

Idiopathic Anaphylaxis: A Form of Mast Cell Activation Syndrome



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1. To identify patients with idiopathic anaphylaxis.
2. To exclude an underlying clonal mast cell disorder in persons with possible idiopathic anaphylaxis.
3. To develop a treatment strategy for patients with idiopathic anaphylaxis.

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Idiopathic anaphylaxis is a condition caused by paroxysmal episodes of sudden-onset multiorgan involvement variably including laryngeal edema, urticaria, bronchoconstriction, dyspnea, hypoxia, abdominal pain, nausea, vomiting, diarrhea, and hypotension. Rarely, the episodes can lead to cardiovascular collapse and death in the absence of a clear trigger, especially in the presence of other cardiovascular comorbidities. Elevated mast cell mediators such as tryptase and histamine have been reported during episodes, and mast cells are considered the

primary cells responsible for driving anaphylaxis in humans. Basophils also secrete histamine and LTC₄ when activated and theoretically can contribute to symptoms. As our understanding of mast cell disorders continue to grow, the classification for these disorders evolves. The purpose of this article was 2-fold: to review the epidemiology, clinical manifestations, and diagnosis of idiopathic anaphylaxis and to discuss the classification of idiopathic anaphylaxis within the broader context of mast cell activation disorders. © 2019 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2020;8:1196-201)

Key words: Mastocytosis; Mast cell activation syndrome; Mast cells; Anaphylaxis; Idiopathic anaphylaxis; Tryptase

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INTRODUCTION

Idiopathic anaphylaxis (IA) is a subset of anaphylaxis involving paroxysmal mast cell activation resulting in multiorgan manifestations including hypotension, hypoxia, diarrhea, urticaria, and upper airway compromise. A recent classification of anaphylaxis has clarified the potential triggers and presentations of anaphylaxis, leading to a better understanding of this complex

Abbreviations used

IA- idiopathic anaphylaxis

MCAS- mast cell activation syndrome

entity.¹ IA is characterized by anaphylaxis in the absence of a clear precipitating factor.

Mast cells are tissue resident effector cells capable of responding to various internal and external stimuli.²⁻⁴ They are the primary cell type responsible for the initiation and propagation of allergic inflammation. These cells are classically thought to develop in the bone marrow, travel to peripheral tissue via the circulation, and mature in the tissue.⁵ Molecularly, they are characterized by expression of the stem cell factor receptor (kit, CD117) and dense FcεR1 expression. More recently, mast cells have been found to express MRGPRX2 receptors, which can be activated through non-IgE pathways by small molecules such as icatibant, quinolones, and neuromuscular blocking agents.⁶ Mast cells release various cytokines, chemokines, and other signaling molecules.⁷ They are the dominant cellular source of tryptase and, along with basophils, release histamine.⁸ Mast cells can also rapidly synthesize lipid mediators such as prostaglandins and leukotrienes via metabolism of membrane-bound arachidonic acid.⁹ Finally, on stimulation, they can release various proinflammatory cytokines and chemokines to propagate inflammation. Basophils can secrete histamine and LTC4 when activated.¹⁰ In drug-induced anaphylaxis, basophils express CD63 and CD203 activation markers, suggesting a potential contribution to anaphylaxis.¹¹ Table I reviews the mediators produced by mast cells and basophils.

Mast cell activation occurs in various clinical conditions.¹² Disorders of mast cell activation have traditionally been divided into clonal and nonclonal entities. More recently, proposed classification has organized mast cell activation disorders into primary (clonal expansion of mast cells), secondary (associated with other allergic and connective tissue disorders), or idiopathic (nonclonal mast cell activation, mast cell activation syndrome [MCAS]).^{13,14} MCAS is defined by episodic presence of symptoms associated with mast cell activation, objective evidence of increased mast cell mediators in the serum or blood, and improvement in symptoms with mast cell-directed therapy.

The purpose of this article was to review the pathophysiology of IA and inappropriate mast cell activation, review the classification of mast cell disorders, discuss diagnosis and treatment of mast cell disorders, and identify areas of research need.

