



Mast cell activation syndrome: is anaphylaxis part of the phenotype? A systematic review

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Purpose of review

Mast cell activation syndrome (MCAS) and anaphylaxis are the result of a spontaneous or triggered pathological degranulation of mast cells (MCs) and might have as substrate normal or pathological MCs (increased burden, aberrant MCs or both).

Recent findings

This review summarizes the most recent evidence on immunoglobulin E (IgE)-mediated and non IgE-mediated mechanisms underlying MC activation and degranulation and highlights the importance of standardized diagnostic criteria for MCAS. Application of these criteria implies that in most cases the clinical presentation of MCAS meets the diagnostic criteria for anaphylaxis.

Summary

Integrating clinical parameters and diagnostic test recognition and underlying clonal MC disease are of utmost importance for a patient-tailored approach. Hereditary alpha-tryptasemia can be encountered in context of anaphylaxis, MCAS and primary MC disorders.

Keywords

anaphylaxis, hereditary alpha-tryptasemia, mast cell activation syndrome, mastocytosis, MRPGRX2, tryptase

INTRODUCTION

Mast cell activation syndrome (MCAS) is characterized by recurrent episodes of symptoms, such as hives, diarrhea and hypotension. Anaphylaxis is a potentially life-threatening systemic hypersensitivity reaction with rapid onset of symptoms. Both clinical entities are the result of a spontaneous or triggered pathologic degranulation of mast cells (MCs) and might occur in the context of a primary MC disorder. This review focuses on anaphylaxis and its peculiarities in the context of MCAS. A Pubmed-based search was performed using the following criteria: English language only; last 18 months; MESH Key words: MC activation (1392 articles), AND anaphylaxis, AND MCAS, AND alpha-tryptasemia, mastocytosis. A total of 176 articles were selected, 43 of which were considered relevant.

Articles of essential importance published more than 18 months ago have been also included.

MOLECULAR PLAYERS AND MECHANISMS

The mechanistic basis of anaphylaxis is MC degranulation causing the rapid release of preformed MC

mediators from secretory granules (SGs) following MC activation either through surface IgE:FcεRI aggregation or through IgE-independent pathways. SGs are a specialized intracellular compartment of MCs containing various amines, proteases, cytokines, and growth factors, most of them being tightly packed on proteoglycan scaffolds. Basic research progress in recent years provides increasing evidence for the translation of molecular events into clinical findings.

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KEY POINTS

- Mast cell activation syndrome (MCAS) is characterized by episodes of multiorgan symptoms caused by degranulation of mast cells.
- Pathologic activation of mast cells might be the result of both IgE-dependent and IgE-independent signaling.
- MCAS can be primary, secondary, or idiopathic.
- Integrating clinical information with available investigations is essential for recognizing an underlying clonal mast cell disorder and a patients' tailored management plan.

A major discovery relating to the SG protease content was the formation of α/β -tryptase heterotetramers, adding to the previously described β -tryptase homotetramer [1[■],2]. The newly described heterotetramer elucidates mechanosensory-induced MC activation, an IgE-independent pathway, typically associated with vibratory urticaria. The released α/β -tryptase heterotetramer partially cleaves, thereby activating, membrane EMR2 (Epidermal Growth Factor-like module-containing mucin-like hormone receptor-like 2, CD312, a member of the adhesion G-protein coupled receptor family) [1[■]].

SG trafficking and fusion need fine tuning of MC activation with actin depolymerization and microtubule formation [3,4], and stepwise involvement of specialized N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs) and regulatory cytosolic proteins [5[■]]. It was recently demonstrated that – depending on the stimulus – the induced actin cytoskeleton remodeling translates into distinct cellular responses such as migration, SG degranulation, or antimicrobial defense [6,7].

The intensity of SG exocytosis is under control of fusion events involving either incomplete fusion between SG and plasma membrane ('kiss-and-run exocytosis' allowing escape of small molecules, mainly amines), full fusion (release of soluble contents of individual SG) or compound exocytosis (fusion between multiple SGs with only one or few SG-plasma membrane fusion points, a launch pad for simultaneous extrusion of the content of multiple SGs, including the proteoglycan scaffold) [3,5[■]]. Additional levels of regulation are introduced by the amount, valency, and affinity of the allergen cross-linking the IgE:Fc ϵ RI complexes [5[■]].

The classical pathway of SG trafficking described in connection to allergen-induced aggregation of IgE:Fc ϵ RI complexes and downstream signaling

[5[■]] was sufficient to explain symptoms of allergen-induced immediate hypersensitivity. The description of an ever-increasing number of IgE-independent receptors capable to activate or alter SG degranulation is expanding our understanding of MC mediator-related symptoms arising without involvement of a specific allergen.

Mas-related G protein-coupled receptors (MRGPR), comprising the orthologues MRGPRX2 in human MC and Mrgprb2 in murine MC, form an area of current intense research. MRGPRs induce immunoglobulin-independent MC degranulation in response to an array of cationic ligands, recently expanded to bacterial quorum-sensing molecules involved in protective antimicrobial immunity [8] and nociceptive neuron-derived substance P resulting in atopic skin itching [9]. IgE:Fc ϵ RI-induced activation causes massive release of SG content by compound exocytosis with release of particular granular content that can travel to regional lymph nodes, whereas MRGPR activation is initiated even faster, but does not involve intergranular fusion and does not release aggregated particular contents [10,11[■]].

