

Prognosis of patients reacting with urticaria to insect sting

Results of an in-hospital sting challenge

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Insect sting challenge in 14 patients with urticarial reaction to last insect sting resulted in two systemic reactions (95% confidence limits 0-6 patients), a reaction rate of 14%. Skin prick test, basophil histamine release, RAST, and allergen-specific IgG, alone or in conjunction, could not indicate the patients to react systemically after sting challenge. Further, the systemic reactions were uninfluenced by type of insect and time elapsed since last insect sting. It is concluded that the reaction to future insect stings cannot be predicted by the immunological tests presently available.

Key words: challenge; insect venom allergy; prognosis; systemic reaction; urticaria.

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CLINICAL ASPECTS

In insect allergy, the indication for immunotherapy is based on the possible reaction to future insect stings, evaluated from previous insect sting reactions and an immunological investigation. The present study concerns 15 patients with urticaria as the only systemic reaction after their latest insect sting. None had received immunotherapy with wholebody insect or venom extract. Fourteen insect sting challenges resulted in two (14%) systemic reactions involving the skin (urticaria and angioedema); more severe systemic reactions were not seen. It is emphasized that immunotherapy is seldom indicated in patients with urticaria after previous insect stings and that an insect sting challenge should be considered before offering immunotherapy.

Systemic reactions after insect stings have been reported in 0.4-0.8% of the population (3, 23). Previous investigations show that 33-50% of those with systemic reactions experience an identical or even worse reaction after a subsequent sting (2, 11, 17, 20, 24). In children with urticaria as the only systemic reaction, approximately 10% react systemically if stung again (21, 22). Skin tests, RAST, IgG-RAST, or IgG/IgE ratio have demonstrated no significant differences in immunological reactivity between patients with single and patients with repeated systemic reactions after insect stings (2, 17, 19, 21).

Immunotherapy with extracts of purified insect venom has become a well-established

treatment despite its being expensive, time-consuming (9, 12, 20) and not without adverse reactions (7). The following study was designed to elucidate the prognosis of patients with urticaria after previous insect stings, and to find immunological tests capable of predicting the results of an insect sting challenge.

MATERIAL AND METHODS

Patients

Fifteen consecutive patients of either sex (median age 45 years, range 18-61 years) with

generalized urticaria as the only systemic reaction after the latest insect sting (all reactions verified by a physician) were seen during two seasons in the Allergy Clinic. All patients had been last stung between 1 and 3 years ago, and by one insect only. Patient No. 14 had experienced generalized urticaria twice, the remaining patients once only. Twelve patients claimed to have been stung by wasp and three by honey bee, which was in good accordance with the results of the immunological investigations carried out within the 2 weeks prior to the sting challenge. None had received immunotherapy with wholebody insect or venom extract, and there were no beekeepers among the patients. One patient (No. 7) was excluded because of cardiac disease. The remaining 14 patients all gave their written consent after being fully informed about the procedure.

Skin prick test

All patients underwent skin prick testing (SPT) in duplicate with extracts of wasp and bee venom, respectively. The concentrations given were 10, 100 and 300 µg/ml dissolved in 50 % glycerol (Soluprick SQ®, ALK, Copenhagen, Denmark), and the DHS needle 1.0 mm was used (28). The results were read using the largest weal reaction and expressed as the mean of the largest diameter and the perpendicular diameter (14).

Radioallergosorbent test

The amount of allergen-specific IgE and allergen-specific IgG was measured by RAST (6, 27). All RAST analyses were performed by Pharmacia, Hillerød, Denmark.

Basophil histamine release test (BHR)

The method used was a fluorometric determination of histamine based on histamine release from blood basophils (25). EDTA-blood was preserved by adding cell culture medium (RPMI-1640, Gipro Bio-Cult, Paisley, Scotland) and storing at room temperature until analysis was performed within 24 h (4). The

histamine release was measured after incubation with allergen and anti-IgE with deduction of the spontaneous histamine release. The results were expressed on a semiquantitative range scale (Table 1) (5). If no histamine release occurred after incubation with anti-IgE, the patient was designated a "non-responder", and BHR was inconclusive. All BHR analyses were performed by Diagnoselaboratoriet, Copenhagen, Denmark.

Insect sting challenge

Insect sting challenges were carried out at the Allergy Clinic, County Hospital, Roskilde, with measures for treating anaphylactic reactions, including cardiac monitoring. The patients were challenged with the species they claimed to have been stung by (wasp [*Vespa vulgaris*] or honey bee [*Apis mellifera*]), since in all instances this had been confirmed by the immunological tests. All insects were taken from natural sources no more than 24 h prior to challenge. The insect, positioned on the forearm, stung for 30 s after which the insect and the sting with attached venom sac were removed with tweezers.

