

Insect allergy. Predictive value of diagnostic tests: a three-year follow-up study

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Summary

One hundred and six adults with various reactions to yellow jacket (YJ), honey bee (HB) or unidentified insects (UI) were tested for allergy to insect venoms. For various reasons none received immunotherapy. Individuals completed questionnaires annually for three consecutive years and described sting reactions within the previous season. Ninety subjects completed all the questionnaires and 77 of these were re-tested at the end of the period. Nine out of 25 patients reacted with a systemic reaction when re-stung. High IgE and low IgG venom-specific antibody levels indicated an unfavourable prognosis, since eight of 11 individuals who initially presented venom-specific IgE > RAST class 2 and venom-specific IgG below detection limit had systemic reactions at re-sting. No such reactions occurred in subjects with no specific IgE and only one out of six with specific IgE as well as IgG reacted systematically. Skin prick tests (SPT) of < 3 mm with YJ venom 1,000 µg/ml excluded later systemic symptoms to stings, whereas larger skin reactions gave an equal chance of systemic or local reactions at re-sting. In individuals not stung by UI, YJ and/or HB the decline in venom-specific IgG and IgE was significant, median values ranging from 41% to 75% over the 3-year period. The decline was unaffected by the type of sting reaction prior to the initial test. SPT results did not change significantly. The findings are relevant when testing patients several years after their last insect sting and the results might indicate that the antibody decline is accompanied by a decrease in clinical sensitivity.

Introduction

Allergy to insect venom, like penicillin allergy, is generally characterized by a short, infrequent, but clearly identified exposure. Furthermore, reactions can be dramatic when the reacting organ is the cardiovascular system. These features make it more

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important but also difficult to establish a true diagnosis—at least when compared to the various inhalant allergies where knowledge from repeated, relatively safe, natural challenge facilitates the foreseeing of reaction to future exposures.

Having established the diagnosis of insect venom allergy, an effective prophylactic treatment is possible as hyposensitization gives good protection in more than 90% of patients [1,2]. Since hyposensitization is expensive and not without risks, and since at least 40% of the patients with systemic allergic reactions to insect stings will react normally to the same insect in the future even without treatment, it is necessary to identify those patients who need therapy.

The correlation between clinical reactions and subsequent allergy tests is not impressive [3, 4]. The explanation for this could be that some of the adverse reactions to stings are, in fact, of non-allergic origin. Other discrepancies can be explained by the fact that these allergy tests detect antibody responses to the last sting rather than antibodies causing this reaction—parameters may very well have changed subsequent to the sting.

The primary aim of the present prospective study was to evaluate the prognostic value of the routine allergological tests with respect to the outcome of future field stings. A secondary aim was to describe the spontaneous changes in test results in subjects who were not stung during the follow-up period.

Materials and methods

Following the 1981 insect season 117 adults with normal and abnormal reactions to insect stings were tested with skin tests and measurement of specific antibodies against Yellow jacket (YJ) and honey bee (HB) venoms. All were referred for allergy testing or seen in the casualty ward following insect stings. Clinical symptoms and test procedures have previously been reported [3]. Skin prick tests (SPT) were performed with venoms in concentrations from 1 to 1,000 $\mu\text{g/ml}$ (Soluprick®, Allergologisk Lab. A/S, Copenhagen). Specific IgE and IgG antibodies to the individual venoms were determined by a radioallergosorbent test, Phadebas RAST® and Phadebas IgG RAST® by Pharmacia A/S, Hillerød, Denmark according to the manufacturers directions [4, 5]. Serum samples from the visit in 1981 were kept at -18°C and IgG RAST was performed simultaneously on these sera and on samples from 1985 to eliminate interassay variation. All assays were run in duplicate. For IgG an intra-assay variation up to 20% was considered acceptable. Eighteen per cent of the tests did not meet this criterion and were repeated. Eleven patients with severe systemic reactions, positive skin prick tests and IgE-RAST of class 3 or 4 were started on hyposensitization with venom and were not included in the present study. Each year for three years the remaining 106 individuals, aged 19–78 years, were asked to fill in a questionnaire which described sting reactions to YJ, HB or other/unidentified insects. Colour plates were provided to help identification. Three years after the initial examination the group still not on immunotherapy was offered a re-test. Seventy-seven subjects took part in this follow-up and a total of 90 completed questionnaires which covered all three seasons.

