

Stinging insect allergy: Progress and problems

Stinging insect allergy has always been a source of great concern to the allergist. Although the number of patients requiring evaluation is small compared to those with respiratory allergies, the reactions from insect stings can be severe with anaphylactic deaths occurring each year. As a result patient and physician concern is intense, and there is great need to assure patients who have had reactions that they may carry on normal daily activities without risk of subsequent sting anaphylaxis. For many years patients were treated comfortably by physicians with injections of whole insect body extracts, now recognized as clinically and immunologically ineffective.¹ In light of our expanding knowledge of the natural history of venom allergy, it is instructive to appreciate the reasons for this false confidence in whole body extract therapy.

With the introduction of purified venoms approximately 8 yr ago, it was hoped that the clinical problem of venom anaphylaxis would be readily resolved. Individuals who had venom-specific IgE, detected by skin test or in the serum by RAST, would be at risk for subsequent sting anaphylaxis and would require specific venom immunotherapy. With large scale testing and follow-up of the clinical reactions to subsequent stings in patients with or without venom immunotherapy, it quickly became apparent that there was not a simplistic relationship between the presence of venom-specific IgE and subsequent reactions. Positive venom skin tests occur in a small number of patients who have "normal" reactions after insect stings. Patients with large local reactions only, without systemic symptoms, may have high antibody titers.² There is no relationship between antibody titer and the severity of the clinical systemic reaction. In the initial studies confirming the efficacy of venom immunotherapy done at Johns Hopkins Hospital,³ approximately 40% of patients believed to be venom-sensitive based on a past history of sting anaphylaxis and the presence of venom-specific IgE failed to react to an intentional sting challenge. Further evaluation of deliberate sting challenges carried out by Parker et al⁴ at the Mayo Clinic again demonstrated the variability of sting response in presumably sensitive patients, leading these authors to conclude that "no in vitro or in vivo tests predicted with certainty the

clinical and immune status of a sting-sensitive person." Their studies are extended in an article in this issue of the JOURNAL by Blaauw and Smithuis.⁵ After sting challenge, 31 of 86 presumed allergic individuals had a systemic reaction, a reaction rate of approximately 36%. As also found by Parker et al.,⁴ there were no immunologic parameters, such as IgE, IgG, or the ratio of IgG to IgE antibodies that could be used to identify susceptible individuals. The clinical data also do not differentiate between the subsequent reactors and nonreactors. The age range is the same in both groups. The data do suggest that those individuals who have very minimal reactions (grade I in their article) are less likely to react to subsequent stings, somewhat analogous to studies of Schuberth et al.⁶ in children who have had urticarial reactions only. Our data in patients who have had sting anaphylaxis and were followed without venom therapy are similar.⁷ Forty field stings in 28 patients resulted in 14 systemic reactions, a reaction rate of 50% per sting or 35% per patient.

The next issue is whether a negative sting challenge is sufficient evidence to assure the continued lack of reactivity to subsequent field stings. In their study, Blaauw and Smithuis⁵ indicate that at least 10 of their patients were spontaneously stung at subsequent times and failed to react. Likewise, Parker et al.⁴ performed repeat challenges and also found no reaction. Our observations in patients in whom venom immunotherapy was intentionally discontinued because of a fall in venom-specific IgE are similar but not as supportive of the predictive value of the failure to respond to a later sting.⁸ Venom immunotherapy has been discontinued in 57 patients. There have been 55 restings in 25 patients with two systemic reactions. The two patients who had systemic reactions had tolerated several earlier stings while they were off therapy with no difficulty, suggesting that sensitivity may be reacquired with repeat exposure.

These data present a perplexing problem regarding the appropriate choice of individuals who should receive venom immunotherapy. Why the initial reaction, and why the inconsistency between clinical sensitivity and immunologic reactivity? One variable might be the antigen exposure itself, the amount and

composition of injected venom. Certainly the amount of venom injected with each sting may vary. Qualitative studies to date suggest that the composition of venom is not affected significantly by the age of the insect nor time of the season.⁹

Is the venom model unique in this dichotomy between clinical reaction and immunologic reactivity? A similar analogy comes from observations of food allergy.¹⁰ Intentional food challenges in presumed allergic children led to reactions in only about 50%. Exercise anaphylaxis, although perhaps unrelated to an IgE pathogenesis, is another example in which repeat exposure (exercise) does not always lead to a clinical reaction.

How should the practicing physician respond to these uncertainties? Sting challenges may well reveal subsequent reactors. Continued observation is necessary to absolutely confirm this possibility. Perhaps the commercial venom injection might serve as a suitable substitute, although differences have been noted between live stings and venom injections.³ This would raise other complications such as the need for suitable conditions to conduct such challenges when anaphylaxis might result. For the time being it appears most reasonable to discuss current recommendations, controversy, and confusion with patients and continue to provide venom immunotherapy for any patient who appears to be at risk. Such therapy is almost 100% effective in preventing subsequent reactions. Hopefully, further clinical and immunologic observations may provide information required to select potentially sensitive individuals more accurately. Although it is easy to be confused by these observations and how to apply them in practice, it is important to realize that they reflect progress in the understanding of insect sting allergy (and perhaps immediate hypersensitivity, in general). The muddy waters will eventually clear.

The second series of articles in this JOURNAL addresses the isolation, identification, and cross-reactivity of allergenic fractions in vespid venoms. The initial studies by King et al.¹¹ identified three major allergens in vespid venoms: phospholipase, hyaluronidase, and antigen 5. With the use of purified venom rather than venom sac extract, Hoffman¹² confirmed these findings. In a second article,¹³ the relative potencies of the different fractions were compared. It should be appreciated that potency comparisons are difficult unless optimal amounts of venom fractions are used for coupling in the RAST procedure. As these fractions are present in only small quantities, it is often impossible to do complete titration experiments. Thus, interpretation of the relative potencies of the different fractions may be inaccurate. Nevertheless, it is clear that patients do react to several different vespid venom

fractions, and there is individual variation in the relative reactivity of each fraction.

The final aspect of these fractionation studies deals with the issue of cross-reactivity between vespid venoms. This is a very important practical issue that has direct application to the practicing allergist in terms of choosing the appropriate venom for immunotherapy. Current recommendations call for administering each of the venoms to which the patient demonstrates positive skin test reactions. Studies in our laboratory have demonstrated extensive cross-reaction between the different hornet venoms¹⁴ and between yellow jacket and hornet venoms.¹⁵ There is less cross-reactivity between *Polistes* venom and the other vespid venoms.¹⁶ In these current studies King et al.,¹⁷ by use of a mouse antibody system, demonstrated in great detail that there is extensive cross-reactivity between antigen 5 and hyaluronidase of vespid venoms and no cross-reaction between the phospholipase of the different venoms. On the other hand Hoffman found cross-reactivity with each of the three fractions, including phospholipase, by use of rabbit antisera and several human sera.¹⁸ Unfortunately, his experiments are not reported in sufficient detail to be critically evaluated.

At present, the time, effort, and cost of obtaining purified vespid venom fractions suggest that these fractions will not become practical diagnostic tools for the practicing physician. It is clear that there is cross-reactivity between the different vespid venoms. Decisions regarding immunotherapy will still rely on the awareness of this information, the interpretation of skin test results, and the clinical history of the culprit sting.

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