

A current review of idiopathic anaphylaxis

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Purpose of review

Idiopathic anaphylaxis is a well established entity that can lead to unnecessary morbidity and costs if not diagnosed and managed properly. To ensure that more patients benefit from proper care, the medical community needs to be better informed of this rare disease.

Recent findings

The classification and treatment of idiopathic anaphylaxis have been fine-tuned over the past 25 years without knowledge of the disease's underlying mechanism, despite much research dedicated towards this end. The observation that idiopathic anaphylaxis is a steroid-responsive disease has led to a more recent view that its underlying mechanism may be autoimmune in nature.

Summary

Although the underlying pathogenesis of idiopathic anaphylaxis remains unknown, thousands of patients in the United States have been successfully treated with the currently recommended regimen of steroids and antihistamines. If diagnosed and treated properly, approximately 85% of patients will have a sustained remission after being tapered off corticosteroids.

Keywords

angioedema, antihistamine, idiopathic anaphylaxis, prednisone, urticaria

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Abbreviation

HRF histamine-releasing factor

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Introduction

Since the first description of idiopathic anaphylaxis in 1978 [1], much has been learned about the diagnosis, classification, and treatment of this rare and occasionally fatal disorder. Unfortunately, idiopathic anaphylaxis still lives up to its name; its cause remains unknown. Given the relatively recent recognition of allergens such as latex as a cause of anaphylaxis, common sense forces the question as to whether some unrecognized allergen exists that could explain the disease. Indeed, physicians were slow to accept idiopathic anaphylaxis as a real entity because of this logic. Despite our limited understanding of the etiology, clinical studies have reported that this serious entity can be managed successfully with published algorithms [2].

Anaphylaxis, a systemic syndrome of immediate hypersensitivity caused by an IgE-mediated release of mediators from mast cells and basophils, presents clinically with bronchospasm, angioedema, hives, and if severe, cardiovascular collapse. Anaphylactoid reactions are clinically indistinguishable from anaphylaxis, but are not IgE-mediated.

Idiopathic anaphylaxis was first described in 1978 by Bacal *et al.* [3], when they published data on 11 patients whose episodes of anaphylaxis could not be explained. The series has been expanded to include over 335 patients who have been followed for over 1100 patient-years without an exogenous allergen being implicated [4]. Atopy was noted in 48% of patients, and represents the exact same percentage reported in a recent Spanish series of 81 patients [5•]. As of 1995, the prevalence of idiopathic anaphylaxis across the United States was estimated to be between 20 000 and 50 000 cases; the same year, Kemp *et al.* [6] published a study of 266 sequential cases of anaphylaxis noting that approximately one-third were idiopathic [7]. The disease exists in all age groups and proves costly if not diagnosed and treated expeditiously [8]. It has been reported that idiopathic anaphylaxis is more common in women, with 65% of 335 idiopathic anaphylaxis patients being women in the literature's largest published case series [4]; in a smaller Spanish series 68% of the 81 cases were women [5•].

Pathogenesis

Multiple theories on the pathogenesis of idiopathic anaphylaxis have been put forward but none have withstood scientific testing. Past investigations into the role of the mast cell and basophil in this disease process did not reveal the underlying mechanism. Over the years

it has been reported that idiopathic anaphylaxis patients and normal individuals have comparable numbers of mast cells in their skin and bone marrow; and that the peripheral mast cells and basophils in idiopathic anaphylaxis patients do not demonstrate hyperreleasability of histamine [9]. Not only do the mast cells of patients with idiopathic anaphylaxis not release more histamine upon stimulation, but they have been reported to display the same threshold response upon exposure to increasing dilutions of various mediators such as histamine, platelet activating factor, and leukotriene D4 when compared with the mast cells of other patients with asthma, chronic idiopathic urticaria, and allergic rhinitis [10].

