

Observations on the aetiology and natural history of stinging insect sensitivity: application of measurements of venom-specific IgE

R. E. REISMAN, C. E. ARBESMAN, and M. LAZELL

Allergy Research Laboratory of the Buffalo General Hospital and the Division of Allergy, Department of Medicine of the State University of New York at Buffalo.

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Summary

Measurements of serum venom specific IgE were used to gain further insight into the aetiology and natural history of stinging insect allergy. Several aspects were studied.

(a) Following sting reactions, sequential sera were examined in the absence of venom immunotherapy. There was a marked individual patient variation in the persistence of venom specific IgE. In nine patients, antibody levels dropped to insignificant levels, suggesting the possibility that sensitivity can be lost spontaneously.

(b) Details of four patients with anamnestic IgE antibody responses after sting reactions are presented. These responses occurred even when prior antibody titres were negligible, suggesting that patients mentioned above (No. 1) will require careful monitoring. The anamnestic responses are insect specific.

(c) Eighteen patients were studied who had typical insect sting anaphylaxis and subsequent insignificant serum levels of venom specific IgE. One third also had negative direct skin tests with venom. These observations suggest that the possibility for a non-IgE pathogenesis for some insect sting reactions may have to be considered.

(d) One patient was identified who became sensitized to non-venom protein in whole body insect extracts as the result of whole body extract therapy.

Introduction

We have previously related the levels and changes of venom specific IgE to exposure to insect stings, diagnosis of stinging insect allergy and venom immunotherapy (Reisman, Wypych & Arbesman, 1975; Light *et al.*, 1977; Reisman, Arbesman & Lazell, 1978). It is the purpose of this paper to present a number of observations relative to the natural history of stinging insect allergy and to identify some of the problems which remain unsolved. Thus, several different aspects will be addressed which have a direct bearing upon the understanding of the factors which affect allergic reactions from stinging

Correspondence: Dr Robert E. Reisman, Allergy Research Laboratory of the Buffalo General Hospital and the Division of Allergy, Department of Medicine of the State University of New York at Buffalo, Buffalo, New York, U.S.A.

insects. The topics to be addressed specifically are (i) individual variation in the persistence of venom specific IgE; (ii) anamnestic IgE antibody response after a sting; (iii) inability to document an IgE pathogenesis for some sting reactions; and (iv) possible sensitization to whole body extracts.

Materials and methods

Patients

The majority of patients in these studies had anaphylactic reactions following an insect sting. Their symptoms were variable but all typical of anaphylaxis. Some patients had large local reactions only. All patients were personally examined at variable time periods following the reaction and blood was obtained for analysis of venom specific IgE. In some cases, skin tests with venom and whole body extracts were performed. At periodic follow-up visits, sequential blood samples were obtained.

Venom and whole body extracts

Bee and yellow jacket venoms for *in vitro* and *in vivo* studies and immunotherapy were collected locally by the method of electrical stimulation (Benton, Morse & Stuart, 1963). Following collection, venom was dissolved in a small volume of buffered saline, filtered and the protein concentration determined on the filtrate. An 0.1% venom was then prepared (1000 µg/ml).

Whole body insect extracts for skin testing were obtained from commercial sources. For *in vitro* studies, whole body extracts were prepared in our laboratory (Shulman *et al.*, 1966).

Measurement of venom specific IgE-RAST

Venom specific IgE and whole bee body extract specific IgE were measured by the radioallergosorbent test (RAST) (Light *et al.*, 1976). When sequential sera were available, all samples were studied at the same time. Results were expressed in relationship to a positive standard and values greater than 10% were considered significant.

Venom skin tests

Serial ten-fold dilutions were prepared from the stock venom concentrate. Preliminary intradermal testing in a control non-allergic population revealed that concentrations of venom as low as 0.1 µg/ml often elicited non-specific reactions. Therefore, reactions elicited by 0.01 µg/ml or less of venom were considered significant.

Results and discussion

Individual variation in persistence of venom specific IgE

The natural history of stinging insect sensitivity as measured by the rate of decline of venom specific IgE was analyzed in nine patients (Fig. 1). All had elevated serum venom specific IgE shortly after sting anaphylaxis. As will be noted from Fig. 1, antibody titres fell to insignificant levels within 3 to 18 months in the absence of specific treatment. One patient in this group has been stung since the last antibody determination without any reaction. These patients are being followed without any specific treatment.