Complex allergen sources such as *Hymenoptera* venoms can induce SG degranulation through a combination of different MC activating signals [12], or enhance it through apparently unrelated noncanonical signaling pathways. For example, mutations in the KARS gene (encoding lysyl-tRNA synthetase) resulted in noncanonical activation of Microphthalmia-associated transcription factor followed by facilitation of MC degranulation, clinically evident following *Hymenoptera* stings in a patient lacking other criteria of MC-related disorders [13]. In another report, anaphylaxis severity was increased by genetic defects of the intracellular Ca²⁺ channel TPC1 via enhanced MC degranulation [14].

MC precursor recruitment and local maturation, SG biogenesis and exocytosis are influenced by multiple factors. Recently, the epidemiological gender bias in the risk of occurrence and severity of MC-related anaphylaxis was associated to the levels of perinatal androgens [15]. Indeed, high levels of testosterone in newborn mice, either naturally occurring in males, or experimentally induced in females, conferred relative protection by means of reduced concentrations of preformed mediators in SG and comparatively reduced release following activation. Another team reported that anaphylaxis was abolished in a murine model of passive anti-DNP IgE systemic anaphylaxis in animals selectively lacking connective MC but possessing intact mucosal MC populations, a finding that might hold true in the equivalent human MC populations [16].

Other important modulators of MC degranulation at the cellular level and well-known cofactors of anaphylaxis in clinics are ongoing inflammation and infection. Thus, inflammatory compounds, direct interaction of MCs with pathogens, tissular damage through alarmins such as IL-33, anaphylatoxins and complement fragments and even exercise are potent modulators of anaphylaxis [17]. Chronic parasitic infections may impact MCs in different ways: (i) by increasing their numbers locally as demonstrated in a clinical study where MC hyperplasia was present during *Opisthorchis viverrini* infestation [18] and (ii) by attenuation of MC degranulation and subsequent anaphylaxis severity, as reported in a murine model [19]. From a therapeutic perspective, the only etiological treatment of anaphylaxis, when available, is allergen-specific immunotherapy, which was recently shown to result in a desensitized MC phenotype with reduced degranulation and increased ability of inducing Treg cells [20].

Figure 1 provides a summary of the properties of the MC as a regulatory and effector hub.

INVESTIGATIONS

Investigation of MC burden and degranulation in clinical practice is limited. Serum tryptase is the most reliable and affordable biomarker, whereas others, including histamine, lipid mediators, and their urinary metabolites, are used on a much lower scale, mainly because of technical difficulties and the lack of validated diagnostic cut-offs [21–23]. Proper recognition of MC degranulation with systemic effects requires a paired sampling of acute and baseline serum tryptase (aST and bST) and the application of the consensus algorithm [11[¶]]. Meeting the international consensus formula for the increase in aST is the prerequisite for laboratory definition of MC activation. bST measurement is also important for suspecting an underlying clonal disease or hereditary alpha-tryptasemia (HαT).

Beside ST, urinary assays that can be used for documenting increased MC-related products include: N-methylhistamine (normal value < 150 μmol/mol creatinine), methylimidazole acetic acid (normal value < 1.9 mmol/mol creatinine), 11b-PGF2α (normal value < 1000 ng/mL), and LTE4 (normal value < 104 pg/mg creatinine)[24]. Although these assays can be helpful for suspecting a primary MC disorder, they are less specific for documenting MC degranulation. To date, the minimal increase of these mediators that would indicate MC degranulation has not been established yet.

An integrated evaluation of clinical parameters, bST and investigation of *KIT* D816V mutation in

peripheral blood are helpful in suspected clonal MC disease [25[¶]]. TPSAB1 genotyping can identify HαT, but currently the test is available in a limited number of centers [2,26[¶]]. A bone marrow (BM) biopsy can confirm or rule out a clonal MC disorder. Specific IgE, skin tests and basophil activation tests (BAT) are applied to define a clinically relevant sensitization in the context of primary and secondary MCAS. Challenge tests can be helpful for assessing the causative role of a specific trigger and/or provide safe alternatives in case of triggered proven anaphylaxis.

Recent reports using plasma proteomics suggest that new biomarkers of MC activation and burden could become available in the future [27].

ANAPHYLAXIS

As indicated above, anaphylaxis is a rapidly evolving, acute, potentially life-threatening reaction. Its pleiotropic manifestations together with the lack of point-of-care testing have made difficult the proposal of universally accepted definition and diagnostic criteria. During the Second NIAID/Food Allergy and Anaphylaxis Network symposium in 2005, a consensus was reached on three diagnostic criteria that identify anaphylaxis as a systemic or multiorgan reaction with cutaneous manifestations in a high percentage of cases [28]. However, as advocated by the experts it has become evident that some refinements are needed. For example, although not multiorgan, isolated respiratory symptoms might be life-endangering and need, therefore, a prompt and rapid treatment. Furthermore, some triggers of anaphylaxis (e.g. α-Gal) might induce a delayed onset of symptoms. These refinements have been included in the WAO proposal in 2019 [29]. Furthermore, some ad hoc diagnostic criteria with levels of certainty have been proposed. A 3-grade of certainty system that is frequently adopted is the Brighton Collaboration Case Definition of Anaphylaxis after vaccination. For all levels of diagnostic certainty, anaphylaxis is a clinical syndrome characterized by a sudden onset and a rapid progression of signs and symptoms and involving multiple (≥2) organ systems. Grades of certainty are defined based on the clinical phenotype with several major and minor mucocutaneous, respiratory, gastrointestinal (GI) and cardiovascular symptoms [30]. Note that a MC tryptase elevation above the upper normal limit is considered as a minor criterion. Interestingly, although the NIAID and Brighton diagnostic criteria have similar diagnostic performances a disagreement in up to 30% of cases can be registered [31,32]. In perioperative settings, another score has been proposed. In this score, points for MC tryptase can be added or subtracted from the clinical score [33[¶]].

