

Clinical Commentary Review

Mast Cell Activation Syndrome: Tools for Diagnosis and Differential Diagnosis

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The current consensus diagnostic criteria for mast cell activation syndrome(s) (MCAS(s)) were first established in 2012 and updated in 2019. This diagnosis has been attached to multiple medical conditions not intended as part of the diagnosis. In this article, the diagnostic criteria are reviewed and other diseases in the differential diagnosis outlined. The goal of this review is to provide a tool for evaluation of patients with conditions that can mimic MCAS. Furthermore, the potential role for hereditary alpha-tryptasemia in this group of disorders is discussed. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Mast cell activation syndrome (MCAS); Mastocytosis; Tryptase; N-Methylhistamine; Prostaglandin; Leukotriene E₄; Diagnostic criteria of MCAS; Differential diagnosis of MCAS; Hereditary alpha-tryptasemia (HAT); Diagnostic algorithm for MCAS

Mast cell activation syndromes (MCAS(s)) have been defined as a group of disorders in which patients experience symptoms precipitated by mast cell mediator release.¹⁻³ The first report in which the term MCAS was coined described a number of patients with symptoms and laboratory findings suggestive of mastocytosis. However, even though the markers of mast cell clonality were found, the diagnostic criteria for mastocytosis were not fulfilled.⁴ The consensus diagnostic criteria for MCAS include 3 sets of requirements.^{1,2} First, the patient should experience acute and recurrent symptoms secondary to mast cell mediator release. Two organ systems are affected simultaneously. Second, the acute episodes have to be associated with elevated mast cell mediator(s). The mediator specified in the reports is tryptase. Elevation of serum tryptase is defined as an increase of 20% + 2 ng/mL above basal levels. Finally, the symptoms should resolve with therapeutic agents directed at blocking mast cell mediator release or their effects.^{1,2} The diagnostic criteria are summarized in Figure 1. A consensus diagnostic algorithm for differentiating different mast cell disorders has been outlined by

Valent et al.² The term MCAS(s) in the diagnostic criteria was used as an umbrella for multiple types of mast cell disorders.

TYPES OF MCAS(s)

There are 2 types of MCAS(s), primary (clonal) and secondary (nonclonal) (Table I). Primary MCAS(s) have clonal markers such as *KIT* Asp816Val mutation, or aberrant expression of CD25 or CD2 on mast cells. The 2 primary groups of MCAS(s) are mastocytosis (cutaneous and systemic) and monoclonal MCAS. Patients with mastocytosis should fulfill the World Health Organization diagnostic criteria for this disorder.^{5,6} There is 1 major criterion and 4 minor criteria. For a diagnosis of mastocytosis, the patient should have a minimum of 1 major and 1 minor criterion or 3 minor criteria (Table II). Patients with monoclonal MCAS fulfill 1 to 2 of the diagnostic criteria for mastocytosis and have evidence of mast cell clonality.

Nonclonal MCAS(s) consist of 2 types; the first is secondary mast cell activation via a known trigger such as IgE-mediated stimulation. The second is idiopathic in which the etiology of the factor(s) activating mast cells is not known (Table I).² Much of the current medical and lay literature uses the term MCAS synonymously with idiopathic MCAS and not with clonal or secondary MCAS(s).^{1,2,8-17}

CONSENSUS DIAGNOSTIC CRITERIA FOR MCAS(s)

First criterion: symptoms

The symptoms of mast cell activation, according to the consensus criteria, are a direct result of mast cell mediator effects. The symptoms should be acute and recurrent; furthermore, at least 2 organ systems should be affected concurrently. The organ systems that can be affected by mast cell mediator release are cutaneous, gastrointestinal, cardiac, respiratory, and neuropsychiatric. Symptoms such as flushing and syncope are highly suggestive of mast cell activation.