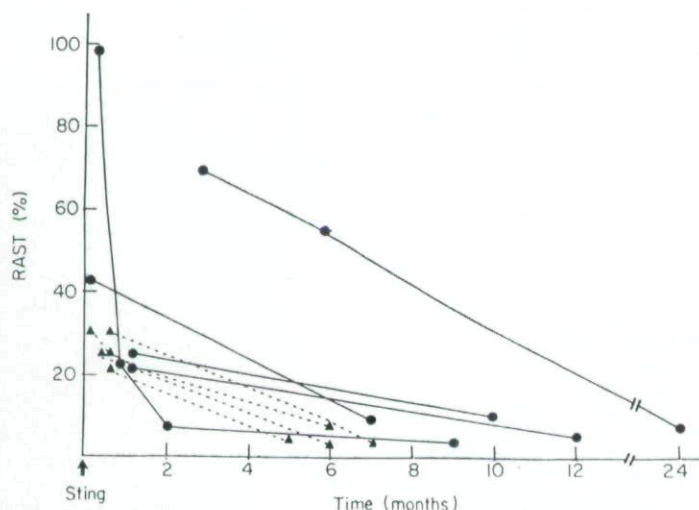


Fig. 1. Levels of bee venom and yellow jacket venom specific IgE in the sequential sera of nine insect allergic patients who have not been given specific immunotherapy. All patients had anaphylaxis following a sting, indicated by the arrow at the bottom of the figure. Sera were obtained at varying time intervals following the sting reaction. RAST levels are expressed as a percentage of a positive standard. Levels above 10% are considered significant. ●—●, Bee venom; ▲—▲, yellow jacket venom.

In contrast with these individuals in whom antibody titres diminished fairly rapidly following a sting, other individuals have been followed whose antibodies persisted for some time. Serum venom specific IgE levels of fifteen patients followed for periods of 2 to 18 months prior to initiation of venom therapy are shown in Fig. 2. In seven patients, antibody titres remained about the same or dropped very slightly. In the other eight patients, antibody levels all fell significantly but treatment was initiated because of the elevated titres.

Criteria such as sex, age, and the presence of atopy were not related to the degree of decline in venom specific IgE in these groups of patients.

This variability in the persistence of insect sensitivity as measured by serum levels of venom specific IgE makes specific tests mandatory if an accurate assessment of any individuals present sensitivity is desired. The spontaneous decline of venom specific IgE may explain why individuals lose their sensitivity with or without any form of therapy. The reason for this variation in individual sensitivity, which is not related to the initial antibody titre, is certainly unknown and deserves further investigation.

These observations concerning the natural decline of venom specific IgE and, therefore, the apparent loss of sensitivity raise important questions concerning the choice of patients for treatment. In some patients, venom immunotherapy has led to a marked rise in venom specific IgE (Reisman, Arbesman & Lazell, 1978; Sobotka, Valentine & Lichtenstein, 1978). This may occur concurrently with the development of venom specific IgG and thus the development of immunity to subsequent stings. However, this stimulation of venom specific IgE may necessitate prolonged immunotherapy in order to avoid prolonged maintenance of sensitivity. Our data strongly suggest that there may be patients who lose their sensitivity if not exposed to venom either as a result of a natural sting or in the form of venom immunotherapy. This concept will require a great deal of further investigation and observation.

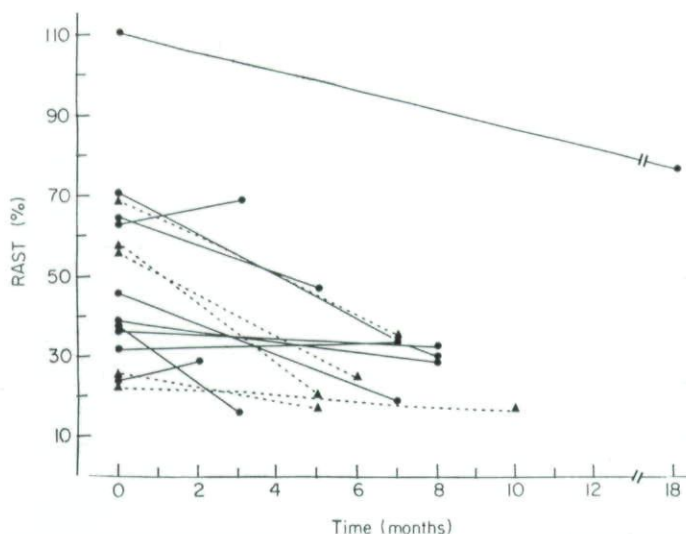


Fig. 2. Levels of bee venom and yellow jacket venom specific IgE in the sequential sera of fifteen insect allergic patients. During the interval between the antibody measurements, specific venom immunotherapy was not administered. Venom immunotherapy was initiated after the last serum IgE antibody determination because of the elevated titre. The sting reactions occurred at varying time intervals (2 weeks—2 years) prior to the first serum antibody determination (time '0'). ●—●, Bee venom; ▲—▲, yellow jacket venom.

