

Insect sting anaphylaxis in patients without detectable serum venom-specific IgE

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(Received in original form 20 July 1984 and in revised form 13 November 1984; accepted for publication 19 November 1984)

Summary

Following insect sting anaphylaxis, twenty-five patients of over 500 evaluated, did not have detectable serum venom-specific IgE. Twenty-two were evaluated within 1 year of the reaction, fifteen within 6 months. Anaphylaxis occurred in six patients after their first sting exposure. The clinical features of the sting reaction were typical of the reaction occurring in insect-allergic patients with serum venom-specific IgE. Eleven of the twenty-five patients had negative venom skin tests. These observations suggest that a non-IgE mechanism may be responsible for a minority of insect sting reactions.

Introduction

For several years, Hymenoptera venoms have been available for the diagnosis and treatment of patients with stinging insect allergy. The majority of individuals who have had anaphylaxis following insect stings have demonstrable venom-specific IgE when evaluated within a reasonable time after the sting reaction. These IgE antibodies usually are detected by skin tests or in the serum by radioallergosorbent test (RAST).

There have been occasional reports of individuals who do not have measurable venom-specific IgE, despite recent typical venom anaphylaxis [1, 2]. This paper reviews our experience with such patients, and raises the question of a non-IgE pathogenesis for some sting reactions.

Materials and methods

During the past 8 years, over 500 patients have been evaluated because of systemic allergic reactions due to insect stings. Intradermal skin tests with venoms and measurement of serum venom-specific IgE by the RAST were done routinely. These data were reviewed and patients selected who did not have elevated titres of serum venom-specific IgE when evaluated within a reasonable time after their sting reaction.

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Intradermal skin tests were performed with honeybee, bald-faced hornet and yellow jacket venoms collected locally by electrical stimulation, and with *Polistes* venom, obtained commercially. Reactions to 0.01 µg/ml of venom or less were considered significant as, in our experience, 25% of insect non-allergic patients react at venom concentrations of 1 µg, and 5–10% react at 0.1 µg/ml.

The radioallergosorbent test (RAST) was performed as previously described, with some modifications [3, 4]. Specific IgE antibodies to honeybee, bald-faced hornet, yellow jacket and wasp venoms were measured. Ten µg of each dialysed vespid venom protein and 100 µg of honeybee venom protein were coupled per disc. Results were expressed in % net binding of a serum pool from ragweed-sensitive patients to ragweed discs. A net binding to the discs of greater than 5% was regarded as significant. A binding of the ragweed standard varied between 11.5% and 12.8% of the total activity added. The background activity with normal human serum (NHS) was 0.7% for the ragweed discs and varied between 0.8% and 1.4% of the total activity added for the venom discs. Average % binding was calculated from the following formula:

$$\text{average \% binding} = \frac{\text{average cpm patient serum} - \text{average cpm NHS}}{\text{total specific cpm added}} \times 100.$$

The background activity was approximately 4% of the total activity noted.

Results

Twenty-five patients with typical sting anaphylaxis were identified who did not have elevated levels of serum venom-specific IgE. Twenty-two of the twenty-five patients were elevated within 1 year of the sting reaction, fifteen within 6 months. Their clinical features are shown in Table 1. The mean age of this group was 23.8 years, with a range of 4–68 years. There were twelve males and thirteen females; seven were atopic. Before the sting reaction prompting this evaluation, nineteen patients had had prior stings, four of which resulted in systemic reactions. Six patients had no history of a previous sting; the sting causing the systemic reaction was their first exposure to venom. Five of these six were children under the age of 15 years.

The anaphylactic symptoms experienced by these patients are shown in Table 2. Hives and oedema occurred in twenty of the twenty-five patients, and were the only

Table 1. Clinical features of twenty-five patients with sting anaphylaxis and undetectable serum venom-specific IgE

Clinical feature	No. of patients
Atopic	7
Previous stings	19
Previous systemic reactions	4
No previous sting	6
Interval between sting reaction and RAST	< 6 months 15
	6–12 months 7
	12–18 months 3

Mean age: 23.8 years, range: 4–68 years.

Sex: 12 males, 13 females.

Table 2. Symptoms of anaphylaxis

Symptom	No. of patients
Hives, oedema:	20
only symptom	16
Cardiovascular	3
Respiratory	6
Gastrointestinal	1

Table 3. Results* of intradermal skin tests with insect venoms

Skin Test†	No. of patients
Negative	11
1+	7
2+	2
3+	4
4+	1

*Results recorded as the greatest reaction to any of the four venoms.