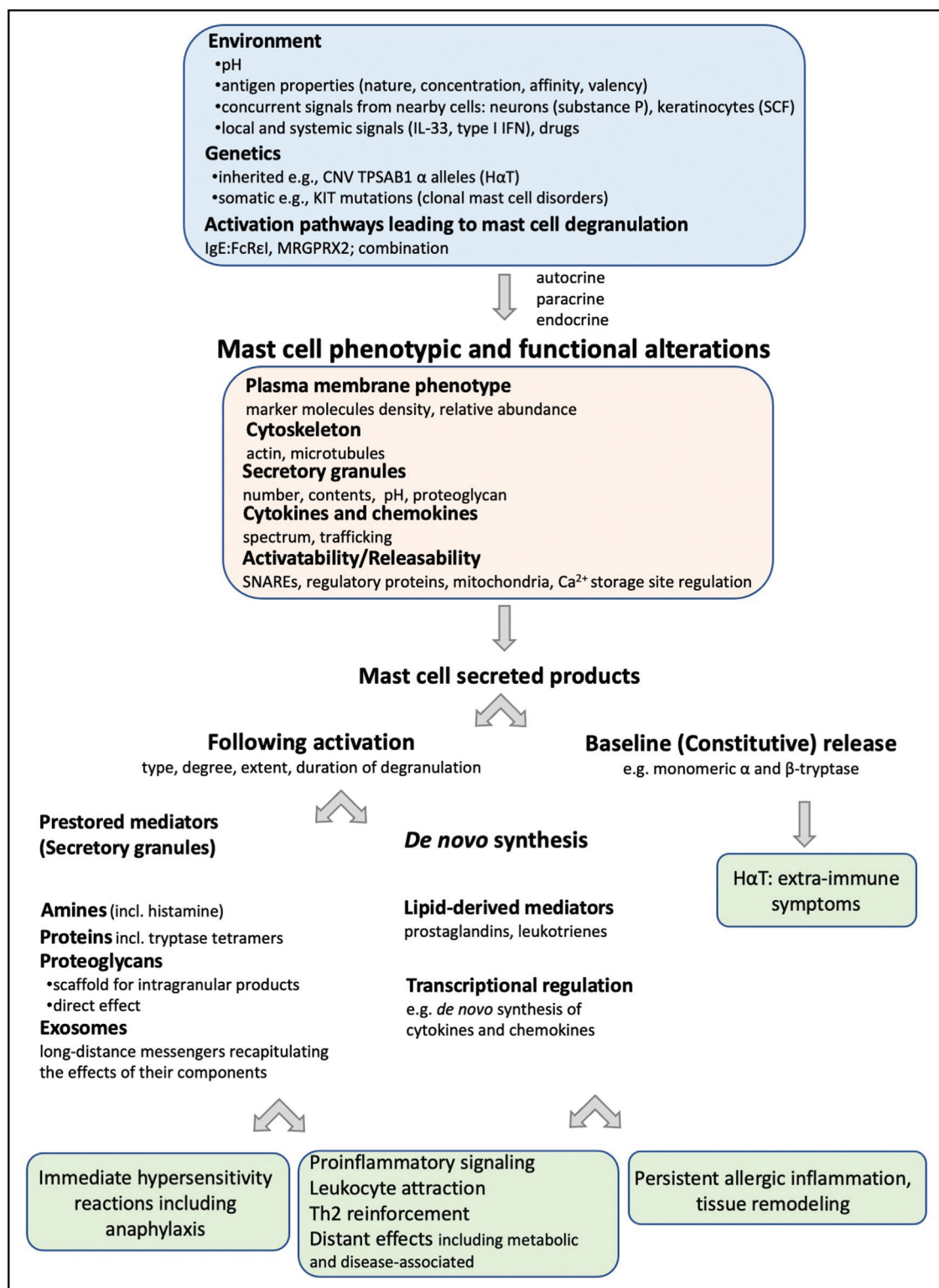


FIGURE 1. The mast cell as a regulatory and effector hub. Mast cells integrate genetic, environmental and activation signals and translate them into phenotypic and functional changes controlling the type and amount of secreted mast cell products, ultimately affecting pathophysiological processes and clinical presentation. CNV, copy number variation; H α T, hereditary α -tryptasemia; IFN, interferon; IL, interleukin; incl., including; SCF, Stem Cell Factor; SNARE, specialized N-ethylmaleimide-sensitive factor attachment protein receptors.

It is important to consider that the predominance of certain symptoms in the clinical phenotype of anaphylaxis can be associated with specific mechanisms (endotypes) accompanied by release of products that might be used as specific biomarkers. Understanding the association between phenotype – endotype – biomarker is crucial to determine the individual risk of reoccurrence, influence of co-factor(s) and role of desensitization [34]. This systematic approach, together with standardized causality assessment, is essential in order to guarantee an efficient and safe mass vaccination campaign during this COVID-19 pandemic [35].

Besides, different grading systems have been proposed to characterize the clinical phenotypes. Presently, the most widely adopted grading systems are inspired by an early publication by Ring and Messmer for the description of reactions to colloid substitutions [36].

MAST CELL ACTIVATION SYNDROME

MC activation syndromes comprise a broad spectrum of clinical conditions caused by pathologic MC degranulation resulting in signs and symptoms involving the skin, GI, cardiovascular, respiratory, and nervous system [22,23,25^{••},37^{••}]. These symptoms are not specific and might be encountered in several other cardiac, neurologic, cutaneous, endocrinologic or GI disorders, infectious diseases and drug toxicity. Therefore, in order to avoid over-diagnosis it is of utmost importance that the patients meet specific diagnostic criteria. The cornerstone of the Consensus criteria for MCAS, described in Table 1, is an aST of 20% + 2 µg/L above the bST value at the time symptoms occur. As shown in Fig. 2, this phenomenon occurs typically when two or more organs are involved, meeting the Consensus criteria for anaphylaxis. MC activation can be IgE-mediated, non-IgE-mediated or unprovoked (spontaneous) and have as substrate normal or pathologic effector cells (increased burden, aberrant phenotype or both) [37^{••}].

