestinal peptide to vasoactive intestinal peptide receptor 1; binding of drugs to the MRGPRX2 receptor; nonsteroidal anti-inflammatory drugs; *Hymenoptera* venom; tumor necrosis factor α; and physical stimuli (pressure and temperature); among others.[4] Several mediators are released after MC activation, including histamine; proteoglycans (heparin); platelet-activating factor; prostaglandin (PG) D2; leukotrienes (LTs), such as LTC4, LTD4, and LTE4; cytokines, such as IL-1, IL-3, IL-8, IL-10, IL-13, IL-16, and tumor necrosis factor α; chemokines; and renin.[5]

MAST CELL ACTIVATION DISORDERS

In MC activation disorders (MCADs), MCs can be increased in number, activity, or both. They are classified as primary, secondary, or idiopathic (**Table 1**).[6] In MCADs, there are episodic symptoms consistent with MC mediator release and increased plasma levels of these mediators. These reactions can usually be successfully treated or prevented with antimediator therapy, such as H1 and H2 histamine receptor antagonists, LT antagonists, and MC stabilizers.[6]

The clinical presentation of MCADs is highly variable because multiple organs and systems, such as the skin (urticaria, angioedema, flushing, and pruritus), gastrointestinal tract (cramping, diarrhea, vomiting, reflux, and abdominal pain), neuromuscular tissues (osteopenia, bone fractures, headache, bone pain, and osteoporosis), airway (shortness of breath, wheezing, throat swelling, and nasal congestion), cardiovascular system (tachycardia, cardiovascular collapse, hypotension, and hypertension), and even the central nervous system (anxiety, shortened memory span, mixed organic brain syndrome, and depression),[5] can be compromised.

Table 1
Classification of diseases associated with mast cell activation

Primary	Mastocytosis Monoclonal MCAS
Secondary	Allergic/atopic (IgE-mediated) disorders MC activation associated with chronic Inflammatory or neoplastic disorders Physical urticarias Chronic autoimmune urticaria
Idiopathic	Anaphylaxis Angioedema Urticaria MCAS

Adapted from Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: proposed diagnostic criteria. J Allergy Clin Immunol 2010;126(6):1101; with permission.

Unfortunately, only a few diagnostic tests are commercially available to clinicians. The measurement of serum tryptase is standardized and commercially available and is the most frequently used test for evaluating MC activity. The urinary (random and 24-h) histamine levels are measured at a few centers. Other tests are still under investigation, including measurements of PGs, such as PGD2 and 11β-PGF2α, LTE4, chromogranin A, plasma histamine, and N-methylhistamine.[5]

It is recommended that at least 2 elevated MC mediator levels be present for a diagnosis of a MCAD. In patients who have a clinical history that strongly suggests MCAD but who have normal levels of tryptase or urinary histamine, a clinician should repeat these tests when the patient is symptomatic.[4]

Several investigators have noted a possible association between MCAD, EDS, and/or postural tachycardia syndrome (POTS).

EHLERS-DANLOS SYNDROME AND MAST CELL ACTIVATION DISORDERS

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of heritable connective tissue disorders that are characterized by joint hypermobility, skin hyperextensibility, and tissue fragility.[7] The estimated frequency of EDS is 1 in 5000 individuals. Of the 13 subtypes, the hypermobility type of EDS (hEDS) is the most common.[7,8] The subtypes are distinct from each other, and the diagnosis is based on family history and clinical criteria, including the degree and nature of involvement of the skin, joints, skeleton, and vasculature.[8]

The genetic basis for the major types of EDS is known, except for the hEDS, which is still unknown (**Table 2**). Clinical classification prevails over genetic classification due to the low global availability of genetic screening.[7]

Some comorbidities have been frequently reported in EDS patients, such as asthma,[9] orthostatic intolerance,[10] eosinophilic gastrointestinal disorders,[11] osteoporosis,[12] and neuropsychiatric conditions.[13] In the past decade, several investigators have described a possible association between EDS and MCAD, particularly in patients with hEDS.[4] In 2011, Luzgina and colleagues[14] noted that patients who sought assistance in cosmetological clinics for connective tissue dysplasia syndrome had a higher density of chymase positive MCs in their undamaged skin. Two years later, Louisias and colleagues[15] noted that patients with joint hypermobility syndrome also had symptoms suggestive of MC degranulation, such as naso-ocular symptoms, asthma, and a history of anaphylaxis. Their study also showed that these patients had a positive response to classic MC/MC mediator antagonists, but the investigators did not observe high levels of tryptase or histamine. In the connective tissues, MCs are located close to peripheral nerves and blood vessels so they can modulate sympathetic activity, vascular tone, and angiogenesis.[16] EDS patients may suffer from peripheral neuropathy that consequently leads to autonomic dysfunction.[17,18]