Results from the initial tests were correlated to the reaction to the first sting during the follow-up period. Subjects re-stung by unidentified insects were excluded from analyses.

For individuals not stung during the follow-up period spontaneous changes in SPT and antibody levels were calculated and related to previous reactions to the same insect.

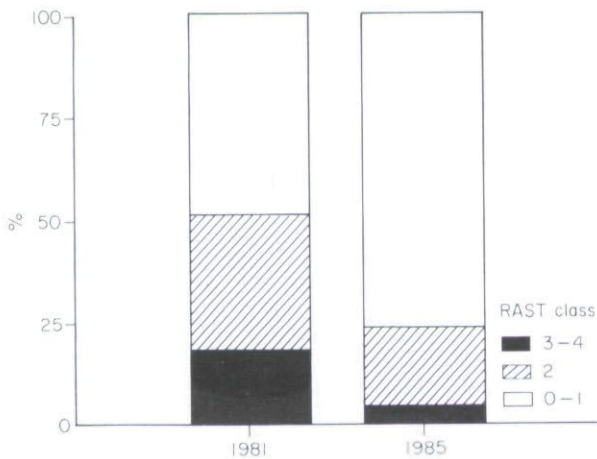


Fig. 1. Venom specific IgE in individuals not stung by honey bee and/or yellow jacket between 1981 and 1985 ($n = 56$).

Changes were expressed as relative differences in antibody concentrations. Values below detection limits, i.e. 0.350 Pharmacia RAST units/ml (PRU/ml) IgE or 20 units/ml (U/ml) IgG were set to 0.20 PRU/ml and 10 U/ml respectively. Observations with both initial and follow-up values below detection limits were omitted from further calculations. Wilcoxon signed rank test was used to evaluate changes within groups and Mann-Whitney test was applied when comparing differences between groups.

Results

Spontaneous changes

Immunological data from two partly overlapping groups, one not stung by YJ and one not stung by HB, were analysed. Individuals stung by unidentified venomous insects were not included. A general decrease in venom-specific antibody levels was observed for both IgE and IgG to the individual venoms (Figs 1 and 2). The changes in IgE RAST classes were unaffected by whether or not systemic or just local reactions to the relevant insect had preceded the first antibody determination ($P > 0.05$) (Table 1).

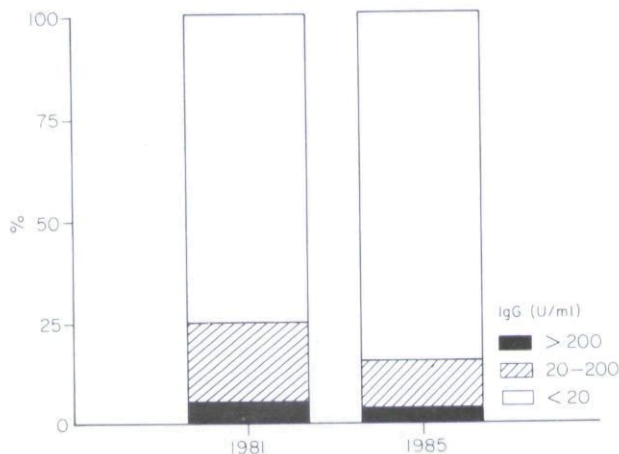


Fig. 2. Venom specific IgG in individuals not stung by honey bee and/or yellow jacket between 1981 and 1985 ($n = 56$).

