

Patients with negative skin tests

Kalliopi Kontou-Fili

Purpose of review

The aim of this article is to present and discuss the clinical problem of systemic anaphylaxis to Hymenoptera venoms in patients without detectable immunoglobulin E, as it appears in recent literature. Reported at variable frequency in large series of patients undergoing evaluation, systemic anaphylaxis was previously considered to reflect lost sensitization or to involve non-immunoglobulin E mediated mechanisms. Sporadic case-reports drew attention to the fact that severe or even fatal reactions may occur in patients with negative skin tests.

Recent findings

A breakthrough article by Golden *et al.*, who performed deliberate stings on skin test negative venom anaphylaxis patients, demonstrated that clinical sensitivity was still present in a subset of these subjects and pointed out to the limitations of present diagnostic methods or reagents. New immunobiochemical methods and highly specific recombinant allergens – when all clinically relevant Hymenoptera venom allergens have been identified, cloned, sequenced and expressed in the proper system – are anticipated to increase the diagnostic yield. Non-specific mechanisms causing anaphylactoid reactions will probably explain some enigmatic, skin test negative radioallergosorbent test negative cases in the future. Occult mastocytosis, predisposing patients to anaphylactoid reactions, has been reported with increasing frequency among skin test negative patients. Lastly, other causes mimicking venom anaphylaxis may on rare occasions contribute to the problem.

Summary

With the present understanding of venom allergy, the practising clinician is not infrequently faced with the dilemma of the skin test negative patient. Once other identifiable causes have been carefully ruled out, referral to a specialized center for deliberate sting-challenges appears in selected cases to be a medically appropriate and ethically justified management approach.

Keywords

hymenoptera, venom, anaphylaxis, skin test negative, seronegative, sting challenge

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Department of Allergy and Clinical Immunology, Division of Internal Medicine, LGD Hospital of Athens, Athens, Greece

Correspondence to Kalliopi Kontou-Fili MD, PhD, Head, Department of Allergy and Clinical Immunology, Division of Internal Medicine, LGD Hospital of Athens, Agiou Thoma 17, Athenai 115 27, Greece
Tel: +30 010 77116920 or +30 010 7456 350; fax: +30 010 6010 842;
e-mail: kontoufk@otenet.gr

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Abbreviations

CCD	cross-reacting carbohydrate determinant
RAST	radioallergosorbent test
sIgE	specific immunoglobulin E

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Introduction

Hymenoptera venom anaphylaxis, a preventable disorder, can have a fatal outcome if it is not treated with venom immunotherapy, if it is inadequately treated or, rarely, years after stopping treatment of supposedly sufficient duration. On the other hand, specific immunotherapy confers almost 100% protection [1,2,3••]. Therefore, the proper management of ideally all patients presenting with a documented history of sting-induced anaphylaxis calls for immunotherapy, the duration of which needs further definition than the usually quoted 3–5 years. All consensus reports and guidelines regarding the initiation of venom immunotherapy agree on the mandatory requirement of demonstrable venom specific immunoglobulin E (sIgE) in the skin or serum of sufferers [4–6].

Despite the availability of standardized pure venom and the refinement of in-vitro assays over the past two and a half decades, venom anaphylaxis with negative skin tests or undetectable circulating sIgE (by radioallergosorbent test (RAST)–UniCAP (Pharmacia & Upjohn) or analogous tests) has been reported to occur in a subset of patients [7,8••,9,10]; such patients are denied specific treatment, since they do not meet the aforementioned consensus criteria. This approach is considered good medical practice, particularly for immunoglobulin E negative patients who undergo evaluation 36 months or more following the latest episode of sting-induced anaphylaxis; these individuals are assumed to have lost their sensitivity naturally over time [9]. A recent study by Golden [11••] on negative venom skin test responders has challenged established views on sting-anaphylaxis and has prompted this review on the subject.

Definition and magnitude of the problem

The term skin test negative venom anaphylaxis refers to sting-induced reactions, which exhibit characteristics of a systemic immunoglobulin E-mediated response, but without demonstrable sIgE upon properly performed intradermal skin tests with all relevant venoms. One microgram per millilitre is generally accepted as the upper limit of venom concentration for intradermal skin tests in order to avoid non-specific, irritant reactions and also limit the number of false negative responses.