DIAGNOSIS AND CLASSIFICATION OF MAST CELL ACTIVATION DISORDERS

Mast cell activation disorders are characterized by paroxysmal release of mast cell/basophil mediators, which elicit a typical set of clinical manifestations.^{13,14} Akin et al¹³ initially proposed a set of criteria for MCAS in 2010, which were accepted in an international consensus meeting in 2012. Table II reviews the consensus diagnostic criteria for MCAS.^{14,15} The consensus criteria describe paroxysmal episodes that involve various organ systems but often include cutaneous and cardiovascular manifestations. There are 3 criteria: typical symptoms of mast cell activation, objective laboratory evidence in the serum or urine of a validated mast cell mediator, and improvement in symptoms with mast cell-directed therapy.^{13,15,16} All 3 criteria must be

TABLE I. Clinically relevant mast cell mediators

Mediator	Information
Tryptase	• Most specific for mast cells but also produced by basophils
	• Should be measured between 30 min and 4 h after symptom onset
	• Acute increases are specific for mast cell activation events
	• Increased baseline is associated with other disorders
Histamine	• Significant increase is defined by 20% + 2 ng/mL
	• Specific for mast cell and/or basophil activation
	• Metabolites can be measured in 24-h urine collection
Prostaglandin D ₂	• Blood levels have circadian rhythm variation
	• Prostaglandin synthesis occurs in many cells, but prostaglandin D ₂ is mast cell specific and not produced by basophils
	• Useful if elevated during an acute episode or at baseline
	• May respond to aspirin therapy
Leukotriene E4	• Leukotrienes produced by many cells but Leukotriene E4 is specific for mast cells and basophils
	• May respond to leukotriene receptor antagonists and 5-lipoxygenase inhibitors

met to attribute a clinical scenario to a mast cell activation event. In addition, alternative diagnoses must be sufficiently excluded.

Once a diagnosis of MCAS has been confirmed, further classification is necessary. Mast cell activation disorders are divided into 3 categories: primary MCAS, secondary MCAS, and idiopathic MCAS.^{14,15} Primary mast cell disorders are characterized by proliferation of an aberrant mast cell clone carrying a gain of function in KIT. Clonal mast cell disorders include monoclonal MCAS and mastocytosis.^{12,17} Secondary mast cell disorders result in symptoms of mast cell activation although they are caused by a primary allergic process. This may include IgE-mediated food allergy, drug hypersensitivity, or allergic rhinitis. Finally, idiopathic MCAS results in mast cell activation symptoms without a clear precipitating etiology.^{13,18}

IA: EPIDEMIOLOGY AND MECHANISM

There are limited epidemiologic data to address the incidence of IA. One study from Patterson et al¹⁹ estimated the incidence to be between 20,000 and 47,000 (roughly 1:10,000) in the United States in 1995. There are no other formal epidemiologic studies to address the incidence of this condition. However, it is possible to understand the incidence by examining all cases of anaphylaxis. Anaphylaxis (from all causes) is reasonably common, with prevalence varying between 0.09% and 5.1%.²⁰⁻²² The most common reported causes of anaphylaxis include medications, food, and insect stings, which cause 35%, 32%, and 19% of anaphylaxis, respectively.^{23,24} Given the average prevalence of all anaphylaxis is estimated to be around 1% and IA accounts for up to 30% of these episodes, the estimated prevalence of IA is about 0.3% of adults.^{25,26}

IA may occur in patients of all ages. The reported age range is 5 to 83 years.²⁷ It is more common in adults although between

TABLE II. Criteria for MCAS

Criterion A: Typical clinical signs of severe, recurrent (episodic) systemic* MC activation are present (often in the form of anaphylaxis)
Criterion B: Involvement of MC is documented by biochemical studies Increase in serum tryptase from baseline (20% + 2 ng/mL) and/or increase in histamine, histamine metabolites, or prostaglandin D ₂ metabolites
Criterion C: 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

MC, Mast cell.
Adapted with permission from Valent et al.¹⁵
*Systemic: Involving 2 or more organ systems.

TABLE III. Selected differential diagnosis of IA

Anaphylaxis/MCDs	Nonanaphylactic disorders
Mastocytosis and other clonal MCDs	Vocal cord dysfunction
Nonclonal MCDs	Flushing disorders (pheochromocytoma, carcinoid, vasoactive intestinal peptide tumors)
Acute urticaria/angioedema	Somatoform disorders
Food allergy	Vasovagal syncope
	Panic attack
	Asthma exacerbation
	Myocardial infarction or other acute cardiac disorder
	Serumbroidosis

MCD, Mast cell disorder.

4% and 16% of patients are children.^{27,28} More than 60% of patients are female.²⁷ Other atopic conditions are strongly associated with IA; up to 48% of patients may have food allergy, allergic rhinitis, or other atopy.²⁸

The underlying mechanism of production of idiopathic events is not well understood. Clinically, the presentation is similar to that of other types of anaphylaxis. In antigen-dependent anaphylaxis, IgE bound to mast cell FcεR1 recognizes antigen and drives cross-linking of FcεR1 receptors. This leads to degranulation of mast cells and systemic release of vasoactive mediators such as histamine, prostaglandins, and leukotrienes. These mediators drive symptoms of anaphylaxis.²⁹⁻³¹ By definition, there is no identifiable antigen in IA. However, because the clinical presentation and available evidence including elevated tryptase levels after an episode support mast cell degranulation, IA is considered a mast cell activation disorder.³²