Studies in the past have also focused on identifying possible culprit antigens that may be surreptitiously evoking the symptoms of idiopathic anaphylaxis. Sonin and Patterson [11] evaluated the role of metabisulfite; they challenged 15 idiopathic anaphylaxis patients with this compound and reported no positive responses. Endogenous progesterone was proposed as a contributing factor when three women with idiopathic anaphylaxis improved after chemical castration; however, further studies reported a lack of correlation between progesterone peaks and the patients' episodes of idiopathic anaphylaxis or increased levels of blood histamine [12,13]. Other investigators have discovered that hypersensitivity to various spices or foods may be responsible for anaphylactic symptoms in a minority of patients with idiopathic anaphylaxis but cannot explain the majority of cases [14]. This last successful attempt at finding an unrecognized culprit allergen raises the possibility that there is no one culprit allergen responsible for all cases of idiopathic anaphylaxis, and that multiple allergens remain to be found. Again, the inability of researchers to find such allergens in the hundreds of published cases of idiopathic anaphylaxis and the thousands of patient-years of follow-up make this possibility doubtful.

Anti-IgE autoantibodies have also been proposed as a possible cause of idiopathic anaphylaxis, although no studies have confirmed this link. Such autoantibodies act on mast cells to crosslink the Fc ϵ RI or IgE bound to this Fc receptor, and have already been described as playing a role in idiopathic urticaria [15]. Fitting with this theory, idiopathic anaphylaxis patients respond to prednisone, which might act by suppressing B-cell production of this autoantibody. However, preliminary studies at Northwestern were unable to detect anti-IgE in 10 idiopathic anaphylaxis patients.

Investigators have also proposed an imbalance between histamine-releasing factors (HRFs) and histamine-releasing inhibitory factors as an underlying cause for patients

with idiopathic anaphylaxis [16]. Again, the success of steroids in treating idiopathic anaphylaxis could be explained by its suppressive effects on activated cells producing such HRFs. Two known HRFs have subsequently been studied at Northwestern, monocyte chemoattractant protein type 1 and macrophage-inflammatory protein type 1a. Levels of each of these HRFs were measured in the serum of normal atopic individuals and idiopathic anaphylaxis patients and no significant differences were found.

More recently, an emphasis has been placed on investigating the possible autoimmune pathogenesis of idiopathic anaphylaxis. Reasoning backwards, it has been thought that as other autoimmune diseases respond to steroids, then the similar responsiveness of idiopathic anaphylaxis may implicate a comparable immunologic mechanism. Grammer and colleagues [17] published recent data to show that patients with acute episodes of idiopathic anaphylaxis demonstrate a higher percentage of activated T lymphocytes in peripheral blood than those idiopathic anaphylaxis patients in remission; and regardless of whether idiopathic anaphylaxis patients were in remission, they displayed more activated B cells than normal individuals [17]. The role of these activated T cells and B cells in the pathogenesis of idiopathic anaphylaxis has yet to be determined.

Clinical presentation

Signs and symptoms in patients with idiopathic anaphylaxis do not differ from patients with other forms of anaphylaxis, and include hypotension, tachycardia, wheeze, stridor, hives, angioedema, pruritus, flushing, nausea, vomiting, diarrhea, dysphagia, light-headedness, and loss of consciousness. In the series of Ditto *et al.* [4] of 335 patients, all of them experienced hives and angioedema, whereas 60% experienced symptoms of upper airway obstruction. Life-threatening symptoms also include the loss of peripheral vascular tone and a concomitant drop in effective vascular volume that may lead to severe hypotension. Unfortunately, cardiovascular collapse from anaphylaxis can occur without the classic clues of wheeze, hives, or angioedema [18], although it is somewhat reassuring that all idiopathic anaphylaxis patients in the series of Ditto *et al.* [4] had at least hives and angioedema. Individual patients may have different combinations of the above-mentioned symptoms but usually tend to have the same manifestations on repeated episodes. Progression from hives and pruritus to the life-threatening symptoms of wheeze, syncope, and laryngeal edema may occur from 10 min to hours after onset depending on the individual.

Diagnosis

Idiopathic anaphylaxis is a diagnosis of exclusion. Only after a thorough history, physical, and review of the

medical record should this diagnosis be entertained. Labwork and testing may also be required to rule out culprit allergens and the numerous diseases that may masquerade as idiopathic anaphylaxis. A thorough history is probably the most important element to the work-up because it will guide subsequent testing. This history should focus on the events surrounding each episode of anaphylaxis, the frequency and severity of attacks, response to treatment, documentation within the medical record of objective evidence of anaphylaxis, and the likelihood that an allergen may be responsible. Known causes of anaphylaxis that must be considered in every patient with a possible diagnosis of idiopathic disease include food, medications, insect stings, latex, radiographic contrast media, and exercise.