Classification of MCAS has been established by a Working Conference in 2012 [38].

Primary MCAS, with or without a specific trigger, include clonal MC disorders with quantitative and/or qualitative defects in MC biology. The typical clinical form is systemic mastocytosis, defined by the 2016 WHO criteria (5), but monoclonal MC activation syndrome (MMAS) can occur when *KIT* mutation(s) (mainly *KIT* D816V) or aberrant CD25 expression are detected without meeting the WHO criteria for systemic mastocytosis. Secondary MCAS include MC activation without an underlying clonal MC disease. Typical etiology is IgE:FcεRI-mediated hypersensitivity. Idiopathic MCAS are cases without clonal MC disorders and without an identifiable trigger [22]. Some MC-related disorders are barely associated with MCAS. For instance, MC hyperplasia is a transient and reversible increase of BM MCs, in response to inflammatory conditions.

In contrast to the episodic multiorgan nature of MCAS, other conditions might be the result of a chronic increase of MC mediators and/or involve other cell types. These include chronic idiopathic urticaria, ADGRE2 associated vibratory urticaria and some chronic manifestations of HαT.

ANAPHYLAXIS IN PRIMARY MAST CELL DISORDERS: WHEN TO SUSPECT IT

As indicated above, clinical presentations of MCAS usually meet the criteria for anaphylaxis [39]. Prevalence of anaphylaxis in patients with systemic mastocytosis ranges from 20 to 50%, with IgE:FcεRI-mediated *Hymenoptera* venom allergy (HVA) being the most common risk factor for recurrent severe anaphylaxis [27,40]. These data point out a risk for anaphylaxis that is 100–1,000-fold higher than in the general population. Therefore, because of the increased risk of recurrent life-threatening anaphylaxis, early recognition of an underlying clonal MC disease is important. Skin evaluation for (monomorphic) maculopapular cutaneous lesions, Darier's sign, indicative of mastocytosis in the skin should lead to the suspicion of an underlying clonal MC disease. Alternatively, patients might suffer from an underlying clonal disease in absence

Table 1. MCAS: diagnostic criteria (refs. 38,22,37). All 3 MCAS criteria (A + B + C) must be fulfilled

Criterion A: Symptoms	Typical clinical signs of severe, recurrent (episodic) systemic MCA are present, involving at least 2 organs or systems
Criterion B: MC markers	Involvement of MC is documented by biochemical studies (preferred marker: increase in serum tryptase level from the individual's bST plus 20% + 2 µg/L; histamine, prostaglandins and leukotrienes and metabolites in serum or urine are also indicated)
Criterion C: Response to therapy	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

MCA, mast cell activation; MCAS, mast cell activation syndrome.

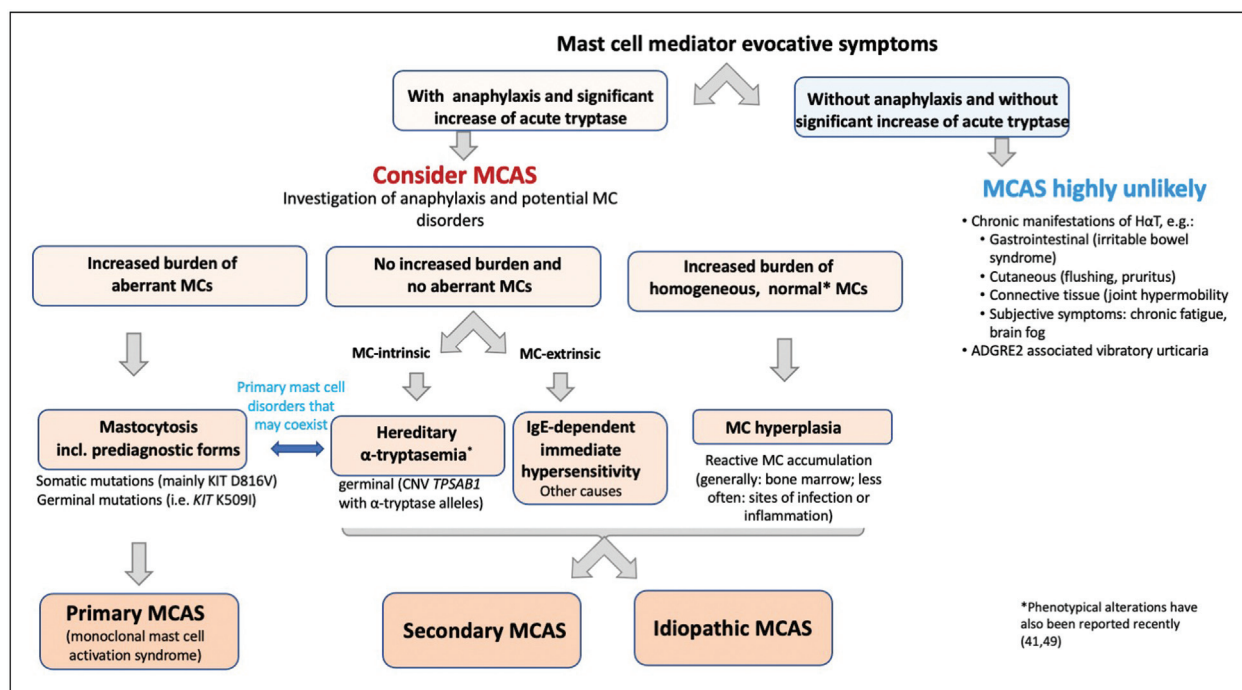


FIGURE 2. Mast cell activation syndrome in the context of mast cell disorders. Depending on the presence or absence of anaphylaxis in a context of symptoms evocative of mast cell mediators, the investigation of suspected MCAS aims at identifying a potential underlying mast cell disorder. ADGRE2, Adhesion G Protein-Coupled Receptor E2; HαT, hereditary α -tryptasemia; MC, mast cell; MCAS, mast cell activation syndrome.

