

Insect Allergy

A Comparative Study Including Case Histories and Immunological Parameters

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One hundred and seventeen persons all stung by yellow jacket (YJ) and/or bee were examined by means of skin prick test with venom of these insects, skin prick test with 10 inhalant allergens and analyses of total IgE, specific IgE and IgG against honey bee and YJ venom. Eighty-seven persons had had a systemic reaction to YJ or bee sting, the rest had reacted normally or with a large local reaction. Positive correlations ($P < 0.05$) were found between results of skin prick tests and specific IgE against venoms and, for YJ, between the severity of symptoms after sting and the size of skin prick test with the venom. That some of the more severe symptoms could have been caused by non-immunological mechanisms could explain why a significant correlation was present only between the results of the prick test and specific IgE and not between these tests and the clinical symptoms. Specific IgE values against YJ and honey bee venom showed covariation, although no correlation could be demonstrated between the clinical symptoms after stings from these insects, or between skin prick test results using the two different extracts. The severity of the sting reactions was not correlated to age, atopic disposition, amount of total IgE, number of stings during life, or positive skin prick test to inhalant allergens. It is concluded that in insect allergy, specific IgE analysis and skin prick tests are supplementary.

Key words: Apis venom; hypersensitivity; RAST; skin tests; wasp venom.

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CLINICAL ASPECTS

Clinical experience with 117 patients who have had large local, systemic or normal reactions following insect stings are reported. No correlation could be demonstrated between the severity of these reactions and age, atopic disease, amount of IgE in serum, number of stings during life or positive skin prick tests to inhalant allergens. Although a tendency was seen towards more severe reactions following subsequent stings, 20% of the patients now presenting only large local reactions to yellow jacket had reacted systemically to previous sting from the same insect. A diversity between the results of IgE-RAST and skin prick test were seen in certain cases with all types of reactions. It therefore seems reasonable to use both analyses at the same time. Venom extracts were used in concentrations up to 1 mg/ml in skin prick test. This implied a better correlation between skin prick test result and both clinical reaction and amount of specific IgE.

Insect allergy has a potentially fatal course. Subsequently, great efforts have been made with respect to treatment and diagnosis. Immunotherapy has proved to be effective – but is not without costs. Therefore, both sensitivity and specificity of the diagnostic methods are of particular importance. In many other allergic conditions the possibility of making provoca-

tion tests exists. But medical and ethical aspects rule out this method in persons likely to have insect allergy – unless only the degree of an effective treatment is to be evaluated.

The aim of the present study is, based on clinical information from the patients, to evaluate the results of routine diagnostic tests.

MATERIAL AND METHODS

Patients

One hundred and seventeen persons (63 women and 54 men) known to be stung by bee or yellow jacket (YJ) were included. Mean age was 40 years (range 14–79). None had been treated with insect venom or extracts. Eighty-seven of these patients were referred to the clinic in Hillerød after reactions to insect stings (mostly systemic) during an 8-month period. Seventeen persons had visited the casualty ward of the same hospital following stings from YJ or bee and were willing to take part in the investigation. In most cases the reactions were only local. The remaining 13 patients were referred for examinations because of atopic diseases (asthma and hay fever); they all had a history of insect sting, most of them with normal reactions.

Case history

All participants were questioned about their reactions to stings by bee, YJ or unidentified insects. The insects were, if possible, identified on a colour plate. In addition questions were asked about: (abnormal) reactions to mosquito bites, number of previous bee and YJ stings, time elapsed from sting to investigation, and atopic diseases among patients, siblings, children or the examined person.

The reactions were classified as normal (mean diameter ≤ 10 cm), large local swelling (diameter > 10 cm) or systemic (i.e. one or more of the following symptoms: urticaria or angio-neurotic oedema apart from the sting, shortness of breath, hoarseness, nausea, diarrhoea, abdominal pain, vomiting, fever with pain in muscles or joints, "near fainting" or fainting).

Skin prick test (SPT)

Prick test was made, using a hypodermic needle in accordance with earlier description (17). The coefficient of variation for the same investigator was 11–46% (4). The skin reactions were recorded as mean of the maximum and per-

pendicular diameter. Histamine-dihydrochloride 1 mg/ml and isotonic saline in glycerole (50% v/v) were used as reference and negative control. A series of 10 common allergens (pollen, animal dander, dust mite and mould) in concentrations: 1:20 or 1:40 (weight extracted: total volume) was included together with honey bee (HB) (*Apis mellifera*) and YJ venoms (*Vespula vulgaris* and other *Vespula* species) in seven dilutions from 1 to 1000 μ g/ml. A minority was tested with HB venom up to 100 μ g/ml, and subsequently excluded from analyses of this parameter. All extracts were supplied in glycerole, 50% v/v solution (Soluprick® by Allergologisk Laboratorium A/S, Copenhagen, Denmark).