In 2017, a review article regarding the association between MCAD and EDS was published.[4] The investigators postulated that migration and differentiation of MC progenitors, MC activation, and the pattern of mediators in the MC granules are affected by components of the extracellular matrix. Thus, they hypothesized that MC dysregulation might be associated with EDS.[4] Vengoechea[19] published a letter discussing that the scientific evidence supporting this association was too “weak” because it was a small case series, the study was not controlled, and the questionnaires used were not standardized.[19,20]

The management of EDS is highly variable, because it depends on different variants of the syndrome and a patient’s clinical presentation and severity. The management of MCADs, however, is mainly based on the blockade of MC mediators. Chronic

Table 2
Clinical classification of the inheritance pattern and genetic basis of Ehlers-Danlos syndromes

Clinical Ehlers-Danlos Syndrome Subtype	Inheritance Pattern	Genetic Basis
Classical EDS	Autosomal dominant	Major: COL5A1, COL5A1 Rare: COL1A1 c.934C > T, p.(Arg312Cys)
Classic-like EDS	Autosomal recessive	TNXB
Cardiac-valvular	Autosomal recessive	COL1A2 (biallelic mutations that lead to COL1A2 nonsense-mediated mRNA decay and the absence of proa2[I] collagen chains)
Vascular EDS	Autosomal dominant	Major: COL3A1 Rare: COL1A1 c.934C > T, p.(Arg312Cys) c.1720C > T, p.(Arg574Cys) c.3227C > T, p.(Arg1093Cys)
hEDS	Autosomal dominant	Unknown
Arthrochalasia EDS	Autosomal dominant	COL1A1, COL1A2
Dermatosparaxis EDS	Autosomal recessive	ADAMTS2
Kyphoscoliotic EDS	Autosomal recessive	PLOD1 FKBP14
Brittle cornea syndrome	Autosomal recessive	ZNF469 PRDM5
Spondylodysplastic EDS	Autosomal recessive	B4GALT7 B3GALT6 SLC39A13
Musculocontractural EDS	Autosomal recessive	CHST14 DSE
Myopathic EDS	Autosomal dominant or Autosomal recessive	COL12A1
Periodontal EDS	Autosomal dominant	C1R C1S

Adapted from Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet 2017;175(1):10; with permission.

glucocorticoid therapy is considered a poor choice for MCADs because of chronic toxicities, including the adverse effects of glucocorticoids on connective tissues. Thus, treatment with glucocorticoids may be an even worse treatment choice for MCAD patients who also have EDS.[4]

POSTURAL TACHYCARDIA SYNDROME AND MAST CELL ACTIVATION DISORDERS

POTS is defined as a chronic, multifactorial syndrome of orthostatic intolerance. Patients have recurrent increases in heart rate on standing without orthostatic hypotension and have other associated symptoms that also worsen on standing. For the diagnosis of POTS, clinicians should exclude other disorders, including prolonged bed rest, hyperthyroidism, medication use, and acute blood loss. The diagnostic criteria for POTS are described in **Box 1**.[21,22]

The evaluation of a patient suspected of having POTS should include a complete history and physical examination, orthostatic vital signs, and a 12-lead ECG.[21]

Box 1
Diagnostic criteria for postural tachycardia syndrome

- An increase in heart rate of ≥30 beats per minute on standing in adults (or ≥40 beats per minute in children) with no orthostatic hypotension (fall in systolic blood pressure of ≥20 mm Hg or diastolic blood pressure of ≥10 mm Hg)
- Associated symptoms that are worse with standing (light-headedness, fatigue, palpitations, and syncope) and better with recumbence
- Additional causes of tachycardia excluded, including prolonged bed rest, hyperthyroidism, medications, and acute blood loss
- Chronicity implying symptoms for longer than 6 months

Adapted from Freeman R, Wieling W, Axelrod FB, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res 2011;21(2):69–72; with permission.

