



A 'difficult' insect allergy patient: reliable history of a sting, but all testing negative

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Purpose of review

Few conditions are as treatable as allergy to stinging insects, with venom immunotherapy (VIT) providing up to 98% protection to subsequent stings. The challenge with VIT is not in the treatment, but in the diagnosis. To offer VIT, one must determine a history of a systemic reaction to a stinging insect in conjunction with the presence venom-specific IgE. Current diagnostic methods, although sensitive and specific, are imperfect, and some newer testing options are not widely available. A conundrum occasionally faced is the patient with a reliable and compelling history of a systemic allergic reaction yet negative venom-specific testing. This diagnostic dilemma presents an opportunity to consider possible causes for this diagnostic challenge.

Recent findings

Our evolving understanding of the role of occult mast cell disease may begin to help us understand this situation and develop appropriate management strategies. Venom-specific skin testing has long been the cornerstone of the evaluation of venom sensitivity and is often combined with in-vitro assays to add clarity, but even these occasionally may fall short. Exploring novel venom diagnostic testing methods may help to fill in some of the diagnostic gaps. Do currently available venom vaccines contain all the key venom species? Are there enough differences between insect species that we may simply be missing the relevant allergens? What is the significance of the antigenicity of carbohydrate moieties in venoms? What is the role of recombinant venom extracts?

Summary

VIT is the definitive treatment for insect allergic individuals. To utilize VIT, identification of the relevant Hymenoptera is necessary. Unfortunately, this cannot always be accomplished. This deficiency can have several causes: a potential comorbid condition such as occult mast cell disease, limitations of currently available diagnostic resources, or testing vaccines with an insufficient coverage of relevant venom allergens. Exploring these potential causes may help to provide important insight into this important diagnostic conundrum. The use of a case report may help clarify this challenge.

Keywords

anaphylaxis, Hymenoptera, hypersensitivity, insect, tryptase

INTRODUCTION

Venom immunotherapy is the definitive treatment Hymenoptera sensitivity and should be offered and initiated, provided the necessary criteria of a reliable history of anaphylaxis and the presence of venom-specific IgE are met. What does one do, however, if the later criterion is not fulfilled? This diagnostic dilemma has been the source of discussion for some time and how best to address this important issue remains an important clinical challenge for the allergist [1,2]. Currently available diagnostic tools including conventional skin testing and new in-vitro methods are complimentary and appear to detect venom-specific IgE in 95–98% of

individuals with a reliable history of sting-related anaphylaxis [3,4].

It is the remaining 2–5% that fall into this diagnostic hole and will be the focus of this review. We will explore several possible sources of this diagnostic conundrum worthy of consideration. First, is

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KEY POINTS

- Understanding mast cell disease remains critical to insect allergy management.
- Current diagnostic methods are sensitive and specific, but are imperfect. Investigational assays including BAT hold promise for improved diagnostic sensitivity.
- As current diagnostic methods are imperfect, negative venom test results in the face of a compelling history of insect allergy should be interpreted with caution.
- Specific insect range may be changing and although there remains considerable cross-reactivity, there may be relevant species differences that may not be entirely covered by currently available testing venoms.

this primarily a problem of the diagnostic sensitivity of currently available methods? Second, is this situation one complicated by other comorbid conditions, such as indolent mast cell disease? Is it caused by a non-IgE, but immunologic mechanism? Finally, commercially available extracts are available for only a small fraction of relevant Hymenoptera species, by the use of species representative available commercially, in which some may lack unique antigens that available testing extracts may not identify. Invasive species of Hymenoptera have become established across the world, and standard testing with endemic species may fail to identify venom-allergic patients in particular. This case may help to illustrate this practical situation.

CASE REPORT

A 38-year-old, otherwise healthy school teacher was stung by a 'bee' while playing golf. Immediate pain was reported, but within 5 min he developed generalized urticaria, dyspnea and cough. He was treated by friends with diphenhydramine and taken to the emergency department in which he was treated with epinephrine, additional antihistamines and corticosteroids. He was referred to an allergist immunologist for possible venom hypersensitivity. History failed to provide clues as to the specific Hymenoptera. Four weeks after the event skin and in-vitro testing were negative; these were repeated 2 and 6 months later with both methods failing to demonstrate venom-specific IgE. Having failed to meet the criteria necessary to initiate venom immunotherapy, the patient was discharged with an epinephrine autoinjector and avoidance counseling. Eighteen months later, he was again stung while playing golf and within minutes he developed a cough, wheezing and loss of consciousness.

