

Studies of the Natural History of Insect Sting Allergy

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ABSTRACT

The natural history of insect sting allergy was studied by observations of the results of re-sting on two groups of individuals who had prior sting anaphylaxis, had demonstrable venom-specific IgE, and did not receive venom immunotherapy. In the first study group, the mean duration between the initial sting reaction and re-sting exposure was 4.5 years; the re-sting reaction rate was 35%/sting and 50%/patient. In the second long-term study, the mean duration between the sting reaction and re-sting was 7.3 years; the re-sting reaction rate was 12%/sting and 12%/patient. Factors influencing the likelihood of re-sting reaction included older age, and the occurrence of cardiovascular/respiratory anaphylactic symptoms.

In a prospective and retrospective study of 133 patients with large local reactions, re-sting observations indicated an extremely high recurrence of similar large local reactions, with little risk of subsequent anaphylaxis.

These data suggest that: (1) insect sting anaphylaxis is a self-limiting process for the majority of individuals, and (2) re-stings in individuals who have had large local reactions have a relatively benign prognosis.

INTRODUCTION

It is usually necessary to understand the natural history of a disease process in order to resolve questions

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regarding appropriate diagnosis and therapy. Insect sting allergy is a prime example. The failure to appreciate the natural history of the clinical disease led to major misconceptions in the past and raises newer questions today. For over 40 years, whole body extracts made from the grinding and crushing of whole insect bodies were used for the diagnosis and treatment of individuals who had sting anaphylaxis. These extracts were felt to be extremely effective allergens. It was not until the 1970's that these extracts were finally delegated to placebo status for several reasons: (1) whole body extract skin tests did not distinguish between insect-allergic and insect-nonallergic individuals; (2) therapeutic failures were recognized with increasing frequency in individuals receiving whole body extract therapy; and (3) venom antigens could not be detected in commercial whole body extracts. It then became clear that the presumed effectiveness of whole body extract therapy must be attributed to other explanations, most likely the natural history of the disease process with the spontaneous loss of clinical sensitivity.

Over the past ten years, purified venoms have been used for the diagnosis and treatment of insect sting allergy. These agents are highly potent and have provided the tools for accurate diagnosis and effective therapy. Current problems, however, do remain. These include questions regarding immunotherapy, such as choice of venom, how much venom and, in particular, how long venom therapy should be continued. These questions are primarily addressed by observations of the effect of re-stings in patients who have received venom immunotherapy.

Table I

Demographic Data		
	Initial Study	Long-Term Study
# Patients	56	29
Age		
range	4½-83	3-67
mean	24	21
Male/Female	36/20	18/11

In order to reliably answer these questions, it is necessary to understand the natural course of the disease process and the effect of subsequent venom exposure on individuals who do not receive venom immunotherapy. Relevant information was obtained years ago with the observation that patients who did not receive whole body extract therapy often had little or no reaction to subsequent re-stings. In more recent years, several studies have addressed this issue. In the initial study done at Johns Hopkins which documented the therapeutic efficacy of venom,¹ approximately 40% of patients receiving either whole body extracts or placebo had no reaction when re-stung, despite a history of sting anaphylaxis and the presence of venom-specific IgE. In a very interesting ongoing study of children who have had dermal reactions as the only manifestations of insect sting anaphylaxis, a very small percentage of patients had subsequent re-sting reactions in the absence of venom immunotherapy.²

This report will review previously published studies which address the question of the natural history of the disease process.³⁻⁵ The results of these studies and the observations made by others, suggest that in the majority of individuals, insect sting anaphylaxis is a self-limiting process. Re-stings in individuals who had initial large local reactions are likely to cause similar reactions, with little risk of progression to generalized anaphylaxis.

MATERIALS AND METHODS

In the studies of sting anaphylaxis, 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 initial evaluation, and (3) did not receive venom immunotherapy.

The initial study reported the followup data of patients who were initially evaluated between 1976 and 1983.³ The second study in 1986, described untreated patients who had had at least a five-year interval be-

Table II

Re-Sting Data		
	Initial Study	Long-Term Study
# Patients	28	17
# Re-Stings	40	25
# Reactions	14	3 (2 pts)
Re-Sting reaction rate		
%/sting	35%	12%
%/patient	50%	12%
Interval between initial sting reaction and re-sting (mean)	4.5 years	7.3 years

tween their initial evaluation and reassessment.⁴ Evaluation was based on the results of reactions to re-stings.