Food allergy probably occurs in 1–2% of the population and is the most common cause of anaphylaxis [19]. Symptoms usually begin 5–30 min after ingestion, occasionally after 1–2 h, but rarely any longer. Consider an alternative diagnosis if the symptoms began many hours after ingestion or if the patient has since eaten the suspect food without a reaction. The most common food allergens are shellfish, fish, peanuts, tree nuts, milk, egg, soy, and wheat, which altogether account for over 90% of all food allergies. Diagnosis is confirmed by skin testing and, in some cases, double-blind food challenge.

Medications are another common cause of anaphylaxis and need to be focused on during the history. Any drugs taken within an hour of a reaction should be noted, especially beta-lactam antibiotics and non-steroidal anti-inflammatory drugs. Care must be taken to question about over-the-counter aspirin formulations that the patient may be taking on an as-needed basis. If the patient has angioedema and takes an angiotensin-converting enzyme inhibitor, it is probably best to stop the medication or switch to an angiotensin receptor blocker if clinically warranted. Angiotensin-converting enzyme inhibitors may cause angioedema late into the course of drug therapy, even after a year in some reports [20]. Reported causes of anaphylaxis include almost any medications or their components, as well as diagnostic and therapeutic agents including ciprofloxacin [21], cytarabine [22], tetanus toxoid [23], ranitidine [24], psyllium [25], cromolyn [26], Okt3 [27], insulin [28], proton pump inhibitors [29], dialysis membranes and ethylene oxide gas [30,31], blood products [32], fresh frozen plasma [33], intravenous gamma globulin [34], multiple chemotherapy agents, anesthesia induction agents, and muscle relaxants.

Exercise-induced anaphylaxis occurs during or after exercise and may present only after eating a specific food. Causes of food-dependent exercise-induced anaphylaxis include celery, shrimp, apples, squid, abalone,

wheat, hazelnuts, grapes, eggs, oranges, cabbage, and chicken [35–37]. Other patients react after eating any food before exercise; some patients react to exercise alone [38]. Familial cases of exercise-induced anaphylaxis have been reported, and approximately half of patients are themselves atopic [39,40]. The pathogenesis is uncertain and diagnosis is made primarily by history and challenge if necessary.

Systemic diseases that may present with symptoms similar to idiopathic anaphylaxis include pheochromocytoma, carcinoid syndrome and mastocytosis. If suspected, the measurement of urinary catecholamines, vanillylmandelic acid, and metanephrines may be ordered to help diagnose pheochromocytoma, whereas urine 5-hydroxyindoleacetic acid levels may help diagnose carcinoid syndrome. Systemic mastocytosis may present with the same symptoms as idiopathic anaphylaxis, although patients with mastocytosis do not usually have angioedema. Many patients with mastocytosis have the unique dermatological finding of urticaria pigmentosa, classically described as salmon-colored macules that urticate upon stroking (Darier's sign). In addition to the skin, mast cell infiltration may occur in the liver and spleen, the bones, and the gastrointestinal tract. Non-invasive studies to aid in diagnosis include a 24 h urine histamine collection or serum tryptase level [41], and further studies may include skin biopsy, bone marrow biopsy, or stomach biopsy.

Hereditary angioedema resembles idiopathic anaphylaxis, but hives or other anaphylactic symptoms are not usually present and the angioedema in this disorder tends to progress slowly, often painfully, and without pruritus. A positive family history of similar symptoms offers an obvious clue to the role of this disease in a patient's symptoms, but the lack thereof is not exclusionary. Episodes may be provoked by dental procedures or other causes of local trauma. Making the diagnosis is important because life-threatening symptoms of upper airway obstruction may not respond to epinephrine. Instead, the manifestations may be prevented by daily doses of androgens such as danazol or stanozolol, which increase the ability of hepatic cells to make C1 esterase inhibitor. Diagnosis is made by finding decreased levels of C4, CH50, and C1 esterase inhibitor concentration or function [42]. An acquired form of the disorder also occurs, and is associated with lymphoproliferative and autoimmune diseases.