of typical cutaneous lesions. Measurement of bST and analysis of KIT D816V mutation can be used together with clinical parameters for suspecting an underlying clonal MC disorder in these patients. Of note, anaphylaxis displays peculiar clinical presentations in patients with systemic mastocytosis with severe cardiovascular manifestations (i.e. hypotension with syncope) and very rarely urticaria/angioedema and/or respiratory symptoms. Based on these observations, the first predictive score – the Red Española de Mastocytosis (REMA) score – was developed by the Spanish Mastocytosis Network and validated for patients who experienced anaphylaxis due to a wide variety of triggers. In this scoring system, male gender, syncope without urticaria and elevated bST levels ($\geq 25 \mu\text{g/L}$) are predictive of an underlying MC clonal disease with a sensitivity of 92% and a specificity of 81% [41]. Subsequently, Gulen *et al.* [42], proposed a modified REMA score (mREMA) with a lower cut-off of bST to $\geq 11.4 \mu\text{g/L}$ in patients with unexplained anaphylaxis and syncope. The NICAS score [43], developed at NIH for patients with idiopathic anaphylaxis, incorporates the detection of KIT D816V mutation in peripheral blood. Furthermore, measuring aST during the anaphylactic event provides important additional information. Patients without increased aST during anaphylaxis have a low probability of an underlying

MC clonal disease and magnitude of tryptase increase during anaphylaxis is high in patients with underlying primary MC disease [43,44^{***}]. Importantly, severe anaphylaxis occurs preferentially in patients with a low burden of neoplastic MCs. Actually, in patients with systemic mastocytosis and HVA there is not constant increase of anaphylaxis risk with increasing of bST level. After a gradual increase for value up to a bST of $28 \mu\text{g/L}$, the anaphylactic risk decreases with a further increase of bST levels [45]. Importantly, the negative predictive value of KIT D816V in peripheral blood is not high in patients with bST between 5 and $30 \mu\text{g/L}$ [44^{***}]. This means that in this group of patients we need to improve our tools for optimized risk identification of an underlying primary MC disorder.

HEREDITARY ALPHA-TRYPTASEMIA: RELATIONSHIP WITH MAST CELL ACTIVATION SYNDROME AND ANAPHYLAXIS

Several studies have demonstrated a positive association between elevated bST and unprovoked or *Hymenoptera* venom-induced anaphylaxis. It is plausible that in some series, underlying primary MC disorders have been overlooked, due to the lack of systematic BM evaluation [46]. On the other hand, it

is clear that an elevated bST in the context of a MCAS with anaphylaxis is not necessarily associated with an underlying clonal MC disorder, but may be the consequence of a H α T [47]. This genetic trait is determined by an autosomal dominant transmission of an increased number of copies of the α -tryptase encoding TPSAB1 gene [48–50]. Features of H α T include a bST > 8 μ g/L, GI symptoms (pain, diarrhea), joint hypermobility, vibratory urticaria, flushing and increased risk of anaphylaxis. In a recent series, about half of 101 patients with H α T displayed signs of unprovoked anaphylaxis [51[■]]. Moreover, it is intriguing to study the association between H α T, anaphylaxis and morphological aberrant MCs in the absence of signs of clonality. A variable percentage of spindle-shaped MCs up to > 25%, which represent a minor criterion of systemic mastocytosis, has been found in symptomatic patients with diagnosed or highly suspected H α T [44[■],52]. This also means that in clinical practice the presence of H α T can be a confounder for suspecting a primary MC disorder in patients with elevated bST. Of note, in patients with systemic mastocytosis a concomitant H α T plays an additive role in relative risk for unprovoked or *Hymenoptera*

induced anaphylaxis [53[■]]. Finally, a recent series on perioperative hypersensitivity showed that a bST > 8 μ g/L is more frequently associated with the occurrence of anaphylaxis. Therefore, it will be interesting to study the role of H α T as a risk factor and its contribution to the severity of anaphylaxis in perioperative settings [54].

CONCLUSION

In order to avoid an overdiagnosis of MCAS, it is critical that MCAS should be considered as an episodic multiorgan clinical entity that meets the diagnostic criteria for anaphylaxis in most of the cases.

A reasoned recognition of signs and symptoms of anaphylaxis together with appropriate diagnostic investigations are crucial for a patient-tailored management plan (Fig. 3).

It is evident that H α T can impact the decision of performing a BM biopsy, especially in patients with low bST. In this perspective, in our opinion, isolated hypotension is more suggestive of a clonal MC disease, whereas the presence of shortness of breath, wheezing and cutaneous manifestations, hives or angioedema and GI symptoms point to H α T.