† $\leq 0.01 \mu\text{g/ml}$ venom.

presenting symptoms in sixteen. Three experienced shock and hypotension, six had respiratory symptoms, including upper airway oedema and bronchospasm, and one had significant abdominal cramping and diarrhoea.

Intradermal skin tests were performed with honeybee, yellow jacket, bald-faced hornet and *Polistes* venoms. Using $0.01 \mu\text{g/ml}$ of venom as the criterion, eleven patients were entirely negative and fourteen showed some reactivity (Table 3). Negative skin tests occurred in patients evaluated at all time intervals after the sting reaction.

None of the patients were given specific venom immunotherapy. Three of the twenty-five were re-stung with no reaction; the identity of the re-sting insect could not be determined reliably.

Discussion

The clinical characteristics and anaphylactic symptoms of the patients without demonstrable serum antibodies were similar to venom-allergic individuals who have demonstrable serum venom-specific IgE. It is particularly important that six individuals, five of whom were children, reported a reaction after their first sting exposure. In a large study of insect anaphylaxis conducted by the American Academy of Allergy and Immunology Insect Committee [5], about 20% of enrolled patients reported that anaphylaxis followed the first known sting. These observations also would suggest that a mechanism other than IgE was involved in the pathogenesis of some insect-sting reactions, as there had been no prior venom exposure to initiate IgE antibody production.

It seems plausible that such patients may react because of the direct pharmacologic properties of venom. Venoms do contain potent components, such as mast cell

degranulating factor, phospholipase, hyaluronidase, and vasoactive amines [6], which would be capable of releasing mediators from the mast cells of a nonimmunologic basis. It is possible that certain individuals are sensitive to small quantities of these components introduced by a single sting. Suggestive evidence for such a mechanism is the observation of three patients with systemic mastocytosis who had typical insect sting anaphylaxis in the absence of serum venom-specific IgE [7].

We have used the determination of serum antibodies as the criterion for identifying these patients, although skin tests may be a more sensitive method of detecting IgE antibody. The RAST was performed with dialysed vespid venoms as the coupling antigens. With some sera, the RAST sensitivity is increased significantly with the use of dialysed venoms [4]. Sera which failed to react with undialysed vespid venoms may become positive with dialysed venoms. Venom-specific IgE does decrease over a period of time in the absence of interval venom exposure. There is considerable individual variation in the persistence of venom-specific IgE [1]. These twenty-five patients were all evaluated during the same time period as the majority of the other 500 insect-allergic patients who did have detectable venom-specific IgE. It seems unlikely that these twenty-five patients had IgE antibodies which decreased to insignificant levels in this relatively short period following their insect sting.

Using our skin test criterion, there were still eleven patients without IgE antibodies. The clinical significance of the very small levels of IgE antibodies which could be detected by skin test and not the RAST, is unresolved. Nevertheless, the other fourteen patients could well have had an IgE mechanism for their sting reaction.

Other observations show no relationship between serum IgE antibody titres and severity of the sting reaction [8, 9]. Only 50% or less of patients with prior sting anaphylaxis and positive venom skin tests, have repeat anaphylaxis when re-stung, in the absence of venom therapy. Patients with severe anaphylaxis and shock may have low antibody titres, while those with large local reactions may have extremely high antibody titres [10]. This relationship is quite different from that of typical IgE-mediated allergy where a reasonably good correlation exists between symptom severity and antibody titre.

Selcow *et al.* [2] reported three children who had insect-sting anaphylaxis shortly following negative venom skin tests. All had had prior sting anaphylaxis. Skin tests became positive following the second allergic reaction. This report also suggests that venom anaphylaxis may occur in the absence of venom-specific IgE.

Remaining is the question of appropriate therapy for patients without detectable IgE antibody. The basic issue is whether production of IgG antibodies, which result from venom immunotherapy, might be protective in such individuals, assuming their reactions are related to the pharmacologic mechanisms of venom. Again, referring to experience with systemic mastocytosis [7], two patients have been able to tolerate full doses of venom therapy, although they have not been re-stung. These observations would suggest that venom immunotherapy may be protective, even though the pathogenesis of the reaction has not been established. Obviously, the use of venom therapy would depend upon the exact identification of the insect which caused the reaction. In the absence of this information, one must rely on the availability of symptomatic medication for such patients.

Acknowledgment

This work as supported, in part, by NIH-NIAI grant 5RO1 AI 140501.

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