An asthma attack may be difficult to differentiate from the bronchoconstriction that may accompany an episode of idiopathic anaphylaxis. However, a past history of repeated asthma exacerbations or the lack of other systemic anaphylactic symptoms may help to eliminate idiopathic anaphylaxis as a possibility. Other disorders that may present with stridor or dyspnea and that may

appear similar to an idiopathic anaphylaxis attack include vocal cord dysfunction, panic attacks, Munchausen’s stridor, and globus hystericus.

Classification

The classification of idiopathic anaphylaxis takes into consideration both the frequency and manifestations of idiopathic anaphylaxis attacks (Table 1). Patients who experience six or more episodes per year or two or more episodes in 2 months are classified as idiopathic anaphylaxis-frequent; patients with fewer episodes are classified as idiopathic anaphylaxis-infrequent. This differentiation is important because patients who experience frequent symptoms will require daily suppressive therapy, unlike those patients with infrequent symptoms. Patients are further categorized according to the extent of their symptoms; patients experiencing angioedema or urticaria without other systemic signs of anaphylaxis are described as idiopathic anaphylaxis-angioedema, whereas patients experiencing the additional symptoms of hypotension, gastrointestinal upset, bronchospasm, or cardiovascular collapse are described as idiopathic anaphylaxis-generalized. In this way, patients

may be categorized in four ways, either idiopathic anaphylaxis-generalized-infrequent, idiopathic anaphylaxis-generalized-frequent, idiopathic anaphylaxis-angioedema-infrequent, or idiopathic anaphylaxis-angioedema-frequent.

In addition to these four descriptors, there are several other variations of idiopathic anaphylaxis that have been named. Patients whose disease is controlled with prednisone yet who still require a daily dose to prevent recurrence are said to have corticosteroid-dependent idiopathic anaphylaxis. Patients with corticosteroid-dependent idiopathic anaphylaxis who require higher doses of prednisone, arbitrarily set at more than 60 mg every other day or over 30 mg a day, are classified as having malignant idiopathic anaphylaxis. Patients who do not respond to prednisone and for whom the diagnosis of idiopathic anaphylaxis is in question may be called idiopathic anaphylaxis-questionable. These difficult-to-diagnose patients may lack any confirmatory evidence of actually ever having had an episode of anaphylaxis or angioedema. If such a lack of confirmation persists despite the patient’s claim of multiple exacerbations, especially ones that include emergency department visits where the evaluating doctor fails to find objective signs of anaphylaxis, then the patient may be further classified as undifferentiated somatoform idiopathic anaphylaxis. This diagnosis should be considered whenever an idiopathic anaphylaxis patient does not respond to steroids, which are generally successful in treating the disease. A diagnosis of idiopathic anaphylaxis-variant is noted in the literature and appears to be similar to idiopathic anaphylaxis-questionable in that it represents an interim diagnosis that may be changed once more confirmatory evidence of the patients’ symptoms are revealed.

Treatment

Treatment recommendations for idiopathic anaphylaxis patients depend on the frequency and severity of their exacerbations. Whereas care should be individualized, some simple guidelines should be universally applied (Figure 1). All idiopathic anaphylaxis patients should be educated about idiopathic anaphylaxis and taught how to manage an acute attack. Immediately after the first signs of anaphylaxis, adult patients should inject 0.3 ml of 1:1000 w:v aqueous epinephrine intramuscularly followed by oral doses of both an antihistamine (e.g. diphenhydramine 50 mg or hydroxyzine 25 mg) and 60 mg prednisone. This emergency kit should always be within reach and should be checked occasionally to make sure it has not expired. After use, patients should be transported immediately to the nearest emergency department.