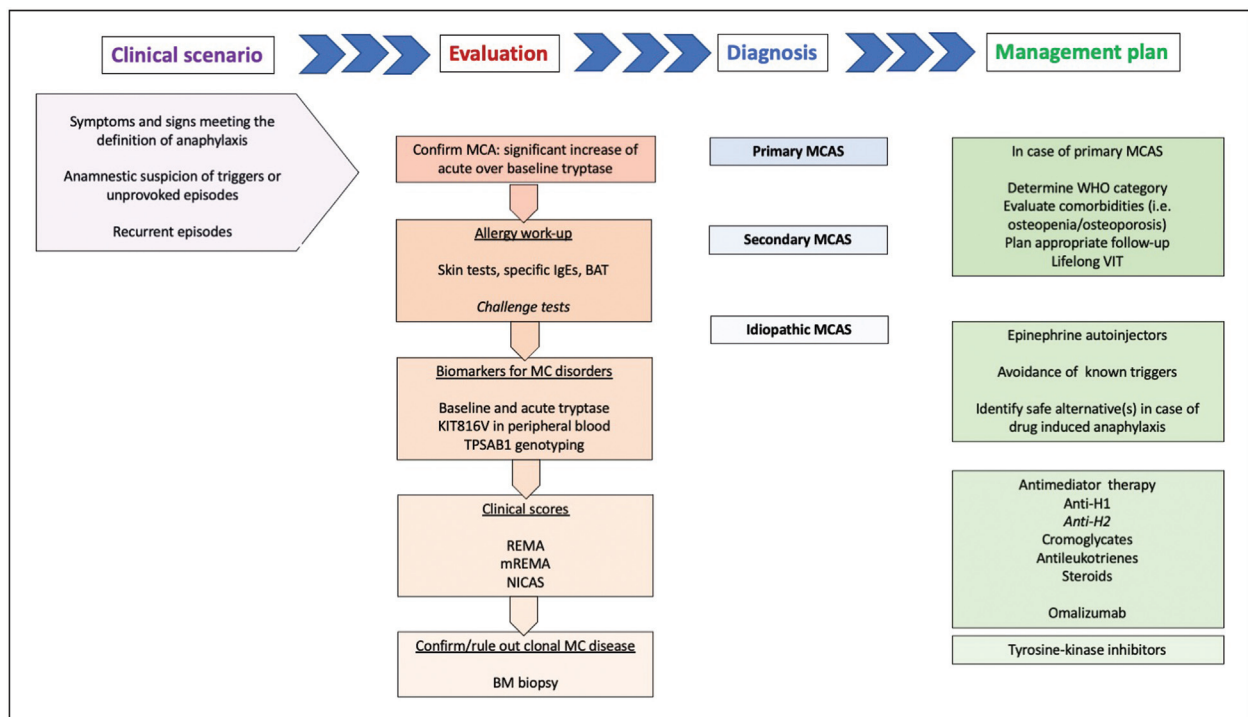


FIGURE 3. Diagnostic and therapeutic tools for the mast cell activation syndrome. MCAS investigation builds upon thorough clinical and laboratory investigations aimed at confirming MCA, identifying an underlying MC disorder, and establishing a therapeutic management plan. BAT, basophil activation test; BM, bone marrow; Ig, immunoglobulin; MC, mast cell; MCA, mast cell activation; MCAS, mast cell activation syndrome; NICAS, NIH Idiopathic Clonal Anaphylaxis Score; REMA, score of the Spanish Network on Mastocytosis; mREMA, modified REMA; VIT, venom immunotherapy.

The clinical significance of MRGPRX2 signaling remains elusive and its role in MCAS is still to be established [55[■]]. At present, the evidence for its role is purely preclinical and results are conflicting. Problems are compounded by the absence of reliable diagnostic tools for MRGPRX2-dependent reactions. It is tempting to speculate that some of the plasma biomarkers recently associated with MC disorders and anaphylaxis might be informative of a MRGPRX2-dependent mechanism.

AIT for anaphylaxis retains a clinical risk of severe reactions. Recent reports harnessing inhibitory molecules, such as CD33 [56] or Siglec-8 [57] suggest the possible extension of safe AIT to patients experiencing severe MCA episodes.

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Conflicts of interest

J.V. reports speaker and consultancy fees in the past 5 years from Meda Pharma (Mylan), Novartis, Sanofi, Thermo Fisher Scientific, outside the submitted work. The other authors declare that they have no COI relevant to this work.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Le QT, Lyons JJ, Naranjo AN, *et al.* Impact of naturally forming human alpha/■ beta-tryptase heterotetramers in the pathogenesis of hereditary alpha-tryptasemia. *J Exp Med* 2019; 216:2348–2361.

Describes a new species of tryptase tetramers with distinct activity from the previously recognized beta-tryptase homotetramers, and elucidates the mechanism of mechanosensory activation of mast cells.

2. Lyons JJ, Yi T. Mast cell tryptases in allergic inflammation and immediate hypersensitivity. *Curr Opin Immunol* 2021; 72:94–106.
3. Lazki-Hagenbach P, Klein O, Sagi-Eisenberg R. The actin cytoskeleton and mast cell function. *Curr Opin Immunol* 2021; 72:27–33.
4. Menasche G, Longe C, Bratti M, Blank U. Cytoskeletal transport, reorganization, and fusion regulation in mast cell-stimulus secretion coupling. *Front Cell Dev Biol* 2021; 9:652077. doi: 10.3389/fcell.2021.652077.