Other disorders, however, need to be considered in the differential diagnosis. Obtaining a detailed medical history and performing an organ-specific physical examination are of critical importance. A number of other clinical conditions can present with acute and recurrent symptoms involving 2 or more organ systems. Symptoms of those conditions can mimic MCAS. A list of the potential symptoms in a number of those disorders is summarized in Table III. Other conditions, not mentioned in the table, have been extensively reviewed by Valent and Akin.¹⁶ The allergist needs to work closely with the patient's primary physician and possibly other subspecialty physicians for the patient's best interest. It is worth noting that some of the conditions listed in Table III are much more common than mast cell disorders. Finally, one should consider symptoms related to

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Abbreviations used

HAT- Hereditary alpha-tryptasemia
LTE₄- Leukotriene E₄
MCAS- Mast cell activation syndrome
N-MH- N-Methylhistamine
PG- Prostaglandin and its metabolites
POTS- Postural orthostatic hypotension with tachycardia syndrome

medication side effects and the possible presence of 2 concurrent conditions.

Second criterion: laboratory findings

To fulfill the diagnostic criteria of MCAS, patients should have an elevation of mast cell mediators at the time of development of symptoms. The only mast cell mediator with a specified increase in level is tryptase.^{1,2,41} This has served the criteria well. Serum tryptase should be collected between 1 and 4 hours after a suspected mast cell activation spell. This level should be compared with baseline/basal tryptase levels. Basal tryptase levels should be collected at least 24 to 48 hours after a suspected mast cell activation event/spell. An elevation of the serum tryptase level by at least 20% plus 2 ng/mL is considered consistent with mast cell activation. The major drawback to this criterion is the availability of sample collection to perform the assay within this time period.

Other validated mast cell mediators include urinary N-methylhistamine (N-MH),⁴²⁻⁴⁵ urinary prostaglandin (PG) metabolites,⁴⁵⁻⁴⁹ and urinary leukotriene E₄ (LTE₄).⁵⁰ Studies have shown that during the symptoms of anaphylaxis the level of 9 α -11 β -prostaglandin F₂ (9 α -11 β -PGF₂) in urine was significantly higher than levels in healthy controls.⁵¹ After anaphylaxis, 9 α -11 β -PGF₂ increased during the 0- to 3-hour period. In contrast, the maximum increase of LTE₄ occurs during the 3- to 6-hour collection interval.⁵¹ Urine LTE₄ is higher in those with anaphylaxis who developed severe hypotension in comparison with those without anaphylactic shock. Significant correlation is found between maximum LTE₄ and 9 α -11 β -PGF₂ in patients with anaphylactic shock.⁵¹ LTE₄ levels returned to normal 20 hours after the spell. The maximum increase was 5.5- to 2-fold above baseline. Furthermore, LTE₄ and N-MH levels rise in parallel during exercise-induced anaphylaxis.⁵² 9 α -11 β -PGF₂ is correlated with idiopathic MCAS, whereas N-MH is a better marker of clonal MCAS.⁴⁶

Assays available for the 3 mediators used to require 24-hour urine collection. Current assays, however, are performed on a random urine sample. The best time frame for sample collection is around 3 hours after the suspected spell. The sample should be a fresh collection, with the bladder emptied at the time of the spell. An elevation by 30% above the upper end of the normal range can be, arbitrarily, considered consistent with an MC activation spell. To date, there are no available data for further validation of the level considered higher than baseline values. The assays are all commercially available at the Mayo Medical laboratory and are Clinical Laboratory Improvement Amendments (CLIA) certified. Once the physician orders the assays, from the Mayo Medical laboratories as a mail in specimen, the patient receives a kit by mail. The kit will always be available to the patient for collection of the urine sample and mailing it back to the laboratory after a suspected mast cell activation spell.

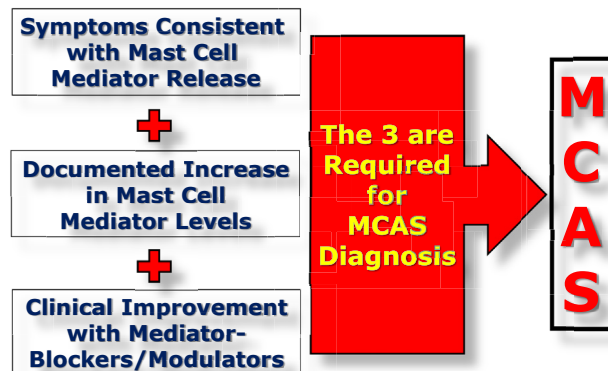


FIGURE 1. Summary of the current diagnostic criteria for MCAS(s). MCAS, Mast cell activation syndrome.