Patients classified with frequent symptoms require maintenance therapy, which should include 40–60 mg

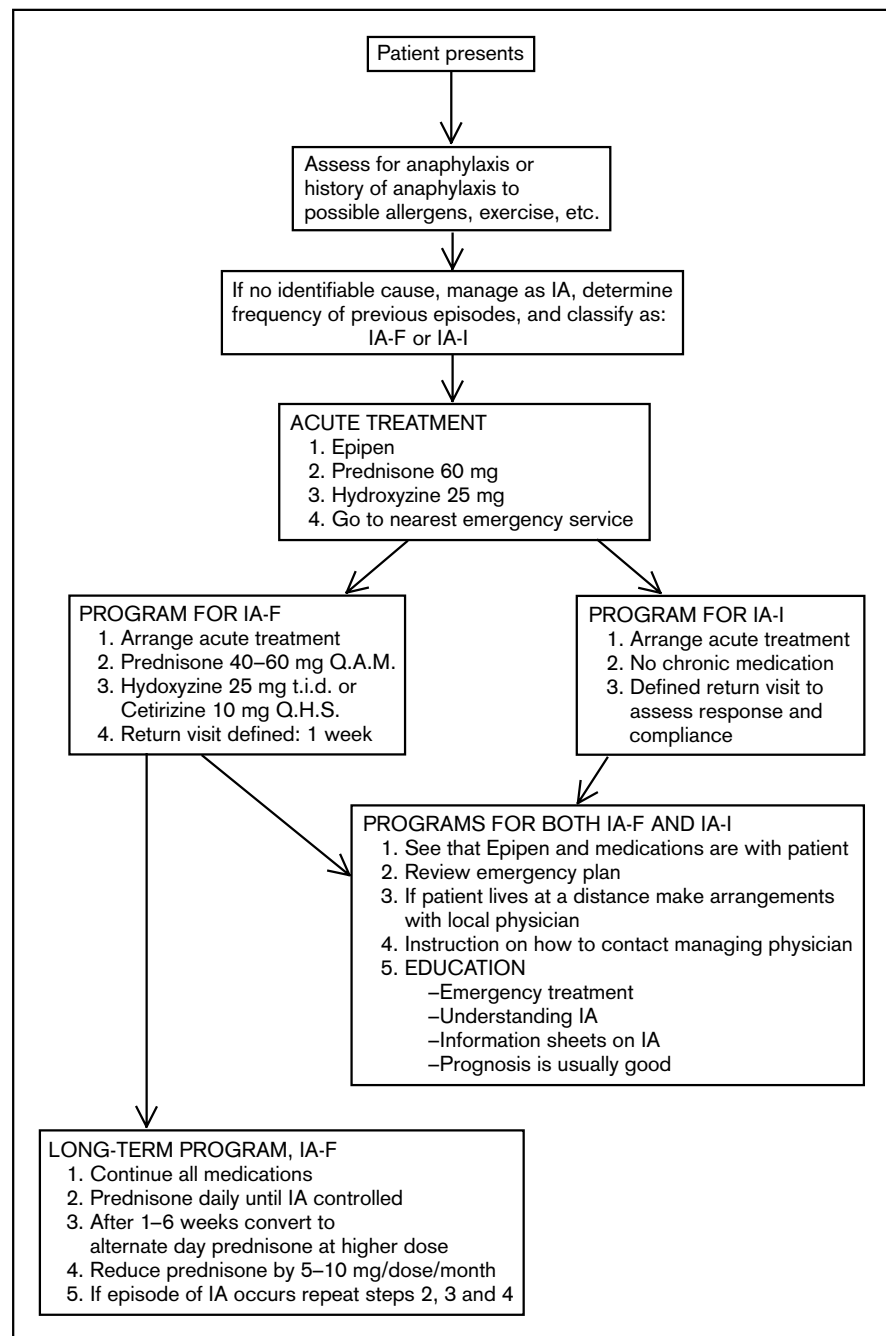
Table 1. Classification of idiopathic anaphylaxis

Disease	Symptoms
Frequency of episodes	More than six times per year or more than two times in 2 months: Frequent Less than six times per year: Infrequent
Generalized	Urticaria or angioedema with bronchospasm, hypotension, syncope
Angioedema	Angioedema with upper airway compromise (laryngeal, pharyngeal, tongue)
Summary of diagnosis	IA-G-F, IA-A-F, IA-G-I, IA-A-I
Corticosteroid-dependent IA	Used when a patient has recurrent IA symptoms below a threshold dose of prednisone
Malignant IA	Used when a patient requires high doses of prednisone for disease suppression, arbitrarily set at 30 mg a day or 60 mg every other day
IA-questionable	Used when a patient has possible IA but where documentation of objective findings is lacking
IA-variant	Used when symptoms of IA vary from classic IA. Diagnosis may eventually be changed to IA-A, IA-G, IA-Q, undifferentiated somatoform IA
Undifferentiated somatoform IA	Used when stated symptoms mimic IA but no objective findings can be documented. Should be suspected when the symptoms do not respond to treatment regimen