Epinephrine administered within minutes and later in the emergency department failed to resuscitate him.

DIAGNOSTIC METHODS

In individuals with a convincing history of a systemic reaction stinging insect allergy, diagnostic testing should be performed. The sensitivity of current venom skin testing ranges from 67% to as high as 90% depending on the component venom being tested. Serum IgE testing alone has been reported to be generally less sensitive than skin testing being negative in 15% to 20% low in most patients and as low as 43% in others [3–6]. Positive intradermal skin testing is defined as a positive reaction at a starting concentration of 0.001–0.01 $\mu\text{g/ml}$ or after increasing by 10-fold increments until a positive reaction or until a concentration of 1.0 $\mu\text{g/ml}$ is reached. Typically, serum IgE testing to venom-specific antibodies is reserved for those patients with negative epicutaneous and intradermal testing yet a history suggestive of stinging insect allergy. Therefore, the two testing methods should be often be combined and considered complimentary [3,6]. It should also be noted that there is some variability in the precise definition of a positive intradermal test result, although either of these definitions is acceptable to confirm the presence of venom-specific IgE antibodies. In North America, Europe, and many other countries, venom extract sufficient to produce a bleb of 3 mm is injected, which is usually a volume of 0.02–0.03 ml. A wheal 3–5 mm greater than the negative control, with appropriate erythema at a concentration 1 mcg/ml or less, is considered positive [7,8]. In the United Kingdom, 0.03 ml of venom extract is injected to raise a bleb of 3–5 mm. A wheal diameter of 3 mm greater than the negative control at 20 min is considered positive [9].

One explanation for negative testing in the setting of suspected insect sting allergy is the timing of testing. Diagnostic testing should be delayed for 4–6 weeks after a sting reaction to minimize false-negative results because of depleted mast cells sensitized for venom-specific IgE [10]. Subsequent stinging insect hypersensitivity reactions after negative skin prick testing and negative serum IgE-specific antibody results have been previously reported. This seems to be rare with less than (1%) of patients with negative skin prick testing and negative serum IgE-specific antibody results having a subsequent systemic reaction with repeat sting as compared with 30–60% of patients with positive diagnostic results having a subsequent reaction [2,4]. Sting challenge has for some time been considered an opportunity to increase diagnostic

sensitivity [10,11]. Subsequent studies [12,13], however, demonstrated concerns with safety, reproducibility, and lack of predictive value for sting challenge. Other novel diagnosis testing methods for insect allergy have been reviewed elsewhere [14]. Recombinant allergen serum IgE antibody testing has the potential to increase sensitivity and specificity; however, current emphasis is directed more toward specificity than to sensitivity (double positive). There is maybe concern that not all relevant antigenic components of venom linked to that cause clinical symptoms are included in current commercially available nonrecombinant venoms [15]. This could explain why patients with a positive history are skin and serum IgE test negative. Several studies [4,10,16,17] have demonstrated a significant improvement in sensitivity after adding recombinant venom allergens to currently used allergens increasing the sensitivity of some from as low as 79% to as high as 96%. This is especially useful in detecting sensitization to a component of venom that otherwise would have gone undetected.

Another limitation of venom skin testing is the irritant effect when using intradermal venom skin testing at concentrations greater than 1.0 $\mu\text{g/ml}$. Dialysis of commercial venom extracts removes low molecular-weight amines that contribute to the false-positive skin test reaction at concentrations greater than 1.0 $\mu\text{g/ml}$. Dialyzed and purified venoms may provide enhanced sensitivity permitting intradermal testing at concentrations greater than 1.0 $\mu\text{g/ml}$ [18,19].

Finally, basophil activation test that is currently being used in the research setting may be another useful diagnostic tool, although it is not widely available for commercial use in the United States. After basophils are exposed to a certain concentration of venom extract, flow cytometry is used to detect CD63+ and CD203c+ which are markers of basophil activation [20]. The data on basophil activation test in patients with negative skin and in-vitro testing are variable. Some investigators demonstrated its usefulness in detecting false-negative individuals with mastocytosis, whereas others did not [10,11,21,22].

It is very important to consider the limitations in venom testing and in-vitro specific IgE antibody testing to venom in a patient with a positive history of a systemic sting event. These individuals could be at risk for subsequent reactions and, if unprepared, this could have fatal consequences.