Antibodies

Serum levels of specific IgE and IgG against YJ or HB venom were measured by radioallergosorbent test (RAST) (5, 18) and the total IgE by paper radioimmunosorbent test (PRIST) (12). All analyses were done by Pharmacia A/S, Hillerød, Denmark. The same raw material was used in the preparation of allergen extracts for SPT and RAST.

Design

SPT and determination of the relevant antibodies, as mentioned above, were done in all cases with both YJ and HB allergens. Where reliable information about stings from both YJ and bee was available, the persons were included in both analysis groups. Because of difficulties in the retrospective identification of the stinging insects an additional analysis was done based on information about each individual's maximum symptoms to insect stings, irrespective of whether the insect had been identified or not.

The type of reaction to insect sting was compared with the amount of specific IgE and IgG against the venom of the same insect and with the total IgE level. A comparison was also made between the clinical reactions and the SPT result with the corresponding allergen extract. Correlations between specific IgE in serum and

SPT were analysed. Finally, cross-reactivity to YJ and HB venom was searched for – both clinically and immunologically.

Statistics

Relations in two-way tables were evaluated by means of Pearson's Chi-Square test, and analyses of variance were used in the description of relations between continuous variables.

RESULTS

Insects and symptoms

Bee and YJ stings were reported by 47 and 82 individuals respectively, and 63% of the examined had had a systemic reaction after an insect sting (Table 1).

In the majority a longer period had elapsed from the last bee sting to the investigation than from the stings of YJ or unknown insects (Table 2).

SPT with YJ venom showed a significantly larger reaction in subjects with more severe reactions after the last YJ sting (Fig. 1). A parallel but insignificant tendency ($P = 0.08$) was observed for HB venom SPT and bee sting. Even though specific IgE against insect venom seemed to be higher following severe reactions (Fig. 2) no statistical significance was found. In the same way no significant correlations could be demonstrated between symptoms and specific IgG values ($P > 0.09$). Fig. 3 illustrates that many patients with systemic reactions had minimal SPT as well as small amounts of specific IgE. No connection was seen between the severity of symptoms and the age of the person, total number of stings during life, reactions to mosquito bites, atopic disposition, total IgE or SPT larger than the histamine reference to one or more inhalant allergens. Exclusion from the analyses of the patients primarily seen because of atopic diseases did not change these results.

Table 1

Patients distributed according to their reactions to last sting from known and unknown insects. Maximum reaction is the most severe reaction in each individual, irrespective of the causing insect

	Normal	Large local	Systemic	Uncertain/ not stung	Total No. persons
Yellow jacket	21	21	40	35	117
Bee	28	12	7	70	117
Uncertain (yellow jacket/bee)	15	15	32	55	117
Maximal reactions (all insects)	15	29	73	0	117

Table 2

Patients distributed according to time elapsed from last sting

	2 weeks up to 6 months	6 months up to 3 years	3 years or more	Uncertain/ not stung	Total No. persons
Yellow jacket	22	30	30	35	117
Bee	5	10	31	71	117
Uncertain (yellow jacket/bee)	26	22	15	54	117
Maximum reactions (all insects)	49	45	22	1	117

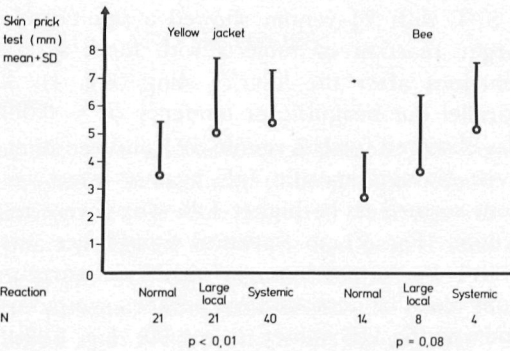


Fig. 1. Maximum skin prick test size in relation to reaction after last sting. (Concentration of extract: 1 mg/ml).

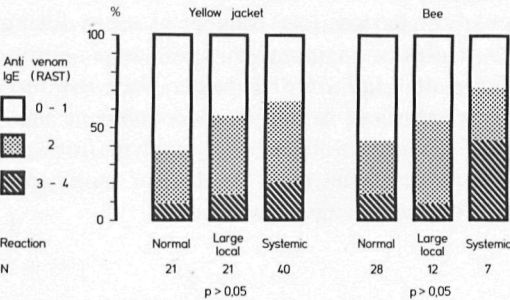


Fig. 2. Occurrence of specific IgE (RAST) in relation to reaction after last sting.

