

Studies of the natural history of stinging-insect allergy: Long-term follow-up of patients without immunotherapy

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This study reports the clinical and immunologic responses of 29 patients who were observed during a prolonged period after insect-sting anaphylaxis without venom immunotherapy. At the time of their initial evaluation, all patients had venom-specific IgE, detected by skin test or RAST. Their mean age was 21 years; 16 patients were 16 years of age or less. There were 18 male and 11 female patients. Eleven patients had urticaria and angioedema as their only symptoms of anaphylaxis, and 18 patients had respiratory and/or cardiovascular symptoms. Reassessment was done 5 or more years after the initial evaluation. The average time at reevaluation was 10.1 years after the initial sting reaction. There had been 25 re-stings in 17 patients, with three systemic reactions occurring in two patients, an overall reaction rate of 12%. The time interval between the initial sting reaction and the follow-up sting was 2 to 14 years, mean 7.3 years. In patients with initial urticaria/angioedema symptoms only, there were 11 re-stings with no reactions. In patients with initial cardiovascular/respiratory symptoms, there were 14 re-stings with three reactions. At the time of follow-up evaluation, venom-specific IgE had generally decreased. In six of 25 patients, venom skin tests became negative, and in eight of 24 patients, the RAST became negative. These observations suggest that in many patients, stinging insect allergy is a self-limited process, with loss of clinical sensitivity and immunologic reactivity. (J ALLERGY CLIN IMMUNOL 1987;80:741-5.)

The natural history of stinging insect allergy is unclear. Patients who have had systemic reactions from insect stings and have venom-specific IgE are considered candidates for VIT. Recent studies have documented the effectiveness of VIT in preventing subsequent anaphylaxis from re-stings.¹

A perplexing problem in these studies of venom allergy has been the persistent observation that approximately 50% of patients who have had sting anaphylaxis and have positive venom skin tests, and who do not receive VIT, fail to react to subsequent re-stings.²⁻⁵ The re-sting reaction rate, particularly in children who have urticaria and angioedema as the only manifestation of anaphylaxis, is extremely low.⁶ The presumed therapeutic efficacy of whole insect body extracts, now recognized to be ineffective,⁷ prob-

Abbreviation used

VIT: venom immunotherapy

ably was due to the lack of understanding of the natural history of stinging-insect allergy.

Patients who decline immunotherapy for various reasons constitute a distinct group for study of the evolution of the natural history of stinging-insect allergy. In this article, we report the long-term clinical and immunologic responses of patients who had venom anaphylaxis and detectable venom-specific IgE, and declined immunotherapy. The results suggest that stinging-insect allergy may be a self-limited process for most patients.

MATERIAL AND METHODS

Selection of patients

Patients were selected who met the following criteria: (1) history of anaphylaxis after an insect sting, (2) venom-specific IgE, documented either by skin test or in the serum by RAST, at the time of their initial evaluation. (3) did not receive VIT, and (4) at least a 5-year interval between the initial evaluation and reassessment.

Anaphylaxis was defined as the occurrence of typical

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Supported in part by National Institutes of Health-National Institute of Allergy and Infectious Diseases Grant 5R01 AI-1450109.

Received for publication April 20, 1987.

Accepted for publication June 4, 1987.

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TABLE I. Demographic data

No. patients	29
Age at time of reaction (mean)	3-67 yr (21 yr)
> 16 years	13
≤ 16 years	16
M/F	18/11
Atopic/nonatopic	12/17
Follow-up since initial sting (mean)	6-22 yr 10.1 yr

allergic symptoms, such as generalized urticaria, angioedema, nausea, vomiting, diarrhea, hypotension, shock, asthma, and laryngeal edema within several hours after the insect sting.

Venom-specific IgE was detected by skin tests with honeybee, yellow jacket, bald-faced hornet, and *Polistes* venoms. Initial skin tests were performed with venoms collected locally by electrical stimulation. Follow-up skin tests were done with commercial venoms. The potency of venoms collected by these methods is similar.⁹ Skin tests were considered positive if reactions occurred to venom concentrations of $\leq 0.1 \mu\text{g/ml}$.⁹ This cutoff concentration was selected because of the large number of positive reactions elicited by higher venom concentrations ($\geq 1.0 \mu\text{g/ml}$) in control subjects nonallergic to insects.

Serum venom-specific IgE was measured by RAST with some modifications.^{10,11} Specific antibodies to honeybee and vespid venoms were measured. Ten micrograms of each dialyzed vespid venom protein and 100 μg of honeybee venom protein were coupled per disk. Results are expressed as percent net binding of a positive control serum containing 100 IU/ml of specific IgE. A net binding to the disks of >5 IU was considered significant. The background activity with normal human serum varied between 0.8% and 1.4% of total activity added for the venom disks.

Follow-up evaluation

Patients were contacted who met the above criteria. Clinical data were collected regarding the history of field re-stings and possible reactions. In some patients, the specific stinging insect could not always be identified. Venom skin tests and RAST were repeated at the follow-up visit. RAST results were compared, analyzing the initial and follow-up sera at the same time.