Several pieces of evidence support IA as a type of mast cell activation disorder. First, the predominant cell type known to cause anaphylaxis in humans is the mast cell. It should be noted that non-IgE, non-mast cell–dependent anaphylaxis has been reported in mice and is thought to be caused by immune complex formulation and activation of myeloid cells such as neutrophils and macrophages.^{33,34} This phenomenon has not been reported in humans, and the relevance outside of mice is not known. Therefore, all human disorders involving anaphylaxis are thought to be predominantly mast cell–dependent. Second, elevated mediators have been identified in patients during acute episodes of anaphylaxis. This includes urinary histamine metabolites and serum tryptase, which are shared by mast cells and basophils.^{32,35-37} Third, patients improve with mast cell–directed therapy including antihistamines, cysteinyl leukotriene receptor antagonists, and corticosteroids.^{27,38,39}

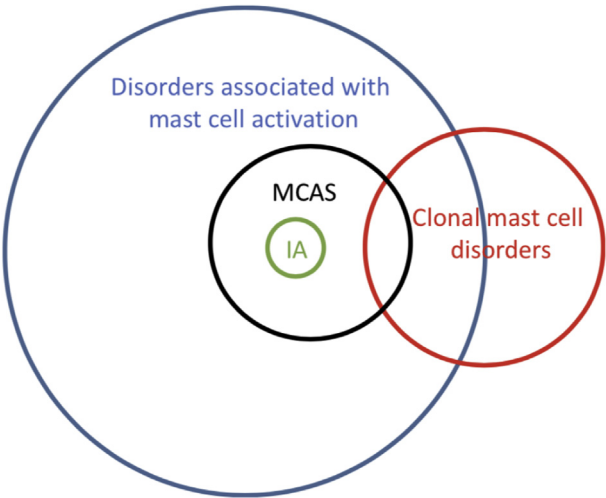


FIGURE 1. Classification of mast cell disorders. Reprinted with permission from Akin.⁴²

Conversely, there are several features that differentiate IA from other mast cell disorders. First, Grammer et al⁴⁰ reported that patients with active IA have more activated T cells (defined by CD3⁺HLA-DR⁺) circulating in peripheral blood.⁴⁰ Second, patients with IA tend to be responsive to systemic corticosteroids. In most cases, prednisone 40 to 60 mg daily can abort episodes of IA.²⁷ Finally, unlike mast cell disorders, IA tends to spontaneously resolve.^{28,41}

IA is classified as a subtype of idiopathic MCAS in a recent review.⁴² Some experts may favor the use of MCAS rather than IA because not all episodes in all patients meet the clinical definition of anaphylaxis. Furthermore, some patients may have idiopathic episodes in addition to those with identifiable triggers, such as exercise, food, or medications.

DIFFERENTIAL DIAGNOSIS

Diagnosis of IA can be challenging. The differential diagnosis is reviewed in Table III. It is most important to distinguish IA from a clonal mast cell disorder.⁴³ One study found that 5 of 12 patients presenting with “IA” had evidence of a clonal mast cell disorder.⁴³ Another study examined characteristics that differentiated patients with clonal and nonclonal mast cell disorders, all of whom presented with anaphylaxis.⁴⁴ They found that young men with cardiovascular symptoms (in particular syncope and hypotension) in the absence of urticaria and angioedema were more likely to have a clonal mast cell disorder. Similarly, in a study of 335 patients with IA, 100% had urticaria or

TABLE IV. Treatment of IA

Acute	Long-term (preventive)
Epinephrine	H1-antihistamines
H1-antihistamines	Prednisone
Albuterol	Omalizumab
Prednisone	
Intravenous fluids	

Treatment of acute episodes is centered around the administration of epinephrine and stabilization of acute pulmonary and cardiovascular complications. The goal of long-term management is to prevent episodes.

angioedema and only 23% had hypotension or syncope.²⁷ Anaphylaxis in patients with clonal mast cell disorders was more likely to be a result of hymenoptera stings. The authors proposed a scoring system to help gauge the necessity of a bone marrow examination (Red Española de Mastocytosis score).^{44,45}

In addition to clonal mast cell disorders, many other clinical conditions can present similar to IA.^{46,47} The differential diagnosis is broad and includes all causes of anaphylaxis such as food, hymenoptera, drugs, and exercise.²⁶ Other allergic conditions such as urticaria, angioedema, and asthma involve a single organ system but often mimic anaphylaxis. Hereditary alpha tryptase-mia is a recently reported disorder characterized by an increase in baseline serum tryptase.⁴⁸ Elevated serum tryptase is caused by autosomal-dominant inheritance of multiple copies of the *alpha tryptase* gene at the TPSAB1 locus. This condition is relatively common and is estimated to affect 6% of the population. A clinical phenotype involving symptoms across multiple organ systems has been proposed although not yet validated, which includes Ehlers-Danlos syndrome-like and postural orthostatic tachycardia-like symptoms, increased hymenoptera-induced anaphylaxis, and flushing.⁴⁹ Flushing, tachycardia, and dizziness may mimic anaphylaxis. Other etiologies include endocrine disorders such as carcinoid, pheochromocytoma, and flushing disorders. Finally, psychiatric conditions such as a panic disorder and somatoform disorder present with similar findings.