MASTOCYTOSIS AND SERUM TRYPTASE

Mastocytosis and occult mast cell disease have emerged as a surprising link in this clinical quandary

of a history-positive individual, yet negative to both skin testing and in-vitro testing [23].

The diagnostic criteria for systemic mastocytosis are discussed elsewhere [24,25], and compared with other causes of anaphylaxis such as drugs and foods, mastocytosis has a unique importance in the management of Hymenoptera allergy [26,27^{***}]. The prevalence of clonal mast cell disease in venom-allergic patients ranges between 1 and 7.9% [28]. This has been particularly important as it relates to venom allergy diagnosis and assessing high-risk individuals for future severe reactions as well as a consideration in the duration and safety of venom immunotherapy [29]. Rueff *et al.* in a multicenter study of 962 Hymenoptera venom-sensitive patients looked at predictors of severe systemic anaphylaxis following a sting. Of the 962 patients, 202 (26%) had severe anaphylaxis following a field sting. The reported severity was either Mueller grade III or IV with the identified risk predictors of sting-related anaphylaxis that included patients taking angiotensin converting enzyme inhibitors; vespid allergy; male sex; and patients with baseline serum mast cell tryptase levels above 5 ng/ml [30]. Bonadonna *et al.* reported a correlation between systemic reaction to Hymenoptera sting and mast cell tryptase. Of 379 patients with a history of systemic insect sting reactions, 11.6% had serum mast cell tryptase levels exceeding 11.4 ng/ml. Of this group, the rate of systemic (Muller grade IV) anaphylaxis was 70.5%. Thirty-four of the patients with elevated mast cell tryptase level underwent bone marrow biopsy; of those patients, 61.8% were ultimately diagnosed with indolent systemic mastocytosis [31]. Blum *et al.* confirmed these findings in a 5-year retrospective study of 868 patients referred for the evaluation severe reactions to Hymenoptera stings. Of the 868 patients, 758 had both total IgE and baseline tryptase levels drawn. Baseline tryptase level ($>11.4\text{ ng/ml}$) was associated with severe systemic reactions ($P=0.026$) [32]. Additionally, because of the dramatic increase in severe sting-related anaphylaxis in patients with mastocytosis, physicians should consider occult mast cell disease in anyone with unexplained anaphylaxis, sting-related anaphylaxis, and especially an individual with a positive history of a systemic anaphylactic reaction to a Hymenoptera sting, with negative venom testing [29].

Not all of these patients have evidence of venom-specific IgE, yet the insect sting is clearly a trigger. There may be a role for non-IgE-mediated immunologically triggered reactions and mast cell disease may provide a new optic to this challenge. Omalizumab may be an additional lens providing insights into the explanation of the history-positive venom test negative patient [33].

Omalizumab, a humanized murine mAb, conjugates with free serum IgE that reduces binding to the high-affinity FcεRI on mast cells and basophils and may provide additional insights. Omalizumab has also been demonstrated to dramatically decrease the high affinity IgE receptor (FcεR1) on mast cell and basophils. Omalizumab also appears to stabilize mast cells making them less reactive and may be used as an adjunctive treatment in individuals with mastocytosis [34]. It may have an important role in decreasing symptoms and adverse effects of venom immunotherapy as well in individuals with non-IgE-mediated insect sensitivity and concomitant mast cell disease. Douglass *et al.* [35] reported in 2009 the effectiveness of omalizumab in treating systemic mastocytosis in a nonatopic patient. Kontou-Fill *et al.* [33] presented similar results when treating a patient with systemic mastocytosis following sting-induced, non-IgE-mediated reactions.

There appears to be a high correlation with mastocytosis when the baseline tryptase exceeds 11.4 ng/ml, suggesting that this diagnosis be entertained in patients with severe anaphylaxis from Hymenoptera and be considered in all patients with anaphylaxis related to Hymenoptera sting. There may be elements and causality to seemingly 'allergic' reactions that may not be IgE-mediated. A greater understanding of the role of omalizumab and its effect on the high-affinity FcεRI and subsequent mast cell stability may provide insight into the clinical dilemma of the history-positive venom test negative individual. In these situations, the treatment of choice would not be VIT, but rather omalizumab may be a better choice.