Table 1. Distribution of individuals according to change in venom-specific IgE-RAST in the group not stung by unidentified insects, yellow jackets and/or honey bees during a 3-year period

Previous symptoms	Change in IgE-RAST classes				
	-3	-2	-1	0	+1
Local	1	4	13	21	0
Systemic	0	2	6	9	1

In individuals with antibody levels above detection limits in one or both tests, statistically significant changes ($P < 0.05$) were observed in IgG and IgE against YJ and HB venoms. A median decline of 41–75% during the 3-year study period was observed (Table 2). Only two subjects who were initially classified as negative had low amounts of specific IgE or IgG antibodies (0.5 PRU/ml and 23 U/ml) at re-testing, even though no stings were reported during the intermediate period.

Table 2. Relative change in venom-specific IgE and IgG in patients not stung by unidentified insects, yellow jackets and/or honey bees during a 3-year period. Individuals with initial as well as follow-up value below detection limits were excluded. Median changes and 95% confidence intervals are shown

Venom-specific antibody	Number	Change (%)
anti YJ-IgE	27	-60 (-70 to -40)
anti HB-IgE	22	-75 (-82 to -67)
anti YJ-IgG	12	-58 (-66 to -34)
anti HB-IgG	10	-41 (-65 to -7)

Weal diameter in SPT with YJ and HB venom (1,000 µg/ml) and with histamine (1 mg/ml) did not change significantly during the three years ($P > 0.05$). Table 3 illustrates test results of both venoms taken together.

Table 3. Results from initial and follow-up SPT with insect venom in individuals not stung by unknown or relevant insects during the period

Prick test 1981 (weal diameter)	Prick test 1985 (weal diameter)		
	< 3 mm	3–6 mm	> 6 mm
< 3 mm	24	5	1
3–6 mm	4	16	15
> 6 mm	1	4	11

Table 4. Individuals classified according to initial specific antibody measurements and to the first reaction to yellow jacket and/or honey bee during study period. Local reactions include large and normal size

Specific antibodies	First reaction after test	
	Local	Systemic
IgE: class 0-1 + IgG: <20 U/ml	6	0
IgE: class 2-3 + IgG: <20 U/ml	3	8
IgE: class 0-1 + IgG: ≥20 U/ml	2	0
IgE: class 2-3 + IgG: ≥20 U/ml	5	1

Table 5. Individuals classified according to initial skin prick test result and to the first reaction to yellow jacket during study period

Prick test (weal diameter)	First sting reaction after test	
	Local	Systemic
<3 mm	5	0
3-6 mm	4	3
>6 mm	4	5

Predictive value

Initial test data from all individuals who reported at least one sting by HB and/or YJ during the 3-year follow-up period were analysed separately. Out of 90 subjects who answered all questions, 21 had been stung by YJ, 4 by HB and 17 by unidentified insects. Eight systemic reactions resulted from first stings by YJ and one followed a HB-sting during this period. Symptoms varied from isolated prolonged nausea ($n=1$), urticaria ($n=2$), respiratory symptoms ($n=3$), headache ($n=3$) to dizziness and near fainting ($n=8$). No life-threatening reactions were seen, and apart from injection with antihistamine in one case and self-administered adrenaline, no medical treatment was instituted. Initial sting by unidentified insects caused five generalized reactions which were not included in the analysis of predictive values. Seven out of 11 patients with previous generalized reactions reacted systemically when stung by the same insect during the follow-up period.

Antibody levels were generally low in the group, but all systemic reactors had a positive IgE RAST (class 2-3) (Table 4). On the other hand only one of the nine systemic reactions occurred in a patient who had venom-specific IgG above the detection limit. In the group stung by YJ a negative SPT (diameter <3 mm) excluded systemic sting reactions, whereas larger SPTs were followed as often by local as systemic reactions to YJ stings (Table 5).

Discussion

Field stings are generally less valuable than in-hospital stings when investigating the allergy status of a patient. This is due to uncertainty in the identification of the stinging

insect and to the lack of sufficient medical information concerning the reaction. The present study was, however, conducted in a region privileged by having very few different *Hymenoptera* species. YJ and HB are dominant, but bumble bees and, less frequently, old world hornet (*Vespa crabro*) occur as well but these seldom sting humans. This facilitates the identification of insects at field stings and simplifies the allergy test procedure. Moreover, in this study we have been able to restrict the final analyses to include reactions to identified insects solely, thereby increasing the reliability of the conclusions.