Adapted from Patterson [2], with permission. IA, Idiopathic anaphylaxis; A, angioedema; F, frequent; G, generalized; I, infrequent; Q, questionable.

Figure 1. Algorithm for the management of idiopathic anaphylaxis

IA, idiopathic anaphylaxis; F, frequent; I, infrequent; tid, three times a day; Q.A.M., every morning; Q.H.S., every night at bedtime.



of daily prednisone and an antihistamine, such as cetirizine 10 mg, hydroxyzine 25–50 mg, or benadryl 25–50 mg. Prednisone should be given daily for at least 1 week, but if symptoms are not controlled after 6 weeks then the diagnosis may be called into question. When the condition is controlled, prednisone may be decreased to every-other-day dosing and subsequently weaned by 5–10 mg each month. After the prednisone is discontinued, the antihistamines may then be tapered.

Although steroids seem to be universally effective in idiopathic anaphylaxis, the natural history of the condition may also lead to remission [43].

Those patients who fail steroid tapering (classified as corticosteroid-dependent idiopathic anaphylaxis or malignant idiopathic anaphylaxis) may be tried on alternative medications. Wong *et al.* [44] studied nine steroid-dependent idiopathic anaphylaxis patients and reported

that the addition of ketotifen helped seven of them significantly reduce or discontinue their steroids. Alternative medications that can be used include oral cromolyn, oral albuterol, or montelukast. To avoid burdensome and costly drug regimens, these second-line agents should be discontinued if they do not obviously decrease the patient's prednisone dose.

Pediatric patients with idiopathic anaphylaxis should be classified and treated in a similar fashion to adults, while taking into account dose adjustments for steroids, epinephrine, and antihistamines [45]. Of the second-line medications, montelukast has been approved for children over the age of 2 years, whereas both cromolyn and albuterol have also been approved for infants.

Although the literature has placed limited emphasis on the perioperative management of idiopathic anaphylaxis, there are cases of surgically induced exacerbations [4,44]. A prophylactic regimen of perioperative steroids is aimed at preventing intra and postoperative anaphylaxis. Patients who experience frequent exacerbations before surgery should not undergo elective procedures until their disease is under optimal control. Patients who have had an episode of idiopathic anaphylaxis within the past year but are well controlled should be treated prophylactically with 40–60 mg prednisone per day on the 5 days preceding surgery and then 100 mg intravenous hydrocortisone every 8 h during surgery and through the recovery period [46].

All patients diagnosed with idiopathic anaphylaxis should receive a Medic Alert bracelet or other identification that clarifies their diagnosis. They should also be educated about what symptoms to look for and how to administer their emergency epinephrine, prednisone, and antihistamine properly. Physicians should reassure their patients that compliance with the prescribed regimen offers an excellent remission rate, in excess of 80% [4]. Patients also benefit from knowing that it is unlikely that an unforeseen external allergen is responsible for their symptoms.

Conclusion

Since its identification 25 years ago, idiopathic anaphylaxis has been classified and treated successfully. Swift diagnosis of this life-threatening disease can help to minimize the medical costs associated with repeated emergency room visits and elaborate diagnostic testing. A thorough initial history tailored to rule out conditions that mimic idiopathic anaphylaxis represents the single most important element in achieving this swift diagnosis. Subsequent treatment according to established algorithms affords patients an excellent prognosis.

Despite these practical successes in the classification and treatment of idiopathic anaphylaxis, research has yet to reveal the underlying mechanism of this disorder. The observation that idiopathic anaphylaxis is a steroid-responsive disease has led to recent investigations into a possible autoimmune etiology. Further studies from this perspective will hopefully offer doctors and patients further insight into this serious disease.

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