The prevalence of skin test negative venom anaphylaxis in the general population is unknown; its relative prevalence among patients, who seek medical attention for sting-induced allergic reactions or those recruited for

clinical trials, ranges from less than 10% to almost 45% [9,10]. In part, this wide variation might reflect differences in a number of areas: (1) the populations studied, (2) the size of the population sample, (3) the technique employed (intradermal versus prick, in certain European centres the latter method is used exclusively), (4) the volume injected (some authors suggest 0.05 ml of each dilution, others consider this volume potentially irritating and recommend 0.01–0.02 ml, while an intermediate amount 0.03 ml has also been proposed), (5) the concentration and quality of reagents used (freshly reconstituted, lyophilized venom proteins versus commercially provided already reconstituted venoms, as practised in Italy for strictly bureaucratic reasons), or (6) the time interval between the latest episode of anaphylaxis and skin test evaluation, relative to the type of offending insect (among 41 skin test negative anaphylaxis patients studied in one European centre more than 55% incriminated vespids; yet, this subgroup of patients was selected from a population of 600 sting-induced anaphylaxis cases, in which the predominant culprit insect (two thirds) was the honeybee) [10,12].

In addition, intra-patient variability in skin test reactivity has been observed and this has led the recommendation for re-testing at least once more on a different site, date and hour in the day. Recently published reviews on the diagnosis of venom anaphylaxis and other types of immunoglobulin E mediated allergy discuss in detail the indications, reagents and techniques used for skin testing, as well as the evaluation of results obtained; the comparative advantages and diagnostic value of in-vivo and in-vitro tests are also pointed out [8•,13•,14•,15].

The paradoxical patient with negative skin test and positive radioallergosorbent test results

The greater diagnostic sensitivity of intradermal skin tests compared with tests detecting circulating sIgE is well established; as skin tests constitute a marker of biological sensitivity it appears paradoxical that up to one sixth of patients with negative skin tests give positive RAST results. By performing sting challenges Golden [11•] demonstrated the clinical significance of this in-vitro positivity and also the existence of a sub-population (approximately one quarter of skin test negative/RAST positive patients), characterized by persisting clinical sensitivity, primarily to vespid venoms, despite the negative in-vivo tests. Had sting challenges not been included in the study design, some of the RAST results might have been regarded, by some sceptics, as false positive due to other causes or as 'burned out' remnants of a previous clinical sensitization. The reported good correlation of the Hopkins RAST results with those obtained from histamine release assays constitute addi-

tional evidence for the biological and clinical relevance of RAST positivity from this laboratory.

Biologically irrelevant, positive serologic test results

For more than 20 years Aalberse [16] has been presenting evidence for cross reactivity between carbohydrate antigenic determinants of various non-mammalian sources. In recent years, biologically inactive sIgE against such non-proteinaceous epitopes has been demonstrated by in-vitro assays in venom allergic patients, who also exhibit atopic (poly)sensitization to common allergens, inhalants or foods. Oligosaccharide side chains of unrelated plant and insect glycoproteins, referred to as cross-reacting carbohydrate determinants (CCDs), appear to contain the cross-reactive immunoglobulin E-binding epitopes [17,18,19•].

Cross reactivity through these moieties appears with a greater frequency in apparent double venom positivity (usually honeybee and yellow jacket), as demonstrated *in vitro* by solid phase immunoassays. Thus, honeybee and vespid venom glycoproteins may cross react with unrelated plant CCDs or with each other and affect the diagnostic accuracy of some in-vitro techniques, as has been demonstrated by Egner *et al.* [20]; the unaware clinician might attribute such results to double sensitization and apply unnecessary treatments. As a rule, anti-CCD antibodies do not cross-link Fcε type I receptors and are clinically irrelevant. Biological extracts containing CCDs do not appear to cause positive skin test responses – at the usual testing concentrations – and are of help in evaluating the false positive in-vitro results they elicit.