5. Blank U, Huang H, Kawakami T. The high affinity IgE receptor: a signaling ■ update. *Curr Opin Immunol* 2021; 72:51–58.
- Comprehensive review on IgE mediate signaling.
6. Klein O, Krier-Burris RA, Lazki-Hagenbach P, *et al.* Mammalian diaphanous-related formin 1 (mDia1) coordinates mast cell migration and secretion through its actin-nucleating activity. *J Allergy Clin Immunol* 2019; 144:1074–1090.
7. Mezouar S, Vitte J, Gorvel L, *et al.* Mast cell cytonemes as a defense mechanism against coxiella burnetii. *mBio* 2019; 10:e02669-18.
8. Pundir P, Liu R, Vasavda C, *et al.* A connective tissue mast-cell-specific receptor detects bacterial quorum-sensing molecules and mediates antibacterial immunity. *Cell Host Microbe* 2019; 26:114–122. e118.
9. Serhan N, Basso L, Sibillano R, *et al.* House dust mites activate nociceptor-mast cell clusters to drive type 2 skin inflammation. *Nat Immunol* 2019; 20:1435–1443.
10. Galli SJ, Gaudenzio N, Tsai M. Mast cells in inflammation and disease: recent progress and ongoing concerns. *Annu Rev Immunol* 2020; 38:49–77.
11. Vitte J, Sabato V, Tacquard C, *et al.* Use and interpretation of acute and ■ baseline tryptase in perioperative hypersensitivity and anaphylaxis. *J Allergy Clin Immunol Pract* 2021; 9:2994–3005.
- Provides evidence supporting the importance of paired sampling in perioperative hypersensitivity.
12. Starkl P, Gaudenzio N, Marichal T, *et al.* IgE antibodies increase honeybee venom responsiveness and detoxification efficiency of mast cells. *Allergy* 2021. doi: 10.1111/all.14852. [Online ahead of print]
13. Ribo P, Guo Y, Aranda J, *et al.* Mutation in KARS: a novel mechanism for severe anaphylaxis. *J Allergy Clin Immunol* 2021; 147:1855–1864.e9.
14. Arlt E, Fraticelli M, Tsvilovskyy V, *et al.* TPC1 deficiency or blockade augments systemic anaphylaxis and mast cell activity. *Proc Natl Acad Sci USA* 2020; 117:18068–18078.
15. Mackey E, Thelen KM, Bali V, *et al.* Perinatal androgens organize sex differences in mast cells and attenuate anaphylaxis severity into adulthood. *Proc Natl Acad Sci USA* 2020; 117:23751–23761.
16. Cardenas RA, Gonzalez R, Sanchez E, *et al.* SNAP23 is essential for platelet and mast cell development and required in connective tissue mast cells for anaphylaxis. *J Biol Chem* 2021; 296:100268. doi: 10.1016/j.jbc.2021.100268.
17. Brockow K, Plata-Nazar K, Lange M, *et al.* Mediator-related symptoms and anaphylaxis in children with Mastocytosis. *Int J Mol Sci* 2021; 22:2684.
18. Sripa B, Haswell MR. Mast cell hyperplasia in *Opisthorchis viverrini*-associated cholecystitis. *Parasitol Res* 2021; 120:373–376.
19. Kropp L, Jackson-Thompson B, Thomas LM, *et al.* Chronic infection with a tissue-invasive helminth attenuates sublethal anaphylaxis and reduces granularity and number of mast cells. *Clin Exp Allergy* 2020; 50:213–221.
20. Takasato Y, Kurashima Y, Kiuchi M, *et al.* Orally desensitized mast cells form a regulatory network with Treg cells for the control of food allergy. *Mucosal Immunol* 2021; 14:640–651.
21. Weiler CR. Mast cell activation syndrome: tools for diagnosis and differential diagnosis. *J Allergy Clin Immunol Pract* 2020; 8:498–506.
22. Valent P, Akin C, Nedoszytko B, *et al.* Diagnosis, classification and management of mast cell activation syndromes (MCAS) in the era of personalized medicine. *Int J Mol Sci* 2020; 21:9030.
23. Leru PM, Anton VF, Ureche C, *et al.* Mast cell activation syndromes - evaluation of current diagnostic criteria and laboratory tools in clinical practice (Review). *Exp Ther Med* 2020; 20:2348–2351.
24. Butterfield JH, Ravi A, Pongdee T. Mast cell mediators of significance in clinical practice in mastocytosis. *Immunol Allergy Clin N Am* 2018; 38:397–410.
25. Matito A, Escribese MM, Longo N, *et al.* Clinical approach to mast cell ■ activation syndromes: a practical overview. *J Investig Allergol Clin Immunol* 2021; 0. doi: 10.18176/jiaci.0675. [Online ahead of print]
- Practical overview for clinical approach to mast cell activation syndromes.
26. Luskin KT, White AA, Lyons JJ. The genetic basis and clinical impact ■ of hereditary alpha-tryptasemia. *J Allergy Clin Immunol Pract* 2021; 9:2235–2242.
- Comprehensive overview on alpha tryptasemia.
27. Gulen T, Akin C. Idiopathic anaphylaxis: a perplexing diagnostic challenge for allergists. *Curr Allergy Asthma Rep* 2021; 21:11. doi: 10.1007/s11882-021-00988-y.
28. Sampson HA, Munoz-Furlong A, Campbell RL, *et al.* Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006; 117:391–397.
29. Turner PJ, Worm M, Ansotegui IJ, *et al.* Time to revisit the definition and clinical criteria for anaphylaxis? *World Allergy Organ J* 2019; 12:100066.
30. Ruggeberg JU, Gold MS, Bayas JM, *et al.* Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007; 25:5675–5684.
31. Erlewyn-Lajeunesse M, Dymond S, Slade I, *et al.* Diagnostic utility of two case definitions for anaphylaxis: a comparison using a retrospective case notes analysis in the UK. *Drug Saf* 2010; 33:57–64.
32. Blumenthal KG, Robinson LB, Camargo CA Jr, *et al.* Acute allergic reactions to mRNA COVID-19 vaccines. *JAMA* 2021; 325:1562–1565.