Instructions to the patient on collection and mailing the sample to the laboratory are included with the kit. The results will be sent to the ordering physician.

It is important to correlate mediator release with the occurrence of symptoms. The importance of this correlation is the elevation of tryptase and some of urinary mediators in other conditions (Table IV). Comprehensive and clinically relevant testing should be an integral part of the patient evaluation (Table IV).

Third criterion: therapeutic response

The third diagnostic criterion is response to therapy. It is clear from the above discussion that the therapeutic response to specific treatments is required to ensure that the diagnosis is correct. Therapies used in MCAS include medications that modify mediator production/stabilize mast cells, and/or medications that block or modify mediator effects or receptor binding.¹⁵ Those medications include different classes and generations of antihistamines, leukotriene antagonists, sodium cromoglycate, 5-lipoxygenase inhibitors, and PG blockers. Injectable epinephrine is only needed for anaphylaxis. It is important to note that the treatment should be tailored to the patients' symptoms. If possible, therapy should target the elevated urinary mediators.⁴⁵ For example, patients with elevated PG metabolites and normal N-MH are more likely to benefit from aspirin, provided they are not aspirin allergic. Other comorbid conditions have to be treated independently and need to receive appropriate therapy. Patients with comorbid conditions should receive appropriate therapies as dictated by standard medical care. The goal is using the least number of beneficial medications at the lowest effective dose. The different therapeutic modalities for patients with MCAS have been reviewed in detail by Castells and Butterfield.¹⁵

Patients with clonal MCAS, not those with idiopathic MCAS, should be followed for the burden of the disease. Patients with clonal MCAS can be offered cytoreductive therapies on a case-by-case basis. Older cytoreductive modalities include interferon alpha,⁵⁶⁻⁶⁵ hydroxyurea,⁶⁶ and cladribine.⁶⁶⁻⁷¹ Patients with aggressive systemic mastocytosis and those with mast cell leukemia could be placed on the newly approved therapy with midostaurin.⁷²⁻⁷⁹ Avapritinib showed therapeutic promise in early studies, but it is not yet available for clinical use.⁸⁰⁻⁸³ Patients with mastocytosis who do not have the *KIT*

TABLE I. Classification of MCAS(s)⁵⁻⁷

Primary (clonal) MCAS(s)	Cutaneous mastocytosis	Fulfills the WHO diagnostic criteria for cutaneous mastocytosis but not systemic mastocytosis
	Systemic mastocytosis	Fulfills WHO diagnostic criteria for systemic mastocytosis
	Monoclonal MCAS	Evidence for clonal mast cells identified; however, the WHO diagnostic criteria for mastocytosis are not fulfilled
Secondary (nonclonal) MCAS(s) and idiopathic MCAS	IgE-mediated mast cell activation	Identifiable trigger(s)
	Direct mast cell activation	Identifiable trigger(s)
	Idiopathic mast cell activation	No clearly identifiable etiology

MCAS, Mast cell activation syndrome; WHO, World Health Organization.

TABLE II. WHO diagnostic criteria for systemic mastocytosis

Criterion	Characteristic
Major criterion	Dense multifocal infiltrates of >15 mast cells in the bone marrow or another extracutaneous organ
Minor criteria	>25% of mast cells are atypical
	<i>KIT</i> mutation in codon 816 in the bone marrow or other extracutaneous organs
	Mast cells in the bone marrow or another extracutaneous organ express CD25 and/or CD2
	Baseline serum tryptase >20 ng/mL in the absence of a hematologic neoplasm*

WHO, World Health Organization.

For the diagnosis of mastocytosis, the patient should have at least 1 major and 1 minor criterion or 3 minor criteria.