The present study estimates the specific antibody levels to be reduced to less than one half during a 3-year period with no antigenic stimulation. These observations confirm a human study [7] which demonstrates the "half-life" for IgE in serum to be at least two years.

Serum IgE has been shown to correlate with IgE bound to basophils in patients not hyposensitized [8]. If, therefore, the absolute amounts of specific IgE and IgG are assumed to play a major pathogenetic role in the development of sting reactions, one would expect the severity of these reactions to weaken with increasing time elapsing from last to present sting. Such tendency has in fact been observed in one study [13]. Further work is required to evaluate the clinical implications.

In our hands the SPT reactions with high allergen concentration did not decrease significantly in the group. Schubert *et al.* (7) found a reduction in skin test in 44% of children and an increase in 21% during a more than 2-year period with or without stings. Diversities could be explained by the established more favourable prognosis of insect allergy in children, and by the SPT probably being less sensitive to small changes than antibody measurements.

Finally, some general toxic effects of the concentrated extracts applied in SPT cannot totally be ruled out although reactions to 1,000 $\mu\text{g/ml}$ correlated better to previous symptoms than did reactions to weaker extracts [3]. No separation was carried out between normal and large local reactions in this study, since the prognosis for both seems to be favourable [9, 10], even though large reactions are often accompanied by immunological findings which indicate sensitization [7, 9, 10]. Likewise, in the present study all four patients who had large local reactions to first stings during the follow-up period initially had specific IgG above the detection limit, and three had specific IgE of RAST class 2+.

The prognosis in non-hyposensitized subjects with respect to re-sting reactions, varies in different study groups. Following a systemic allergic sting reaction, the risk of generalized symptoms to a subsequent in-hospital sting with the same insect varies from 34% [11] to 44% [9] and 58% [1]. Field stings, where the identification of insects usually is more doubtful, resulted in repeated systemic reactions in 17% [7] to 50% [12] or 60% [13]. This is in accordance with the reaction rate of 64% in the present study in which reactions to unidentified insects have been left out.

In our selected group of patients, almost all (8/9) systemic reactions occurred in patients with low levels of specific IgG together with positive IgE RAST. This reaction pattern in immunoglobulins seems to indicate an increased risk at future stings, but it should be noticed that several patients presented the same pattern without reacting systemically to future exposure. Other groups have found measurement of specific immunoglobulins less valuable in foreseeing future generalized reactions to stings [7, 9, 11, 14]. In a study by Schuberth *et al.* [7] IgE-RAST or venom specific IgG above 4 $\mu\text{g/ml}$ could not predict future sting reactions in children, but in this group the predictive

value of a low IgG together with high IgE was not analysed. Furthermore, many of the patients were probably not stung by relevant insects, and identification was done indirectly by evaluation of increase in IgE-RAST. Parker *et al.* [9] stated that neither skin test, venom-specific IgE nor venom-specific IgG could predict the clinical immune status of the patients. However, six out of seven patients, who had systemic reactions to challenge, had low levels of specific IgG and five of the seven had elevated specific IgE. Although the number of non-reacting patients with the same antibody pattern was not specified, these findings are in agreement with those presented here. In a large study of Blaauw *et al.* [11], no correlation between IgG-/IgE-ratio and the outcome of sting challenge was observed. Contrary to the less sensitive patients in this study, all patients included were candidates for hyposensitization. In spite of the pessimistic attitude about the prognostic value of immunoglobulin levels, several groups have advocated the use of specific IgG measurement when deciding whether or not immunotherapy should be terminated [15, 16].

Abnormalities such as spontaneous hypokallikrein have been demonstrated in allergic bee-keepers [17] and in order to improve the predictive value of diagnostic tests in the future, they probably should include assays which focus on the toxic/biochemical aspects of the venom-victim interactions as well as the immunological parameters investigated in the present study.

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