In the context of the above data, one might argue that RAST positive results in patients with negative skin tests are explained by the presence of clinically insignificant anti-CCD antibodies. The previous history of anaphylaxis and the high yield (24%) of positive reactors to a single deliberate sting in the Hopkins patient group [11•] negate such an oversimplification. In addition, the RAST assay developed and the materials used, we are assured, are free of any 'additional components' that could interfere with the test's diagnostic accuracy [11•].

The radioallergosorbent test negative, skin test negative patient and new in-vitro developments

Following the introduction of the RAST shortly after the identification of immunoglobulin E, several immunoassays became commercially available for the semi-quantitative determination of circulating sIgE. However, as early as 1978 – about the time pure venoms became commercially available for diagnosis and therapy – the

Hopkins group utilizing the RAST technique showed that sIgE was elevated in only 80% of patients with positive skin tests to venoms [21]. Since then the test has been modified, but efforts to improve its diagnostic value continue through to today (Tasios *et al.*, unpublished data) [15,22]; this is particularly pertinent to vespid venom allergy, for which a concordance rate of less than 75% between RAST and skin test results has been reported [23].

Additional, highly sensitive immunoassays, developed since the 1980s due to the urgent need for early identification of AIDS patients and carriers, have also been employed in the diagnosis of venom allergy with encouraging results, in terms of both sensitivity and specificity [24,25•,26•]. Still under evaluation as diagnostic tools of venom allergy, they have been tested against the sera of anaphylaxis patients with known cutaneous sensitivity, but not of those found in the 'grey zone' of skin test or RAST negativity. According to an earlier report, all RAST seronegative patients were found to have detectable sIgE by Western blotting; no patient in this study, however, had negative skin tests [27]. Furthermore, these assays require specialized laboratories and personnel and, as a consequence, cannot meet the immediate needs of clinicians in daily practice.

In reference to this double negative group of Golden's patients, the 14% yield of positive venom challenges – it might have been higher or lower had more subjects consented to the test – is not negligible. If a patient with these characteristics sustains a reaction upon a field sting, for this patient the reaction rate and consequences thereof are 100%, not 14% or less.

Recombinant venom allergens and future perspectives

Because of problems in composition and variability of natural allergens, even when 'standardized' by all available methods, recombinant allergens were genetically engineered and introduced over the past decade, in order to improve both the diagnosis and therapy of allergic diseases. Several major inhalant and food allergens, as well as nine Hymenoptera venom allergens (three from each of honeybee, *Vespula* spp. and *Dolichovespula* spp.) have been cloned, sequenced and expressed in various systems [28,29,30•]. Once the proper expression system for each of all relevant allergens is established (in order to guarantee their production in the correct molecular conformation, essential for immunoglobulin E binding) and complete panels of recombinant allergens become available, more accurate diagnostic tests will also be provided. Identification and purification of all clinically important allergens of each insect's venom is an essential prerequisite. The

recent identification and description of a new, allergenic protein (Api m 6) in honeybee venom [31•] suggests that more basic research is still required, before all advances offered by molecular biotechnology can be applied clinically.

The skin test negative, radioallergosorbent test negative patient due to other causes or mechanisms

Alternative mechanisms involving non-IgE mediated activation of mast cells have been postulated to be involved in some cases of systemic anaphylaxis to Hymenoptera venoms, without detectable sIgE; other causes of 'anaphylaxis' misidentified as flying Hymenoptera should also be considered, as briefly noted in the paragraphs that follow.

Occult mastocytosis mimicking skin test or radioallergosorbent negative venom anaphylaxis

Systemic anaphylaxis with or without demonstrable immunoglobulin E has been known to occur in patients with mastocytosis [32,33]. The total number of mastocytosis cases reported by each investigator is small and the relative frequency of patients with negative skin test and RAST to those with detectable sIgE varies from 25% to 66% [10,32]. Venom-induced anaphylaxis is often the presenting complaint and the only manifestation of the underlying mast cell disorder; this was the case in 75% of 12 patients with severe sting-induced reactions and elevated levels of basal tryptase reported by Ludolf Hauser last year [34•]. Similarly, 80% (11 of 14) of mastocytosis patients, who presented or were referred to our centre for the management of venom anaphylaxis, were diagnosed *de novo* as suffering from the systemic or cutaneous form of the disorder [10].