Selected patients might benefit from thyroid function testing and a hematocrit evaluation, 24-hour Holter electrocardiography, a transthoracic echocardiogram, and exercise stress testing. If a patient's orthostatic vital signs are normal and the clinical suspicion of POTS is high, a tilt-table test might be helpful because it can provide vital signs during longer periods than in a simple stand test.[21]

Some symptoms of autonomic dysregulation are common in both patients with POTS and those with EDS, such as lightheadedness, palpitations, presyncope, chest pain, and syncope.[23] Furthermore, autonomic testing in EDS patients shows sympathetic cardiovascular control similar to patients with POTS. With regard to patients with hEDS, studies of autonomic function confirmed a high prevalence of POTS-like orthostatic symptoms and orthostatic intolerance. These symptoms can be induced by exercise, meals, standing, or a hot environment.[17,18]

In a study of a POTS population, a prevalence of 18% was observed in patients who met the criteria for EDS, but its prevalence in the general population was approximately 0.02%.[24] It has been reported that hEDS is the most common disorder associated with POTS.[25] The exact relationship between POTS and hEDS is still unclear. Alterations in the connective tissue caused by EDS could lead to vascular laxity and predispose patients to orthostatic blood pooling in the lower extremities.[22,23] In conclusion, there is now more scientific evidence showing an association between EDS and dysautonomia/POTS.

In 2005, Shibao and colleagues[26] described a group of patients with POTS who were also suffering from episodes of flushing, shortness of breath, headache, lightheadedness, excessive diuresis, and gastrointestinal symptoms, such as diarrhea, nausea, and vomiting. They hypothesized that these individuals had abnormal MC activation beyond POTS and compared them with patients with isolated POTS and normal controls. The group of patients identified as "POTS plus MC activation" had higher levels of urine methylhistamine than did the other 2 groups, which suggested a probable role for MCs as the effector cell in this phenotype. They concluded that MC activation should be considered in patients with POTS presenting with flushing.[26] After this pivotal description, a few review articles[10,27] have replicated this information, citing the data first published by Shibao and colleagues.[26]

The management of POTS is complex. It is essentially based on nonpharmacologic approaches, such as a high amount of fluid intake and aerobic exercise. The US Food and Drug Administration has not approved any drug for treating POTS. Many medications have been used to improve the symptoms of POTS, mainly by decreasing the

influence of sympathetic tone on the heart. One of these therapeutic agents is propranolol.[10] If a patient presents with POTS and features of MCAD, however, clinicians should avoid the use of β-blockers because they may increase the severity of bronchospasm or hypotension during an anaphylactic reaction and are associated with an increase in anaphylaxis fatalities.

EHLERS-DANLOS SYNDROME, POSTURAL TACHYCARDIA SYNDROME, AND MAST CELL ACTIVATION DISORDERS: A NEW DISEASE CLUSTER?

In 2015, Cheung and Vadas[28] presented a study during the annual meeting of the American Academy of Asthma, Allergy & Immunology. They used a screening questionnaire to look for symptoms compatible with MC activation syndrome (MCAS) and suggested a possible new disease cluster: MCAS, EDS, and POTS. Patients diagnosed as having POTS and EDS were asked to answer a questionnaire, and 66% of the respondents reported symptoms suggestive of MCAS, indicating an association among these 3 syndromes.[28] The investigators defined the study, however, as a pilot study because the sample size was small (15 individuals) and there was no control group.

With regard to the mechanisms involved in this new disease cluster, recent data involving familial cases with high levels of serum tryptase have become available. In 2014, it was demonstrated that familial hypertryptasemia could be associated with MCAS.[29] Moreover, another group described 9 families with an autosomal-dominant inheritance pattern of increased basal total serum tryptase levels and identified an association between MCAS symptoms and tryptase levels; however, none of the patients was diagnosed with monoclonal systemic mastocytosis.[30]

In 2016, the same group of researchers identified germline duplications and triplications in the *TPSAB1* gene, which encodes alpha-tryptase, that segregated with inherited increases in basal serum tryptase levels in 35 families presenting with associated multisystem complaints. Moreover, individuals harboring alleles encoding 3 copies of alpha-tryptase had higher basal serum levels of tryptase and were more symptomatic than were those with alleles encoding 2 copies, which suggested a gene-dose effect. They showed that of the 96 patients, 28% had EDS (2× higher than the general population incidence); 46% were orthostatic intolerant; 51% presented with urticaria, pruritus or flushing; and 16% had previously reacted to *Hymenoptera* venom (2×–3× higher than the general population incidence).[31]

SUMMARY

Preliminary data that were recently published suggest a possible association between MCAD, EDS, and POTS. Nonetheless, the studies had small samples and were based on epidemiologic associations without control groups. Moreover, it remains unclear how elevated basal serum tryptase levels could contribute to these multisystem disorders. The quality of life of patients who have these syndromes is usually low and might be decreased in patients who have several of these syndromes. A multidisciplinary approach, including the participation of allergists, dermatologists, neurologists, cardiologists, physical therapists, and nurses, is needed to better clarify the relationship among MCAD, EDS, and POTS and to find better management for these cases.

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