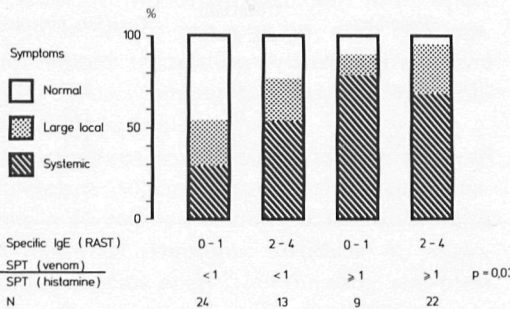


Fig. 3. Clinical symptoms after yellow jacket sting related to both size of skin prick test and specific IgE against the venom. (Persons with abnormal reactions to unidentified insects are excluded).

Specific IgE

The maximum value of specific IgE against both venoms was lower the longer the interval from the most severe sting reaction to the in-

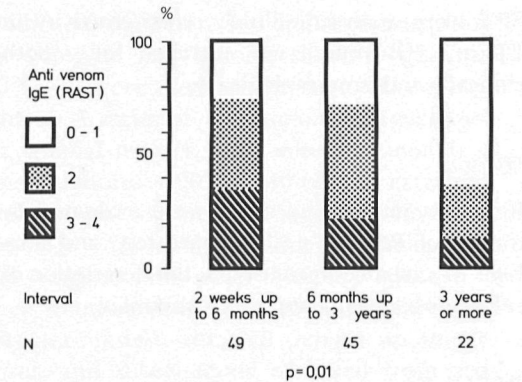


Fig. 4. Maximum value of specific IgE against insect venom related to time elapsed from maximum sting reaction (irrespective of the causing insect).

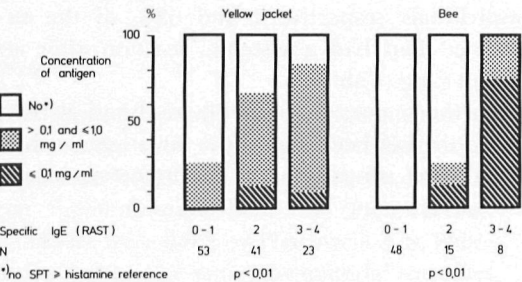


Fig. 5. Relationship between the occurrence of specific IgE (RAST) and skin prick test results against the same venom. (Expressed as the minimal concentration of antigen giving prick size $\geq$ histamine reference).

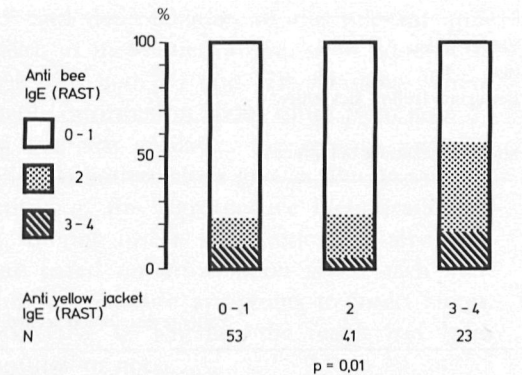


Fig. 6. Relationship between the occurrence of specific IgE against honey bee and yellow jacket.

vestigation (Fig. 4). This significant difference ($P = 0.01$) was not caused by a shorter period from sting to time of investigation with more

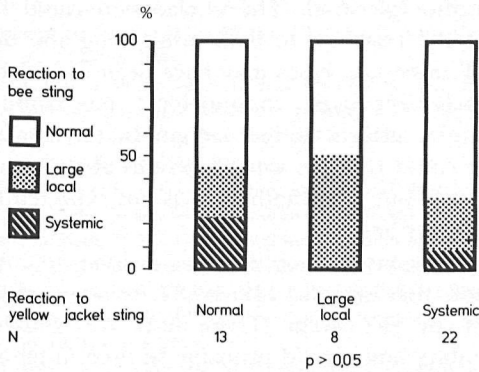


Fig. 7. Relationship between the reaction to last bee and yellow jacket stings.

severe maximum reactions. High levels of specific IgG and specific IgE were associated ($P < 0.05$) with both YJ and HB allergens.

Skin prick tests

A positive correlation was found between size of SPT and specific IgE against the same allergen (Fig. 5). This correlation weakened if the highest concentrations of the allergen used in the SPT (300 µg/ml and 1 mg/ml) were left out in the analysis.

Cross reactions/multiple allergy

In contrast to the specific IgE, where some covariation was seen (Fig. 6); no significant correlation was found between the clinical reactions to bee or YJ stings (Fig. 7) nor between the SPT results using the two insect venoms.