VENOM CONTENT

There are many species of Hymenoptera capable of inducing anaphylaxis; commercially available extracts exist for only a small proportion of these. Although there is substantial cross-reactivity among venoms of closely related species of Hymenoptera, some species do have unique antigens that do not cross-react with other members of the genus [36]. One notable example is the unique antigenicity of *Vespula squamosa* (Southern Yellow Jacket) among the other yellow-jacket venoms studied [37]. The commercially available extracts for *Vespula* in North America consist of mixtures of venom from multiple yellow-jacket species. While *V. squamosa* is included in the commercially available yellow-jacket venom extract mixes, it highlights the possibility that species not included in the mixes may result in missed identification of venom-sensitized patients. These mixes do contain other European species that

are invasive globally, and therefore may be used to identify *Vespula*-sensitized patients in other countries. The possibility, however, remains that native species not included in this mixture may be the primary sensitizer of patients in other countries. Species composition varies geographically, even within North America [38].

Missing sensitized patients is less problematic with species of *Dolichovespula* because of the smaller number of closely related species. Of the five species in North America, only two species (*D. arnenaria* and *D. maculata*) are commonly encountered and linked to hypersensitivity reactions [39]. There are commercially available extracts to both of these species. North American *Dolichovespula* are presumed to overlap in antigens with species common in Europe (*D. media*, *D. saxonica* and *D. sylvestris*).

As with *Vespula* extracts, the commercially available extracts of *Polistes* venom in North America are mixes from a handful of species, venom from the majority of the 21 North American species not included. Because of the close phylogenetic relationship of these North American paper wasps, the mixes are expected to identify most cases of hypersensitivity. The possibility of missing sensitization, however, exists in those species that are less commonly encountered that are not included in these mixes. Because of difficulty in collecting all species for the yellow-jacket and paper wasp venom mixes, not all lots contain every species (according to the Hollister–Steir insert) (Table 1).

Unfortunately, there is limited cross-reactivity between the North American species and European species of paper wasp [40]. This is of major concern in selecting extracts in countries outside North America. In addition, *Polistes dominulus* (European paper wasp) is now a widespread, invasive species in North America, with no commercially available extracts for this species available in North America and elsewhere. This species highlights the growing concern for invasive species in which phylogenetically distinct insects may not be identified using extracts from native species.

Anaphylaxis to *Vespa crabro* (the invasive European hornet), another invasive species to North America, appears to be rare, although there are no commercially available extracts to conduct skin testing for this species in North America. Because of extensive cross-sensitization, *Vespula* extracts may be useful in diagnosing and desensitizing patients with *Vespa crabro* sensitization; however, it is not clear whether this can be extended to other *Vespa* species [41].

Failure to identify venom-sensitized patients is a particular challenge in those sensitized to bumble

Table 1. Commonly available venom test for Hymenoptera venom sensitization

Genus	No. of species in NA	ALK extracts	Hollister–Stier extracts	Phadia immunoCAP
Apis	1	Apis mellifera	Apis mellifera	Apis mellifera
Bombus	46	0	0	Bombus terrestris
Vespa	1	0	0	Vespa crabro
Dolichovespula	5	<i>D. arenaria</i> <i>D. maculata</i>	<i>D. arenaria</i> <i>D. maculata</i>	<i>D. arenaria</i> <i>D. maculata</i>
Vespula	13	One mix of six species	One mix of five species	One mix of six species
Polistes	21	One mix of five species	One mix of three species	One mix of five species <i>P. dominulus</i>

bee, where there are no commercially available extracts for any of the 54 native species encountered in North America, and to *Bombus terrestris*, an imported European species used for commercial pollination [42]. Bumble bee-induced anaphylaxis is best described for those with occupational exposure; however, the possibility exists that others may be missed when only honey bee venom is used in diagnostics. There is incomplete cross-reactivity in these different genera [43,44].

CONCLUSION

The patient who has a history of anaphylaxis following an insect sting, yet all testing fails to identify venom-specific IgE, creates both a diagnostic challenge and therapeutic dilemma. This failure does not provide the opportunity to offer venom immunotherapy, which carries a protective level approaching 98%. There are many potential sources for this diagnostic challenge. Current diagnostic testing for venom allergy is sensitive and specific, but is imperfect and many important diagnostic opportunities are missed. Unfortunately, newer options are not widely available. Occult mast cell disease and potentially other immunologic, non-IgE-mediated causes may account for a segment of these affected patients. However, in the end, it may be as simple as not testing for the correct insect.

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Conflicts of interest

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