RESULTS

Twenty-nine patients were identified who met the selection criteria. VIT had been recommended to all patients but was declined for a variety of reasons. All patients had been instructed in the appropriate use of emergency medication and prescribed epinephrine in preloaded syringes. At the time of their initial evaluation, the patients ranged in age from 3 to 67 years, with a mean age of 21 years. There were 18 male and

TABLE II. Re-sting data

No. patients	29
No. re-stings	25
No. patients re-stung	17
No. reactions	3
Interval from initial sting reaction to re-sting (mean)	2-14 yr 7.3 yr

11 female patients; 13 patients were more than 16 years of age, and 16 were 16 years or less. Twelve of the 29 patients had a history of atopic disease. The reactions after the initial sting were generalized urticaria and angioedema in 11 patients, respiratory symptoms in eight, and cardiovascular symptoms in 10 patients. The mean follow-up interval from the initial sting to reassessment was 10.1 years, with a range from 6 to 22 years (Table I). There were 25 re-stings in 17 patients, resulting in three systemic reactions in two patients (Table II). The interval between the initial sting reaction and the subsequent sting ranged from 2 to 14 years, mean 7.3 years. The re-sting data are further analyzed in Table III. There were 11 patients who had urticaria and angioedema only as the initial anaphylactic symptoms. In this group, 11 re-sting episodes occurred with no systemic reactions. In patients with initial anaphylactic respiratory symptoms, there were eight re-stings, resulting in one systemic reaction consisting of urticaria alone. In the 10 patients who had cardiovascular symptoms initially, there were six re-stings, with two systemic reactions manifested by shock and hypotension in one patient.

In patients 16 years of age or less, there were 15 re-stings with no systemic reactions. In patients more than 16 years of age, there were 10 re-stings with three systemic reactions (Table IV).

The histories of the two patients who had anaphylaxis after re-stings are as follows:

Patient T. N., a 19-year-old male patient, was stung in 1979 by a yellow jacket and developed urticaria and respiratory symptoms. Five years after the initial sting, he was re-stung with a local reaction only. One year later in 1985, he was re-stung by 10 yellow jackets and developed generalized urticaria. A single yellow jacket sting in 1986 was tolerated with no reaction.

Patient A. C., a 17-year-old male patient, was stung in 1974 by a honeybee. He developed severe anaphylaxis, including hypotension and shock. Two years later (1976), a re-sting resulted in anaphylaxis of the same intensity. In 1978, after another honeybee sting, he had a third systemic reaction with similar symptoms of shock and hypotension. He has not been stung since.

TABLE III. Relationship of re-sting reactions to type of initial anaphylactic symptoms

Symptoms after initial sting	No. pts	No. re-stings	Reactions
Urticaria and angioedema only	11	11	—
Respiratory	8	8	1
Cardiovascular	10	6	2 (1 patient)

Pts = patients.

At the time of the initial evaluation, 25 patients had positive venom skin tests. Nineteen of the 25 patients retained the positive venom skin tests at follow-up evaluation. In general, the degree of skin test sensitivity had decreased (Table V). RAST titers also decreased (Fig. 1). The two patients with increased titers had had recent re-stings.

DISCUSSION

This study was designed to obtain further insight into the natural history of stinging-insect allergy. The most important conclusion is that clinical sensitivity may be lost with the passage of time alone, in the absence of further venom exposure. Immunologic reactivity, as defined by the immediate skin test reaction or the presence of serum venom-specific IgE, also decreases with time. In some patients, specific IgE may be undetectable, although most patients retain some reactivity in the absence of clinical sensitivity. An analogy might be made to patients with "burned-out" ragweed hay fever, who retain positive skin tests long after the clinical symptoms disappear.

In this study, 29 patients were reexamined 5 or more years after their initial evaluation. All had had sting anaphylaxis and detectable venom-specific IgE and had declined VIT. Follow-up clinical examination was dependent on the response to field re-stings; failure to identify the causative insect may influence the interpretation of these observations. For example, yellow jacket-sensitive patients may not always be allergic to a honeybee and might tolerate honeybee stings without difficulty. Nevertheless, the data do demonstrate that tolerance to insect stings does occur after a prolonged interval after the initial sting reaction. The average interval between the initial sting and the subsequent re-sting was 7.3 years. The time interval may be an important factor. In our initial study of re-stings in untreated patients, there was a 50% incidence of reactions with an average time interval of 4.5 years.⁵

In the present study, there were only two patients who had reactions after re-stings. The first patient

TABLE IV. Relationship of re-sting reaction to age of patients at time of initial sting anaphylaxis

Symptoms after initial sting	No. pts	Age at time of sting reaction	
		>16 yr	≤16 yr
Urticaria and angioedema only	11	2 (1)	9 (10)
Respiratory	8	4 (5)*	4 (3)
Cardiovascular	10	7 (4)*	3 (2)

Pts = patients, number of re-stings presented in parentheses

*Reaction in two patients.