33. Hopkins PM, Cooke PJ, Clarke RC, *et al.* Consensus clinical scoring for ■ suspected perioperative immediate hypersensitivity reactions. *Br J Anaesth* 2019; 123:e29–e37.
- International consensus on grading score for perioperative anaphylaxis.
34. Castells M. Diagnosis and management of anaphylaxis in precision medicine. *J Allergy Clin Immunol* 2017; 140:321–333.
35. Castells MC, Phillips EJ. Maintaining safety with SARS-CoV-2 vaccines. *N Engl J Med* 2021; 384:643–649.
36. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. *Lancet* 1977; 1:466–469.
37. 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. e1121.
- International expert consensus on management of MCAS.
38. Valent P, Akin C, Arock M, *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; 157:215–225.
39. Gonzalez-de-Olano D, Matito A, Alvarez-Twose I. Mast cell activation syndromes and anaphylaxis: multiple diseases part of the same spectrum. *Ann Allergy Asthma Immunol* 2020; 124:143–145. e141.
40. Jarkvist J, Brockow K, Gulen T. Low frequency of IgE-mediated food hypersensitivity in Mastocytosis. *J Allergy Clin Immunol Pract* 2020; 8:3093–3101.
41. Alvarez-Twose I, Gonzalez-de-Olano D, Sanchez-Munoz L, *et al.* Validation of the REMA score for predicting mast cell clonality and systemic mastocytosis in patients with systemic mast cell activation symptoms. *Int Arch Allergy Immunol* 2012; 157:275–280.
42. Gulen T, Hagglund H, Sander B, *et al.* The presence of mast cell clonality in patients with unexplained anaphylaxis. *Clin Exp Allergy* 2014; 44: 1179–1187.
43. Carter MC, Desai A, Komarow HD, *et al.* A distinct biomolecular profile identifies monoclonal mast cell disorders in patients with idiopathic anaphylaxis. *J Allergy Clin Immunol* 2018; 141:180–188. e183.
44. De Puyssseleir LP, Elst J, Ebo DG, *et al.* Diagnosis of primary mast cell ■ disorders in anaphylaxis: value of KITD816V in peripheral blood. *J Allergy Clin Immunol Pract* 2021. S2213-2198(21)00569-9. doi: 10.1016/j.jaip.2021.04.062. [Online ahead of print]
- Describes usefulness and pitfall of KIT mutational analysis in peripheral blood in patient with low mast cell burden.
45. van Anrooij B, van der Veer E, de Monchy JG, *et al.* Higher mast cell load decreases the risk of Hymenoptera venom-induced anaphylaxis in patients with mastocytosis. *J Allergy Clin Immunol* 2013; 132:125–130.
46. Bonadonna P, Scaffidi L, Boni E. Tryptase values in anaphylaxis and insect allergy. *Curr Opin Allergy Clin Immunol* 2019; 19:462–467.
47. Khoury P, Lyons JJ. Mast cell activation in the context of elevated basal serum tryptase: genetics and presentations. *Curr Allergy Asthma Rep* 2019; 19:55.
48. 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.
49. Sabato V, Chovanec J, Faber M, *et al.* First identification of an inherited TPSAB1 quintuplication in a patient with clonal mast cell disease. *J Clin Immunol* 2018; 38:457–459.
50. Sabato V, Van De Vijver E, Hagendorens M, *et al.* Familial hypertryptasemia with associated mast cell activation syndrome. *J Allergy Clin Immunol* 2014; 134:1448–1450. e1443.
51. Giannetti MP, Weller E, Bormans C, *et al.* Hereditary alpha-tryptasemia in 101 ■ patients with mast cell activation-related symptomatology including anaphylaxis. *Ann Allergy Asthma Immunol* 2021; 126:655–660.
- Useful for anaphylaxis phenotypes in patients with hereditary alpha-tryptasemia.
52. Giannetti MP, Akin C, Hufdhi R, *et al.* Patients with mast cell activation symptoms and elevated baseline serum tryptase level have unique bone marrow morphology. *J Allergy Clin Immunol* 2021; 147:1497–1501. e1491.
53. Lyons JJ, Chovanec J, O'Connell MP, *et al.* Heritable risk for severe anaphy- ■ laxis associated with increased alpha-tryptase-encoding germline copy number at TPSAB1. *J Allergy Clin Immunol* 2021; 147:622–632.
- Provides evidence of additive role of hereditary alpha tryptasemia in relative risk for anaphylaxis.
54. Ebo DG, De Puyssseleir LP, Van Gasse AL, *et al.* Mast cell activation during suspected perioperative hypersensitivity: a need for paired samples analysis. *J Allergy Clin Immunol Pract* 2021. S2213-2198(21)00436-0. doi: 10.1016/j.jaip.2021.03.050. [Online ahead of print]
55. Ebo DG, Van der Poorten ML, Elst J, *et al.* Immunoglobulin E cross-linking or ■ MRGPRX2 activation: clinical insights from rocuronium hypersensitivity. *Br J Anaesth* 2021; 126:e27–e29.
- Attempt to explore clinical and biological features in IgE-dependent and likely MRGPRX2-dependent rocuronium anaphylaxis.
56. Duan S, Koziol-White CJ, Jester WF Jr, *et al.* CD33 recruitment inhibits IgE-mediated anaphylaxis and desensitizes mast cells to allergen. *J Clin Invest* 2019; 129:1387–1401.
57. Duan S, Arlian BM, Nycholat CM, *et al.* Nanoparticles displaying allergen and siglec-8 ligands suppress IgE-FcεpsilonRI-mediated anaphylaxis and desensitize mast cells to subsequent antigen challenge. *J Immunol* 2021; 206:2290–2300.