Anamnestic response following an insect sting

We have previously described the anamnestic response in venom specific IgE following a sting reaction (Light *et al.*, 1977). Four case histories are further illustrated to point out the occurrence of the anamnestic response, even in an individual with previously unmeasurable antibody levels, and the specificity of the response.

Case histories

Case 1 Mrs A.S., a 70-year-old woman, was initially seen in October of 1959 because of two previous yellow jacket stings each of which caused a large local reaction lasting several days, and accompanying nausea. Skin tests with yellow jacket whole body extracts were equivocal and as was customary at that time, injection therapy with a mixed whole body extract was initiated. Injections were given for approximately one year and discontinued. She returned in June 1968 because of large local reactions following multiple bites from an unidentified insect. She was concerned about the possibility of similar reactions from stinging insects. Skin tests with whole body extracts were again equivocal. Whole body injection therapy was initiated and continued until 1975, when stopped because of the lack of immunological evidence for sensitivity. In September 1976, one year later, she was again stung by a yellow jacket and developed a large local reaction which lasted approximately 5 days.

Venom specific IgE was measured in serum specimens from 1974 until the present time (Fig. 3). In November, 1974 yellow jacket venom specific IgE was not detectable and shortly thereafter whole body insect extract therapy was discontinued. Serum was next obtained several weeks following the sting reaction in September 1976, and found to contain an extremely high titre of venom specific IgE, indicative of a marked anamnestic response from the sting. Yellow jacket venom immunotherapy was initiated and has been continued until the present time. Her venom specific IgE has

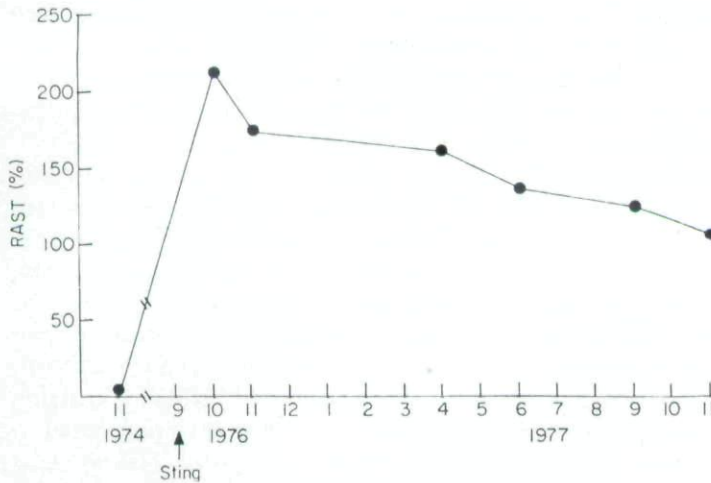


Fig. 3. Yellow jacket specific IgE in serum of patient A.S. A marked anamnestic response occurred following a sting and a large local reaction. See text for details.

slowly fallen from a RAST level of 217% to a present level of about 100%. Currently she receives 100 μ g of yellow jacket venom monthly without adverse reaction.

Case 2, Mr. D.F., a 42-year-old male, had 4 bee stings in May 1972 without reaction. In August 1974, he was stung again and developed a large local reaction lasting about 5 days. He was seen several weeks later at which time his venom specific IgE was 30%. One month later, in September 1974, it had dropped to 23%. Over the next two years he was treated with whole body extracts and a blood examined in September 1976, revealed a RAST level of 24%. Thus his venom specific IgE had been stable for approximately 2 years.

He returned again in July 1977. Two weeks earlier he had been stung again and developed a large local reaction accompanied by severe malaise. His serum venom specific IgE level was 37%, which subsequently remained stable for several months. Treatment was started with bee venom and has been continued up until the present time. The bee sting appeared to stimulate further venom-specific IgE production.

Case 3, K.T., a 15-year-old female, was seen in November 1975, shortly following a honeybee sting which resulted in a large local reaction. Yellow jacket venom-specific IgE was 12% and bee venom-specific IgE 29%. In August 1976, she returned having had another insect sting with no reaction. She was unable to identify the insect. Blood taken four weeks following this sting revealed a yellow jacket venom-specific IgE of 56% and a bee venom-specific IgE of 19%. Thus, the sting had markedly stimulated yellow jacket-specific IgE without affecting the bee venom titre. One year later in August 1977, the yellow jacket-venom-specific IgE had dropped to 18% and the bee venom-specific IgE was not detectable. She had not received any type of specific immunotherapy.