RESULTS

Two (14 %) systemic reactions occurred (95 % confidence limits: 0–6) among 14 insect sting challenges, both within minutes of the challenge. No delayed systemic reactions were seen. Patient No. 3 experienced generalized pruritus and urticaria, and patient No. 8 experienced gener-

Table 1
Basophil histamine release test

BHR-class	Histamine released %	Venom concentration /ml whole blood
0 (negative)	0–8	all
1 (doubtful)	9–19	all
2 (positive)	≥ 20	> 200 ng/ml
3 (strongly positive)	≥ 20	≤ 200 ng/ml

Definition of classes, ratio between histamine released after allergen incubation and histamine released after cell lysis by perchloric acid (4).

alized urticaria and angioedema of the face and throat. Both responded to treatment with epinephrine, antihistamine and glucocorticoid. There were no symptoms from the central nervous and cardiopulmonary systems, or the gastrointestinal tract. Patient Nos. 8 and 14 developed large delayed local reactions.

Immediately prior to the sting challenge all patients had shown signs of sensitization to the insect venom used in at least one of the immunological tests (Table 2). Both patients with systemic reactions after the sting challenge (Nos. 3 and 8) had positive SPT, RAST and BHR. However, no tests alone or in conjunction could indicate whether the patients would develop a systemic reaction after the sting challenge. The most severe clinical reaction was seen in the patient with the highest allergen specific IgG (No. 8). Allergen-specific IgG measured 1 month after the sting challenge increased in those patients with detectable amounts prior to challenge. Only one patient without detectable allergen-specific IgG prior to challenge developed this 1 month later (No. 12).

DISCUSSION

Schubert (21, 22) found reaction rates of 10.8% and 9.2%, respectively, in two series of un-

treated children with urticaria after previous insect stings. Nüsslein (16) reported a reaction rate of null after sting challenges, but his eight untreated adults had been carefully selected with regard to absence of reactivity in BHR and only weak systemic reactions previously. However, untreated patients with more severe reactions after their latest insect sting have shown much higher reaction rates on challenge (2, 11, 17, 20, 24).

In our investigation, we found a systemic reaction rate of 14% after challenge in adults reacting only with urticaria after their latest sting. In agreement with earlier findings there was no consistent correlation between the results of the immunological tests done immediately prior to the sting challenges and the systemic reactions seen afterwards (2, 11, 20, 24). Some of the non-reactors had only weak signs of sensitization towards the insect in question, which indicates a possible non-IgE-mediated reaction after their previous systemic reaction (15). The time elapsed since the last insect sting was less than 3 years in all patients and was not correlated to the reactions seen after the sting challenges.

It is often claimed that high levels of allergen-specific IgG protect against future systemic

Table 2

Results immediately prior to sting challenge in 14 patients with urticarial reaction to their latest insect sting. The same species as the patients were stung by was used at challenge

Patient No.	Age (years)	Sex	Time (months)	Insect	SPT (mm)	IgE (PRU/ml)	IgG (U/ml)	IgG/IgE	BHR
1	54	M	12	wasp	3.5	0.59	< 20*	0	**
2	54	F	13	wasp	4.0	< 0.35*	< 20	0	2
3	52	M	12	wasp	4.0	2.20	< 20	0	2
4	58	F	15	bee	3.0	2.50	32	13.5	3
5	52	M	25	bee	0.0	< 0.35	26	-	2
6	21	F	12	wasp	2.5	< 0.35	< 20	0	1
8	19	M	14	bee	3.5	6.90	87	12.6	3
9	61	M	13	wasp	0.0	1.10	< 20	0	0
10	19	M	14	wasp	4.0	0.50	< 20	0	2
11	18	M	35	wasp	2.5	< 0.35	< 20	0	2
12	51	F	14	wasp	2.5	< 0.35	< 20	0	**
13	39	M	12	wasp	5.0	0.39	< 20	0	**
14	25	M	13	wasp	2.5	6.10	< 20	0	1
15	34	M	24	wasp	3.5	< 0.35	< 20	0	**

M: Male; F: Female; Time: since latest insect sting; SPT: skin prick test, 300 µg/ml; BHR: basophil histamine release test;

*Level of detection; ** Inconclusive, "non-response" after incubation with anti-IgE.

reactions (8, 9, 10, 14, 26), though not all investigations agree (18). However, these statements are generally based on the fact that patients have received immunotherapy (8, 9, 10, 26). Our results do not support a direct correlation between allergen-specific IgG and reaction in untreated patients when re-stung. The biggest problem today is the selection of patients to be treated. Data indicating previous insect sensitization were only available for 59 of the 400 fatalities studied (1). A recent Danish investigation is in agreement (13). It seems, therefore, that deaths from insect stings are not necessarily due to repeated systemic reactions. The most important indication for immunotherapy with insect venom is the prevention of deaths. Our investigation and those of others (16, 21, 22) have shown that milder systemic reactions such as generalized urticaria, seldom occur with repeated stings, and more severe systemic reactions are even more infrequent. Consequently, the indication for immunotherapy is doubtful in these patients unless they are heavily exposed to insect stings.

In conclusion, we found a systemic reaction rate of 14% after insect sting challenge in patients with urticaria as the only prior systemic reaction. This is lower than the rate for most other previous reactions. We found no consistent correlation between immunological test results prior to challenge and the subsequent systemic reactions. Before proposing immunotherapy, an insect sting challenge should be considered.

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