*If the patient has another associated hematologic neoplasm, tryptase cannot be used as a diagnostic criterion.⁵⁻⁷

TABLE III. Differential diagnosis of symptoms resembling MCAS

Organ system	Symptoms Disorder	Derm			GI		CV			Rsp		NP
		F ¹⁸⁻²²	U ^{23,24}	AE ^{24,25}	Da ²⁶⁻³⁰	AP	S	HTN	TC	Ds	W	A/O
Cutaneous	Angioedema acquired	+	+	+	+	+	+		+	+	+	+
	Hereditary angioedema			+		+	+			+		+
Endocrine	Thyroid disorders	+	+	+	+	+		+	+			+
	Adrenal disorders	+	+		+	+	+		+			+
	Menopause	+	+			+			+			+
CV	Arrhythmias, myocardial infarction	+					+	+	+	+	+	
GI	Inflammatory bowel disease		+		+	+				+	+	
	Irritable bowel syndrome				+	+			+			+
Infectious diseases	Organ specific or systemic	+	+	+	+	+	+		+	+	+	+
Neurogenic	Stroke						+	+	+			+
Neoplasms	Hematologic myeloid	+	+	+	+							+
	Genitourinary		+	+	+	+						
	Medullary thyroid carcinoma	+			+				+			+
	Carcinoid	+			+	+					+	+
	Pheochromocytoma	+			+			+	+		+	+
	VIPoma or other secretory tumors	+			+	+						
Autoimmune disorders	Systemic or organ specific	+	+	+	+	+	+		+	+	+	+
	Vasculitides	+	+	+	+	+	+	+	+	+	+	+
Medication	Serotonin syndrome ³¹	+	+	+	+	+	+	+	+	+		+
	SSRI ³¹⁻³⁴	+				+			+			+
	Toxic or allergic reactions ³⁵	+	+	+	+	+	+	+	+	+	+	+
Toxins	Scombroid/histamine ³⁶⁻⁴⁰	+	+	+	+	+				+	+	+
Psychiatric	Panic attacks	+			+	+	+		+	+	+	+

AE, Angioedema; A/O, anxiety and/or other neuropsychiatric symptoms; AP, abdominal pain/dyspepsia; CV, cardiovascular; Da, diarrhea; Derm, dermatologic; Ds, dyspnea; F, flushing; GI, gastrointestinal; HTN, hypertension; MCAS, mast cell activation syndrome; NP, neuropsychiatric; Rsp, respiratory; S, syncope; SSRI, serotonin reuptake inhibitors; TC, tachycardia and/or arrhythmia; U, urticaria; VIPoma, vasointestinal peptide (VIP) secreting tumor; W, wheezing.

“+”: symptom combinations that can be potentially present in patients with the listed disorder.

Asp816Val mutation can benefit from imatinib mesylate.^{66,84-93}
Other agents, such as dasatinib, have not been successful.^{94,95}
Cyto-reductive agents should not be used in patients with

idiopathic MCAS. For a more detailed evaluation of the risks and benefits of the therapeutic agents, see the review by Castells and Butterfield.¹⁵

TABLE IV. Laboratory findings: disorders in the differential diagnosis

Cell or system	Disorder	Laboratory results									
		Trypt	N-MH	PG	LTE4	5-HIAA	MTN	TSH	Cort	Cltn	G/VIP
Mast cells	Clonal MCAS	+	+	+	+						
	Secondary MCAS	+	+	+	+						
	MCAS of other known etiology	+	+	+	+						
	Idiopathic MCAS	+	+	+	+						
Eosinophils	Hyper eosinophilic syndrome(s)	+		+	+						
Cutaneous	Angioedema acquired	+						+			
Endocrine	Hyper- or hypothyroidism							+			
	Adrenal disorders								+		
GI	Inflammatory bowel disease ⁵³⁻⁵⁵		+								
Renal	Insufficiency	+									
Respiratory	AERD				+						
Neoplasms	Immature myeloid progenitors	+									
	Genitourinary			+							
	Medullary thyroid carcinoma							+		+	
	Carcinoid					+					
	Pheochromocytoma						+				
	VIPoma or other secretory tumors										+
	Proton pump inhibitors ³⁵										+
Toxins	Scombroid/histamine		+								