TABLE V. Change in venom skin test reactivity

Initial evaluation	25 Patients with positive venom skin tests
Follow-up evaluation	
Skin test negative*	6
Unchanged	8
Decreased 1 log	4
Decreased 2 log	6
Increased 2 log	1

*A negative skin test was defined as no reaction to venom concentrations of ≤0.1 μg/ml.⁸

reacted to multiple stings, having tolerated a yellow jacket sting both before and after this reaction. The second patient had several severe systemic reactions at 2-year intervals and had not had a prolonged freedom from venom exposure. Thus, neither patient might be considered a true failure of the postulate that a prolonged interval without venom exposure promotes the loss of clinical sensitivity.

There have been other studies that examined the interval between the systemic reactions after an insect sting and the subsequent reaction to a re-sting in untreated patients. Settupane and Chafee¹² reported that two thirds of 19 patients had a "better" response to a re-sting after a 5-year interval, compared to a similar response in only one third of 74 patients whose re-sting occurred in less than 5 years. It is not clear whether these patients had only a local reaction or systemic symptoms. The authors interpret their data to suggest that the response to a re-sting is significantly improved if the interval between stings is more than 5 years.

Parker et al.³ reported the results of intentional re-stings in patients with prior sting anaphylaxis. Although their numbers are small, there was no difference in the reaction rate to the intentional sting in

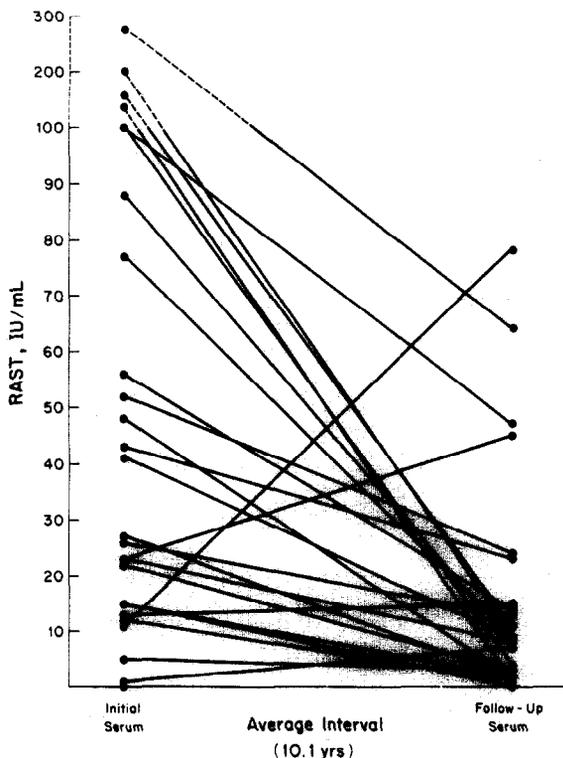


FIG. 1. RAST titers of initial and follow-up sera. Analysis of paired sera was done at the same time. RAST results are expressed as international units per milliliter.

patients whose prior stings had occurred less or more than 5 years previously.

During the 1960s, the Insect Committee of the American Academy of Allergy carried out a long-term follow-up study of patients with insect-sting allergy. In their last study in 1972,* there was no major difference in the reaction rate after re-stings less or more than 3 years after the initial sting reaction. On the other hand, more than 90% of these patients had a "better" response. This study is somewhat flawed by a number of factors, which include the use of symptomatic medication by most patients after re-stings and lack of data regarding age, specific type of reaction, and nature of the insect causing the reaction.

In this study, the initial symptoms of anaphylaxis varied and included both dermal reactions only and more significant cardiovascular and respiratory symptoms. Patients' ages varied, with re-stings in both the older and younger 16-year-old groups. The results do confirm the remarkable tolerance of children who have

urticaria and angioedema as the only manifestations of anaphylaxis for subsequent re-stings. Although the numbers are small, the data do suggest that patients more than 16 years of age and patients with cardiovascular and respiratory symptoms also lose their reactivity if the time interval between venom exposure is sufficient.

As noted, about 25% of the patients had negative skin tests and/or RAST at follow-up. Most of the other patients had decreased reactivity with less intense skin tests and lower serum antibody levels.

The bottom-line clinical question raised by this study is the appropriate management of a patient who had a systemic reaction to an insect sting more than 7 years previously and has either positive skin tests or detectable serum venom-specific IgE. The data reported here suggest that the patient is at small risk for another systemic reaction and might be adequately managed by the availability of emergency medication without VIT.

These observations further raise the issue of the indications for performing skin tests and RASTs in patients who fall into this category, if VIT is not to be administered. Until these data can be extended, measurement of venom-specific IgE is advisable. If tests are positive, recommendations for emergency medication are prudent, whereas negative tests would suggest that sensitivity is no longer present.

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