Patients with mastocytosis – with or without detectable sIgE – appear to be at risk for life threatening or fatal anaphylaxis upon insect stings; reactions during specific immunotherapy are also more severe in mastocytosis patients and are the reason for discontinuing treatment prematurely. Whether the heightened clinical reactivity of mastocytosis patients, particularly those without demonstrable immunoglobulin E, relates to the obvious quantitative differences in mediator cells or other mechanisms, which might augment mast cell 'release-ability', thus causing anaphylactoid reactions, remains to be elucidated.

C' activation and alternative pathways of anaphylaxis

Mechanisms, other than immunoglobulin E, have been postulated to operate in some cases of patients with venom negative skin test or to contribute to the severity of true anaphylactic reactions. C' activation, calcitonin gene-related peptide overproduction, inappropriate response or dysfunction of the renin–angiotensin system

have been incriminated in venom anaphylaxis. Definitive proof for an exclusive role of such mechanisms in venom negative anaphylaxis in humans is still lacking [35–38].

Data from experimental models suggest alternative mechanisms for antigen-induced anaphylaxis and mediator release, other than histamine. In sensitized rodents administration of the relevant antigen caused anaphylaxis, phenotypically similar to that induced by monoclonal anti-immunoglobulin E; yet platelet activating factor was the primary mediator involved and dependency on macrophages as well as Fc γ receptor III was demonstrated elegantly in this study just published by Strait *et al.* [39**]. Despite the presence of Fc γ receptor III on human macrophages, it would be premature to postulate an analogous mechanism in humans. However, teachings from murine and other experimental models might lead scientific thought to new directions for breakthrough discoveries in the future.

Other culprits misidentified as flying Hymenoptera

Because of the characteristic pain the stinging insects cause, misidentification of other culprits as Hymenoptera is improbable, but not impossible. Rare as it may appear, mislabeling of the offending insect might lead to diagnostic pitfalls and false diagnosis of immunoglobulin E negative venom anaphylaxis [40]. In our geographic area *Tabanus* spp. induced anaphylaxis was wrongly attributed on a couple of occasions to Hymenoptera stings by patients, who misidentified the ‘stinging’ insect. In other regions (Far East, Australia, USA) members of the Formicidae family, other than the fire ant, have been reported to cause anaphylaxis in specifically sensitized individuals [41•,42**]; the allergenic relationship of their venoms to those of flying Hymenoptera has not been clearly established. The practising specialist should be aware of the growing list of geographically relevant insects which are potential sources of anaphylaxis.

Factitious Hymenoptera venom anaphylaxis

The Munchausen syndrome, a rare occurrence in various clinical disorders, has been reported as a hypersensitivity reaction to Hymenoptera venoms [43]. Among the first 41 patients presented to our centre as venom anaphylaxis with negative skin test and RAST the case of an 18-year-old daughter of a highly atopic mother was seen. She had previously witnessed several episodes of true food-induced anaphylaxis in her mother. Subsequently she mimicked her mother’s problem for a secondary gain and was treated aggressively in an emergency room as true venom anaphylaxis. The correct diagnosis was suspected after the negative work up and was successfully managed with psychiatric counselling.

Conclusion

Sting-challenges performed for the first time on a large number of patients with previous episodes of anaphylaxis and negative venom skin tests, demonstrated the inadequacies of present day diagnostic methods or reagents. The high percentage of positive findings brings into focus new diagnostic techniques as they apply to venom diagnosis and studies that attempt to further elucidate the mechanisms of anaphylaxis, as well as those dealing with the identification and bioengineering of all relevant venom allergens. Meanwhile, the skin test negative patient remains a management-enigma for the practising clinician who has no access to appropriate facilities for sting challenges or no experience in their performance. Even the sting-challenge specialist might not have an answer or sting to offer to the problem-patient with negative skin tests, who has recently sustained repeated and well documented, near fatal reactions. Lastly, the natural course and long term prognosis of those skin test negative patients, who on a single sting-challenge appear also negative, is presently unknown.

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