5-HIAA, 5-Hydroxyindole acetic acid; AERD, aspirin-exacerbated respiratory disease; Cltn, calcitonin; Cort, cortisol; GI, gastrointestinal; G/VIP, gastrin or vasointestinal peptide; LTE4, leukotriene E4; MCAS, mast cell activation syndrome; MTN, metanephrines and/or catecholamines; N-MH, N-methylhistamine; PG, prostaglandin metabolites; Trypt, serum tryptase; TSH, thyroid stimulating hormone; VIPoma, VIP secreting tumor.

“+”: mediator combinations that can be abnormal in patients with the listed disorder.

TABLE V. Prevalence of disorders and symptoms associated with HAT

Organ system	Condition	Percentages of patients with HAT who have the concomitant diagnosis*
Atopy	Environmental allergies or asthma	94
	Anaphylaxis	21-28
	Venom allergy	14-22
Gastrointestinal	Irritable bowel syndrome	49-58
	Gastroesophageal reflux disease	65-100
	Cramping abdominal pain with diarrhea	87
Cutaneous	Flushing and/or pruritus with or without urticarial	51-80
Skeletal	Congenital skeletal abnormalities	26-53
	Retained primary teeth	21-47
Chronic pain	Chronic arthralgia	45-73
	Headaches and generalized pain	47-73
Connective tissue disorders	Hypermobility joints	28-37
Dysautonomia	POTS	46
Neuropsychiatric diagnosis	Anxiety/depression	50
	Sleep disturbance	39-73

HAT, Hereditary alpha-tryptasemia; POTS, postural orthostatic hypotension with tachycardia syndrome.

*The percentage of symptoms and other conditions, henceforth the range, increase with higher alpha-tryptase gene copy number.^{122-124,128}

CURRENT CONFUSION

A number of publications suggested that idiopathic MCAS, a misdiagnosis, is associated with a myriad of chronic medical conditions.^{9,14,17,96-108} The conditions reported in association with idiopathic MCAS include neuropsychiatric disorders,^{9,109} solid organ malignancies,^{96,102,108,110} blood disorders,^{98,101} nonspecific peripheral blood mutations,¹¹¹ and other rare conditions.⁹⁹ Within this confusion, the use of chemotherapeutic

agents,¹⁰⁰ monoclonal antibodies,^{103,105,107} and tyrosine kinase inhibitors^{103,105,112} for idiopathic MCAS has been reported. The concern with this line of aggressive therapy is the lack of a clear diagnosis and lack of identified cellular targets.

Patients who are reported to have this misdiagnosis of “chronic” form of MCAS are reportedly disabled with multiple other chronic comorbidities.^{113,114} In a number of case reports and published patient surveys, the diagnosis of