Laboratory evaluation can help investigate the underlying etiology of symptoms. The initial evaluation should be conducted at baseline. Laboratory studies include baseline serum tryptase and complete blood cell count with differential. If hypotension and/or syncope occurred, consider KIT D816V mutation in peripheral blood. The KIT D816V mutation can be detected in peripheral blood of 85% to 95% of patients with systemic mastocytosis.^{50,51} Additional tests may be obtained in a symptom-driven manner. Repeat evaluations are necessary at the onset of symptoms. This should include serum tryptase and a 24-hour urine collection for *n*-methylhistamine and prostaglandin F2. The most specific marker is tryptase level. A formula of 20% of baseline + 2 ng/mL has been proposed as a cutoff for clinically significant tryptase elevation after anaphylaxis.⁵²

DIAGNOSTIC CHALLENGES AND PRACTICAL MANAGEMENT

Many patients present with symptoms of mast cell activation or self-report of anaphylaxis. However, not all patients meet criteria for IA or MCAS. The relationship between mast cell activation disorders, MCAS, and IA is represented graphically in Figure 1.

The diagnosis of IA requires 2 primary criteria: confirmed diagnosis of anaphylaxis and no identifiable trigger. Initial presentation of anaphylaxis often includes hypotension and/or hypoxia. Some patients may present with single-organ involvement or milder paroxysmal symptoms. Single-organ involvement is not compatible with anaphylaxis although mast cell activation may still be diagnosed. In patients who do not meet criteria for anaphylaxis or MCAS, an alternative etiology of symptoms should be considered. It is important to note that evidence of elevated mast cell mediators is not required for the diagnosis of IA although it is required for the diagnosis of MCAS.

Management focuses on reducing the frequency and severity of episodes although it is outside the scope of this review. Acute treatment of anaphylaxis is managed similar to other forms of anaphylaxis.²⁴ Table IV provides a brief overview of recommended pharmacotherapy for IA.

GAPS IN THE LITERATURE AND FUTURE RESEARCH

There are significant knowledge gaps in the epidemiology and pathogenesis of IA. Very limited epidemiological data exist for IA—it is difficult to understand the true burden of this disease. Historical literature was limited by a lack of diagnostic techniques to definitely identify a clonal mast cell disorder. Furthermore, additional entities such as food-dependent exercise-induced anaphylaxis, exercise-induced anaphylaxis, and alpha gal-related anaphylaxis have been described.^{53,54} Therefore, much of IA may actually be anaphylaxis caused by a previously undiagnosed clonal mast cell disorder or an unidentified IgE-mediated trigger.^{43,55} Modern studies are needed to clarify the true prevalence, symptoms, and disease characteristics of IA.

Second, a better understanding of mechanism is necessary. Multiples models of pathogenesis have been proposed. It seems likely that this is a heterogeneous disorder with myriad mechanistic causes. Do some patients have an unidentified allergen trigger? Is there an intrinsic mast cell abnormality? Circulating factors such as anti-IgE antibodies? Contribution by other cells such as basophils? Further studies should address the possibility of these causes as well as other triggers for mast cell activation.

Finally, there is some data that indicate a reactive mast cell abnormality in some patients with IA. Many patients have upregulation of CD203c in mast cells.⁵⁶ A larger number of lymphocytes express activation markers in patients with ongoing episodes of IA.⁴⁰ However, mast cells appear to respond normally (ie, are not hyperresponsive) to IgE-mediated stimuli.⁵⁵ There is a paucity of literature examining the presence, function, and intrinsic changes (or lack thereof) in mast cells within this patient population.

CONCLUSIONS

IA is a disorder characterized by paroxysmal mast cell mediator release symptoms in the absence of a clear precipitating factor. IA is thought to be a form of mast cell activation disorder. Symptoms are characterized by hypotension, syncope, bronchoconstriction, and urticaria. Evidence supporting a mast cell-dependent mechanism includes elevations in mediators such as histamine and tryptase during acute episodes. Patients also improve with mast cell-directed therapy. IA is a diagnosis of exclusion and care must be taken to rule out clonal mast cell

disorders and other conditions that present with similar symptoms.

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