Case 4 C.S., an 18-year-old male, was first examined in August 1975, because of a large local reaction and generalized pruritus following an insect sting. Elevated titres of bee venom (34%) and yellow jacket venom IgE (64%) were found. A subsequent follow-up serum in May 1976, showed diminished but still elevated titres (bee venom—15%; yellow jacket venom—25%). Bee venom therapy was initiated (yellow jacket venom was not available at that time). He returned in January 1977 and in June

1977 for further evaluation. Essentially stable but elevated titres persisted (bee venom—24%; yellow jacket venom—30%). In October 1977, he was stung by a yellow jacket and had a mild systemic reaction. Blood analysis 3 months later (January 1978) showed a marked rise in yellow jacket-specific IgE (76%) and unchanged bee venom-specific (22%). Yellow jacket venom now has been added to the venom therapy.

These cases illustrate the possibility of a fairly marked anamnestic IgE antibody response following an insect sting. The first case is the most impressive in our experience. We felt this woman was no longer sensitive to insect stings yet with the resulting large local reaction, she developed a fairly marked anamnestic response, putting her at risk for more serious reactions in case of subsequent stings. It is of interest to note that large local reactions in several individuals seem to be associated with this marked anamnestic response. This experience points up the dilemma associated with the use of low or undetectable levels of venom specific IgE as the criterion for discontinuation of therapy. Such individuals, while perhaps not predisposed to anaphylaxis at the time of a subsequent sting, may mount a response, making them susceptible in the future. The third case history (K.T.) illustrates the fact that this response may occur even without a local or anaphylactic reaction. The clinical significance of these responses cannot be underestimated. Any individual in whom treatment has been discontinued will have to be re-examined should he have further, even uneventful, stings.

Cases 3 and 4 also show the specificity of the IgE antibody response. Both individuals had somewhat elevated levels of both bee and yellow jacket venom specific IgE. Following the sting, only the specific IgE level rose, in both instances yellow jacket venom specific IgE.

Failure to detect serum venom specific IgE following sting reactions

Over the past year we have seen eighteen individuals who had typical anaphylaxis following stings, probably yellow jacket stings. Specific IgE antibodies reacting with bee, yellow jacket and hornet venoms could not be detected in the sera of these individuals. Clinically, the group did not differ from patients with insect anaphylaxis and serum antibodies.

The patients ranged in age from 5 to 47 years with the median age of 20. Four of the eighteen were atopic. Sting sites were primarily on the extremities but all areas were involved. Serum was obtained from less than 2 weeks to more than 3 months following the sting reactions. In most of these individuals, further serum specimens were obtained for analysis and the results were unchanged. The skin test reactions with yellow jacket venom revealed six patients with negative reactions and five with borderline reactions. Seven patients did have positive intradermal skin test reactions.

None of these patients has been given venom immunotherapy. To date, one has been re-stung with no reaction.

We have considered several alternatives for these findings. The first is technical. It is possible that the antibody levels were too low to be detectable by this RAST methodology, yet still be significant. These sera were re-examined a number of times with the same results. In most instances, second, and even third samples were measured. Positive control sera were included in all RAST determinations. More recently, we have used several yellow jacket venom preparations for the RAST without changing these results.

Finally, there is the question of a non-IgE pathogenesis for these reactions, an

attractive alternative but one without other support at the moment. We have elected not to treat these individuals without solid knowledge of the pathogenesis of their reactions. These observations, however, strongly suggest the possibility that there may be a non-IgE pathogenesis for some insect reactions.

Whole body extract sensitization

The problem sensitization from whole body insect extract injections has been reported previously. One case history (Hunt *et al.*, 1978), well studied, suggested that symptoms of fever and joint pain several days following an injection, occurred as a result of an immunologic reaction to whole body extracts and specifically, to non-venom proteins. We have identified one other individual who may have been sensitized by whole body extract therapy. His clinical story and laboratory are as follows:

Mr. J. B. was initially seen in 1972, at which time he was 16 years of age. He was an atopic individual with mild hayfever and asthma. In July 1972, he was stung by an unidentified insect and developed a large local reaction with generalized hives occurring approximately 48 hr later. Several weeks later, at the time of his examination, intradermal skin tests with whole body extract were strongly positive (4+ reaction; 1/100,000 dilution of 1/10 whole body extracts). Mixed whole body extract therapy was initiated and continued for 4 years.

Following injections in August 1974, and in August 1976, he had systemic reactions.