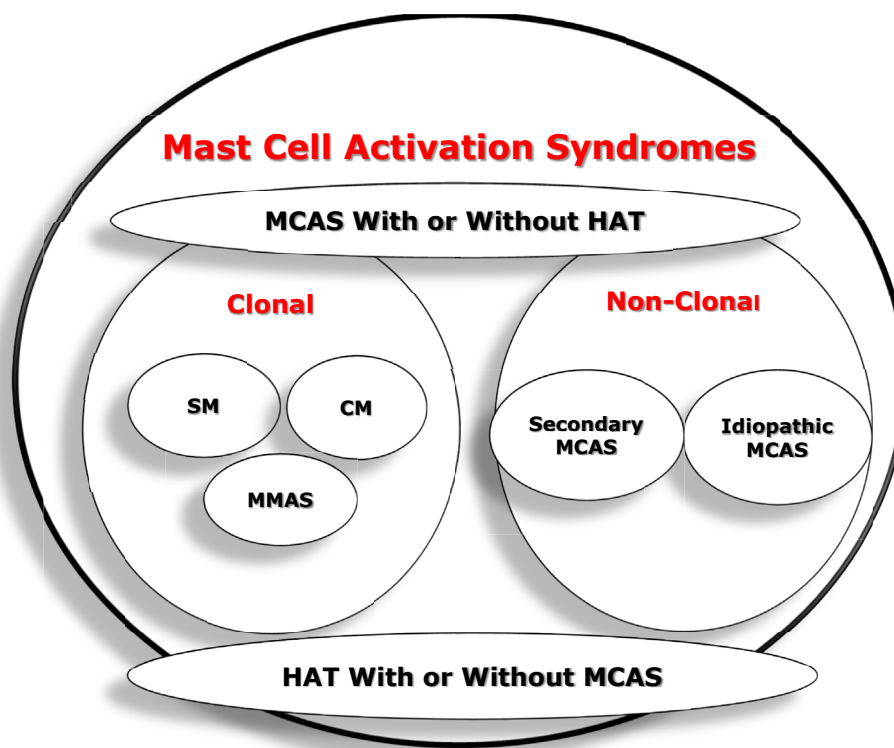


FIGURE 2. Types of different MCAS(s). *CM*, Cutaneous mastocytosis; *HAT*, hereditary alpha-tryptasemia; *MMAS*, monoclonal mast cell activation syndrome; *MCAS*, mast cell activation syndrome; *SM*, systemic mastocytosis.

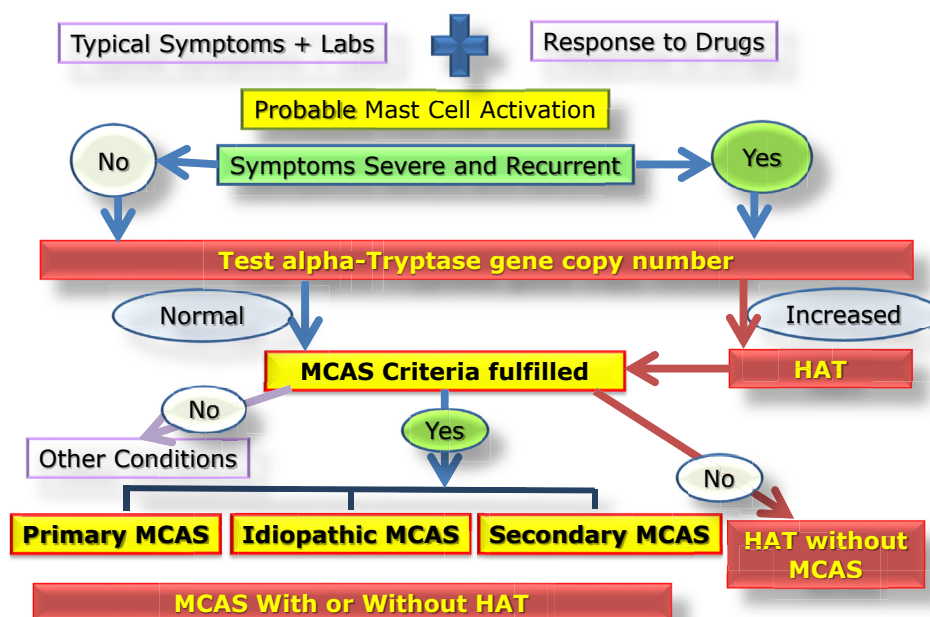


FIGURE 3. Proposed diagnostic algorithm for MCAS(s) in the setting of HAT. *HAT*, Hereditary alpha-tryptasemia; *MCAS*, mast cell activation syndrome.

idiopathic MCAS was associated with the comorbid diagnoses of postural orthostatic hypotension with tachycardia syndrome (POTS)¹¹⁵⁻¹¹⁷ and/or joint hypermobility or Ehlers-Danlos syndrome,^{113,114,116,118-120} among others.