In the study of large local reactions,⁵ patients were selected who had reactions defined as swelling and erythema contiguous with the sting site, peaking at 48 to 72 hours, and often lasting as long as one week. Patients with systemic symptoms were excluded. The data were collected both retrospectively and prospectively.

Venom-specific IgE was detected by skin tests with honeybee, yellow jacket, bald-faced hornet, and Polistes venoms. Initial skin tests were done with venoms collected locally by electrical stimulation; followup skin tests were done with commercial venoms. The potency of the venoms collected by these methods is similar.⁶ Skin tests were considered positive if reactions occurred at venom concentrations of $\leq 0.1 \mu\text{g/ml}$.⁷ Serum venom-specific IgE was measured by the RAST with some modifications.⁸

RESULTS

Sting Anaphylaxis

The data from the two studies will be presented in parallel and labeled as the "initial" study and the "long-term" study. The basic difference in the patient population is that in order to qualify for the second "long-term" study, there had to be a five-year interval between the initial evaluation and reassessment.

The demographic data are shown in Table I. In the initial study, there were 56 untreated patients ranging in age from 4½ to 83, with a mean age of 24. In the long-term study, there were 39 patients ranging in age from three to 67, with a mean age of 21. The male:female ratio was approximately the same in both studies.

Table III

Relationship of Age at Time of Initial Sting Reaction to Subsequent Re-Sting Reaction

Age at time of initial sting	Initial Study		Long-Term Study	
	<16 yrs	≥16 yrs	<16 yrs	≥16 yrs
# Re-Stings	21	19	15	10
# Patients	15	13	10	7
# Reactions	6	8	0	3 (2 pts)
Re-Sting reaction rate				
%/sting	29%	42%	0	30%
%/patient	40%	62%	0	29%

Table IV

Relationship of the Nature of Anaphylactic Symptoms Which Occurred with Initial Sting Reaction to Symptoms From Subsequent Sting Reactions

Initial Anaphylactic Symptoms	Initial Study		Long-Term Study	
	Urticaria/Angioedema Only	Cardiovascular or Respiratory	Urticaria/Angioedema Only	Cardiovascular or Respiratory
# Patients	18	10	6	11
Re-Sting Reactions				
urticaria/angioedema	6	2	—	1
cardiovascular/respiratory	—	6	—	1
no reaction	12	2	6	9

In the initial study, there were 40 re-stings in 28 patients with 14 reactions, representing a reaction rate of 35%/sting and 50%/patient. In the long-term follow up study, there were 25 re-stings in 17 patients, with three reactions in two patients. This represents a reaction rate of 12%/sting and 12%/patient. In the initial study, the mean interval between the initial sting reaction and the re-sting was 4.5 years; in the long-term study, the interval was 7.3 years (Table II).

In order to evaluate other factors which might influence re-sting reaction rates, data were analyzed according to age at the time of the initial sting reaction and the nature of the clinical symptoms which occurred with the the initial sting reaction. In the initial study, there were six reactions following 21 re-stings in 15 patients under 16 years of age, a reaction rate of 29%/sting and 40%/patient. In those 13 patients over 16 years, there were 19 re-stings with eight reactions, a reaction rate of 42%/sting and 62%/patient. In the long-term study, in those patients under 16, there were 15 re-stings in ten patients with no reactions. In those

patients over 16, there were ten re-stings in seven patients with three reactions in two patients, a reaction-rate of 29%/patient and 30%/sting (Table III).

Patients were analyzed depending upon the nature of the initial anaphylactic symptoms and divided into two groups—those with urticaria/angioedema only, and those with associated cardiovascular/respiratory symptoms (Table IV). In the initial study, there were 18 re-stings in patients who had initial urticaria/angioedema reactions only. Following these 18 re-stings, there were six reactions, all with urticaria/angioedema only, and in the other 12 instances, there were no reactions. In patients who had initial cardiovascular/respiratory symptoms, there were ten re-stings with two urticaria/angioedema reactions, six cardiovascular/respiratory reactions, and in two instances, no reaction.

In the long-term study, six patients who had initial urticaria/angioedema reactions had re-stings with no reactions. There were 11 patients who had initial cardiovascular/respiratory symptoms; two patients reacted to re-stings, one with urticaria/angioedema,

Table V

Results of Re-Stings in Patients Who Had Large Local Reactions After an Insect Sting

Patient Group	Initial No. of Patients	No. of Patients Evaluated	Re-sting Data*		
			No. of Re-stings (No. of Patients)	Large Local Reactions	Systemic Reactions
RAST-negative	66				
Retrospective data		66	49 (28)	49 (100%)	
Prospective data		33	26 (10)	25 (96%)	0
RAST-positive	67				
Immunotherapy	24	24	31 (14)	23 (74%)	0
No therapy	43	22	24 (18)	17 (70%)	1
Total	133		130 (70)	114 (88%)	1

* From: Mauriello PM, Barde SH, Georgitis JW, Reisman RE. Natural history of large local reactions from stinging insects. *J Allergy Clin Immunol* 74:494-498, 1984.

and one with cardiovascular/respiratory symptoms on two occasions.