Serum was available for analysis from the time of his initial evaluation in July 1972, until 1977. Over this 5-year period of time, bee venom specific IgE and whole bee body specific IgE levels were determined and the results are shown in Fig. 4. At the time of his initial evaluation, antibodies could not be detected reacting with either one of these substances. He never developed significant titres of bee venom specific IgE. On the other hand, whole bee body extract specific IgE rose remarkably following initiation of therapy and then slowly fell over a period of time. Therapy was ultimately discontinued

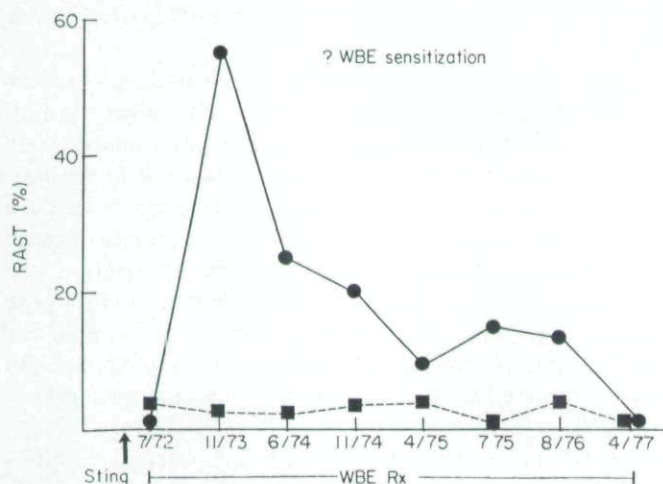


Fig. 4. Bee venom and whole bee body specific IgE in the sera of patient J.B. See text for details. There was a rise in titre of IgE antibodies to whole body extract following initiation of WBE therapy and negligible levels of bee venom specific IgE. These findings suggest the probability of sensitization to non-venom protein in the whole body extract. ●—●, whole body extract; ■---■, venom.

in late 1976. At the time of the systemic reactions following injection therapy, he did have significant levels of IgE antibodies reacting with the whole body extract.

In all probability, this individual was sensitized by the administration of whole body extracts resulting in the two systemic reactions. The failure to find specific IgE antibodies reacting with bee venom suggests that he may well have been sensitized initially by some other insect. The exact pathogenesis for the reaction remains somewhat in doubt in that hornet and yellow jacket venom specific IgE could not be demonstrated. It should be emphasized that only after therapy was initiated was there a significant rise in whole bee body extract IgE antibodies.

Discussion

The observations in this paper were lumped together in order to obtain a better perspective concerning the practical problems in the everyday diagnosis and management of stinging insect allergy. Several extremely important conclusions were reached from the presented data.

Probably the most important observation is that patient sensitivity may be lost as a result of time alone with the lack of any further exposure. This may well explain why whole body insect extracts appear to have been an effective form of therapy for many years. These extracts are now known to be immunologically ineffective. Patient improvement probably occurred as a result of time, and lack of any exposure to insect stings rather than to the effect of specific treatment. These observations also suggest that it might be advisable to follow sensitive patients for a short period of time to determine the rate of decline of their IgE antibodies prior to initiation of therapy. There are patients who may not require venom therapy. Furthermore, venom therapy regimes will have to be developed in such a manner as to not stimulate excessive amounts of IgE antibodies.

The second major point is that while we have used the lack of decline of venom specific IgE as a criterion for withholding therapy, there may be some patients who develop anamnestic responses after further stings. The observations made in several patients indicated the need for continued follow-up in insect-sensitive patients even after uneventful stings.

The third observation of the failure to document clearly an IgE pathogenesis for some insect reactions is certainly disturbing to our current views on the subject. It may well explain, however, why some patients, usually children, have had anaphylaxis following the first sting and yet had no history of the contact required to develop sensitization. The mechanisms for these reactions is not known. One may speculate concerning the actions of the pharmacologically-active ingredients in venom. If these observations are verified, the proper therapeutic approach for such patients is not clear. It is not known whether venom therapy leading to development of IgG type antibodies would provide protection in this situation. Finally, it should be pointed out that the presence of both an IgE and a non-IgE mechanism for anaphylactic-like reactions is not unique. A similar experience has been reported with reactions following plague vaccine (Reisman, 1970).

The final observation of the occurrence of typical IgE mediated systemic reactions following whole body extract and the apparent sensitization by non-venom proteins in the whole body extract supports a previously reported study. This may well explain why some patients on whole body extracts cannot tolerate high doses. Furthermore, the potentially harmful effects of whole body extracts, in addition to their clinical and

immunologic ineffectiveness, strongly indicate that they have no place in the modern day treatment of stinging insect sensitivity.

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