This misdiagnosis does not meet the consensus diagnostic criteria that specify the acuteness of symptoms. There is no evidence, to date, that implicates mast cell activation in any of those conditions.¹²¹

HEREDITARY ALPHA-TRYPTASEMIA

A new disorder in which patients and their family members have elevated serum tryptase was first described in 2014.¹²² This disorder is inherited in an autosomal dominant fashion. Hereditary alpha-tryptasemia (HAT) is highly prevalent and affects an estimated 4% of the general population.^{122,123} Patients with HAT are atopic and experience multiple atopic, connective tissue, gastrointestinal, and neuropsychiatric disorders.^{122,123} The severity of the symptoms affecting patients with HAT is directly correlated with the level of serum tryptase. Further study of this patient population revealed duplication of the tryptase alpha gene.^{123,124}

The tryptase gene locus, on chromosome 16p13.3, has 4 paralogous genes: *TPSG1*, *TPSB2*, *TPSAB1*, and *TPSD1*.^{123,124} Serum tryptase is encoded by 2 of those genes that express the alpha- and beta-isoforms.¹²⁵⁻¹²⁷ Beta-tryptase is encoded by *TPSB2*. *TPSAB1*, on the other hand, can encode either alpha- or beta-tryptase.^{123,124} *TPSG1* encodes gamma-tryptase, which is membrane bound and not released in the circulation. *TPSD1* is not expressed. Patients with HAT have increased copy number of the *TPSAB1* gene encoding alpha-tryptase.^{123,124} This results in an increase of levels of serum tryptase. Serum tryptase levels reflect the *TPSAB1* copy number. The higher the gene copy number, the higher the serum tryptase and the higher/worse the patient symptoms and comorbidities (Table V).^{123,124}

Analysis of the tryptase gene copy number is currently available commercially. The company that performs the assay is "Gene by Gene, LTD." The details of ordering and mailing samples are available on the company's website. The order has to be placed by a physician and requires a buccal swab. The cost of the assay is \$169 and might not be covered by the patient's insurance.

HAT AND MCAS(s)

The clinical findings in patients with HAT overlap with those reported in the "chronic" form of MCAS(s). Many of the symptoms and conditions identified in patients with HAT¹²²⁻¹²⁴ have been associated with "chronic" MCAS.¹²⁸ Patients with HAT have a high prevalence of environmental allergies, asthma, anaphylaxis, urticaria, flushing, abdominal pain, and diarrhea. Furthermore, they can have connective tissue disorders, hypermobile joint disorders, neuropsychiatric diagnoses, chronic musculoskeletal pain, and POTS (Table V). The etiology of this symptom complex remains to be known. At this point in time, the only other gene identified in close proximity to tryptase is *CACNA1H*.¹²⁹ *CACNA1H* can be coinherited with the tryptase genes, but the clinical significance of this coinheritance is yet to be identified.¹²⁹

HAT is not part of the definition of MCAS(s). It is, therefore, clinically beneficial to consider HAT in the differential diagnosis of patients with chronic symptoms. Not all patients with unusual symptoms have HAT. However, all patients with those symptoms want a diagnosis. Even though current treatments are directed at each associated condition, a diagnosis is what patients are seeking. Information regarding the commercial availability of the assay is discussed in this article.

HAT AND MCAS, MORE QUESTIONS

The identification of HAT puts forth more questions than answers regarding MCAS(s).¹²⁸ The percentage of patients with

clonal and idiopathic MCAS(s) who have HAT, and vice versa, is unknown. Are all the patients with idiopathic MCAS actually patients with HAT? Is serum tryptase responsible for the symptoms? Are there multiple types of idiopathic MCAS(s)? Is HAT a clonal mast cell disorder? Is there linkage disequilibrium between the *TPSAB1* and other genes or gene promoters/inhibitors resulting in those acute and chronic symptoms and syndromes? Should HAT gene testing be part of the diagnostic algorithm?

CONCLUSIONS

Despite well-delineated criteria for diagnosis of clonal, secondary, and idiopathic MCAS, the field is in a state of flux. At this point, adhering to the diagnostic criteria and therapeutic recommendations is in the best benefit of patients (Figure 2). Each patient should undergo an evaluation of the disorders in the differential diagnosis. The role HAT should or does play in the diagnosis is evolving. A proposed diagnostic algorithm, modified from the international consensus diagnostic criteria for MCAS,² is outlined in Figure 3. It is clear, at this juncture, that further research is needed to address the questions posed above.

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