DISCUSSION

In general, the agreement between clinical data and SPT or specific IgE levels was not impressive. Investigations including provocations have been similarly disappointing with respect to the correlation between the clinical history and the test results (10, 16). A reason for this could be a discrepancy between the allergens in the extracts and in the venom of the actual stinging insects. In Denmark there are 250

kinds of bees and 10 types of vespids. In the latter group the *Vespula* species dominates totally. The common yellow jacket (*Vespula vulgaris*) occurs frequently in the region whereas the hornet (*Vespa carbo*) is infrequent (O. Lomholdt, Zoological Museum, University of Copenhagen, personal communication). At least among the vespids the venoms have many antigens in common (13, 19, 21).

The poor accordance between tests and history is more likely to be explained by the pathogenetic mechanisms than by an imperfection of the tests: in addition to allergic also vascular or neurotoxic mechanisms may play a variable role (7). Immunologic mechanisms which are not solely mediated by IgE could also partly explain the discrepancy between symptoms and specific IgE values (14). The mechanisms behind large local reactions without generalization have been discussed. Some investigators have found immunologic conditions parallel to the systemic reactions (1, 6, 9), while others have seen indications of cell-mediated (type IV) immunologic mechanism (3). In the present study this was not tested for. Nevertheless, individuals with eczema, which could be caused by T cell-mediated type IV allergy, did not show a higher frequency of large local reactions than the rest of the group. There were indications that large local reactions had an intermediate status – judged by the size of SPT and specific IgE (Figs. 1 and 2). This could reflect a higher proportion of cases of non-immunologic origin and that lower antibody levels generally would mean milder reactions to stings. The last explanation was sup-

Table 3

Patients distributed according to their reaction to yellow jacket sting

Reaction to last sting	Maximum reaction to earlier stings			Total No. persons
	Normal	Large local	Systemic	
Normal	20	1	0	21
Large local	5	7	3	15
Systemic	14	10	10	34
Total	39	18	13	70

ported by the fact that more than 30% with systemic reactions to YJ stings had had large local reactions to previous stings. On the other hand, the finding that nearly half of the group with large local reactions reported identical previous reactions could reflect a separate mechanism (Table 3).

Even in cases where immunologic reactions (type I) play an important role, the antibody production could very well have been modified both qualitatively and quantitatively by the last sting. Consequently, the actual status must be seen as a result rather than a cause of the clinical events.

The correlation between the amount of specific IgE against HB and YJ described in this study did not seem to be caused by a similar concordance when looking at symptoms following HB and YJ stings. Neither could it be explained by unspecific reactions accompanying high levels of total IgE. Nevertheless, a parallel occurrence of antibodies to both venoms seems to be a general phenomenon, as demonstrated by both RAST, RAST inhibition and histamine release from basophil leucocytes (8, 20).

In the SPT, HB and YJ venom were used in the same concentrations (dry weight). A tendency was seen towards less allergenicity per weight for the HB venom, and it could possibly be an advantage to include even higher concentrations of HB venom in the SPT. On the other hand, the IgE RAST seemed to give slightly higher values following bee than YJ stings – when the same clinical types of reactions were compared (Fig. 2).

Several investigators have found the intracutaneous test with venom extract useful when investigating insect allergy (22). SPT has been used by others (2). 100 µg/ml is normally the highest concentration used for both immunotherapy and cutaneous test with insect venom. We have, without adverse reactions, been able to increase the concentrations used in SPT and found a better correlation to both symptoms and the amount of specific IgE. This would not have been the case if unspecific (toxic) effect had dominated – as could have been feared.

The correlation between SPT and symptoms seems to be better than between symptoms and

specific IgE level. The explanation could be that the reactions to both insect sting and the SPT in certain cases may have been caused by non-IgE-mediated immunologic mechanisms or toxic effects of the venom. In these cases one could fear the same reactions after future stings – but immunotherapy is not expected to be of any help.

As a consequence it is not possible to conclude that specific IgE RAST is better than SPT or vice versa. These tests are complementary and should probably be used in parallel. When it has been reported that systemic reactions to YJ stings came without warning in even higher numbers than the approximate 40% found in this study (11), it is not to be expected that even the most effective immunotherapy could prevent all deaths from insect stings. That the specific IgE value seems to be lower 3 years or more after the sting adds additional problems to the diagnosis of allergy. It is also possible that a long period without stings would weaken a subsequent allergic reaction. Reports of lack of reproducibility of severe sting reactions support this point (10, 16). Even though deaths following insect stings are fairly seldom (15) there still is a group of patients with severe reactions and indications of allergy, where immunotherapy could be helpful.

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