Large Local Reactions

One hundred-thirty-three patients were evaluated who had had large local reactions following insect stings. These patients ranged in age from two to 80, with a mean age of 35. The incidence of atopy was approximately 27%. The patients were divided into two groups, depending upon analysis of serum venom-specific IgE at the time of their evaluation. Sixty-seven patients were RAST-positive and 66 RAST-negative. The patients were further evaluated depending on whether they had received venom immunotherapy. When venom was initially available, patients who had had large local reactions and had detectable venom-specific IgE were given venom immunotherapy.

The results of these data are summarized in Table V. Results indicate that almost all patients (88%) who have had large local reactions are likely to have similar reactions following subsequent stings. The data are not significantly influenced by the presence or absence of venom-specific IgE or the use of venom immunotherapy. In this study, only one of the 133 patients had a subsequent systemic reaction following an insect sting.

DISCUSSION

The clinical data indicate that the majority of individuals who have had insect sting anaphylaxis and do not receive venom immunotherapy, do not react to subsequent re-stings. These clinical observations suggest that insect sting allergy is a self-limiting disease for

most individuals despite the persistence of venom-specific IgE. Unfortunately, there are no immunologic markers that correlate with this spontaneous loss of clinical sensitivity. Thus, there is a dichotomy between the immunologic reactivity and clinical sensitivity.

The loss of clinical sensitivity appears to be related to the time interval between the initial sting reaction and the subsequent re-sting. As the time-interval increased, the percent of individuals who had re-sting reactions decreased. Similar findings have been noted in the studies of the natural history of penicillin sensitivity.

The age at the time of the initial reaction and the nature of the clinical symptoms of the initial reaction are relevant factors which influence the natural history of the disease process. Individuals under the age of 16, have a remarkably low re-sting reaction rate. Schubert and colleagues² first made this observation in individuals under age 16, who had urticaria and angioedema as the sole manifestation of insect sting anaphylaxis. Our own data suggest that children with respiratory and cardiovascular reactions also may have a lower re-sting reaction rate.

The nature of the systemic reaction may be very important. There appears to be a very low re-sting reaction rate in individuals who have had urticaria and angioedema, both in children, as noted above, and in adults as well. On the other hand, those individuals who have cardiovascular and respiratory symptoms appear to have a somewhat higher re-sting reaction rate. More recent observations of a large number of individuals who have had severe anaphylactic symptoms, do suggest an increased systemic reaction rate in untreated individuals.⁹

In our initial publications of these data,^{3,4} the observations made in other studies were reviewed and generally support the concept of spontaneous loss of clinical sensitivity in a large number of individuals who have had insect sting anaphylaxis.

Observations of individuals who have had large local reactions from insect stings suggest the recurrence of similar reactions after subsequent re-stings, with a very low likelihood of the development of systemic reactions. The large local reaction is not influenced by the presence or amount of venom-specific IgE. Venom immunotherapy administered to a relatively small number of patients, also did not influence the likelihood of a large local re-sting reaction. In this study, the effect of time between stings was not analyzed.

Overall, these observations show the need to understand the natural history of insect sting allergy in order to make appropriate recommendations regarding risk factors and modifications with venom immunotherapy. The studies with large local reactions are well-defined. Individuals with large local reactions have small risk of subsequent anaphylaxis and, therefore, do not require venom immunotherapy or even venom testing. They should be advised of the likelihood of subsequent large local reactions and possible symptomatic therapy with antihistamines and/or steroids.

Advice for individuals who have had venom anaphylaxis and have detectable venom-specific IgE is certainly not as clear cut. Risk factors⁹ for the persistence of sting anaphylaxis appear to be (1) the nature of the initial reaction with the occurrence of cardiovascular/respiratory symptoms, (2) perhaps older age, (3) use of

medications, such as beta-blockers, (4) the presence of cardiac disease, and (5) perhaps the occurrence of multiple stings. All of these issues deserve careful discussion with the patient prior to the initiation of venom immunotherapy.

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