

On the significance of severe local reactions to Hymenoptera stings

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Summary

Of 317 patients with hypersensitivity to Hymenoptera stings forty had severe local reactions (SLR) only, fifty-nine reported severe local reactions before their first and seven after their last systemic reaction (SR). The probability to develop a life threatening systemic reaction when restung after a severe local reaction was calculated to be about 5%. In 80% of the patients with severe local reactions only, hypersensitivity to either bee or yellow jacket venom could be demonstrated by skin tests and/or RAST. A fair correlation of skin test and RAST results was observed. In patients with severe local reactions hyposensitization therapy with venoms is not generally indicated. In exceptional patients whose allergy is proven by skin tests or RAST and who are at a high risk of being restung, hyposensitization may be considered.

Introduction

It is well known that patients with systemic allergic reactions following Hymenoptera stings sometimes report having suffered from severe local reactions to previous stings (Mueller, Schmid & Rubinsztain, 1975). Several authors have observed that venom-specific IgE antibodies may be detected in the serum of some patients with large local reactions (Hoffman, 1977; Müller, Spiess & Roth, 1977; Reisman, Wypich & Arbesman, 1975). There is thus both clinical and serological evidence suggesting that severe local reactions are of an allergic rather than of a toxic or infectious origin and this might have therapeutic implications.

The aim of this study was to investigate a larger group of patients with severe local reactions with regard to the indication for specific hyposensitization therapy with venoms in these patients (Abrecht & Eichler, 1980; Müller *et al.*, 1979).

Materials and methods

Patients

Case histories of 317 patients who attended our medical division between 1967 and

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1978 because of adverse reactions to Hymenoptera stings were analysed with regard to the occurrence of severe local reactions (SLR) exceeding 10 cm in diameter and 24 hr in duration. Of 277 patients with systemic reactions (SR) fifty-nine reported SLR previous to their first SR and seven after their last SR. Forty patients attended the division for SLR only. In all patients the following data were recorded: (1) age at first SLR or SR, (2) number and extension of SLR, (3) reaction time between sting and swelling, (4) culprit insect, (5) grade of first SR following a SLR according to Mueller *et al.* (1975) (see Table 1), and (6) history of atopy.

The forty patients with SLR without any SR were all reexamined in 1978. Their clinical data are given in Table 2.

Antigens

Venom preparations for RAST and skin tests and diluents for the preparation of skin test solutions were kindly supplied by Pharmacia Diagnostics AB, Uppsala, Sweden. Bee venom was obtained by electrostimulation, yellow jacket (*Vespula maculifrons*) venom by preparation of venom sac extracts. Bee venom phospholipase A was purchased from Mack Nachf., Illertissen, Bayern, FRG.

Skin tests

Lyophilized bee venom (BV) and yellow jacket venom sac extracts (YJ) were dissolved in the diluent (0.9% saline, 0.4% phenol, 0.03% human serum albumin) and tenfold serial dilutions from 10^{-1} to 10^{-6} mg/ml in the same diluent prepared. Venom

Table 1. Grade of systemic reactions (SR) (according to Mueller *et al.*, 1975) following severe local reactions (SLR) in fifty-nine patients

Grade of reaction	Signs and symptoms	No. of all patients	No. of patients with previous SLR (%)
Grade I	Generalized urticaria, itching, malaise, anxiety	65	14 (22)
Grade II	Any of the above plus two of following: angioneurotic oedema, dizziness, constriction of chest, abdominal pain, nausea, vomiting, diarrhoea	70	15 (21)
Grade III	Any of the above plus two of following: dyspnea, dysphagia, hoarseness or thickened speech, confusion, feeling of impending disaster	79	21 (27)
Grade IV	Any of the above plus two of following: cyanosis, fall in blood pressure, collapse, incontinence, unconsciousness	63	9 (14)
Total		277	59 (21)

Table 2. Clinical features in forty patients with severe local reactions (SLR) to Hymenoptera stings

Age at first SLR	range	1-60
	mean	15.3
Sex	male	19
	female	21
History of atopy		7
Extension of swelling	large*	21
	very large†	19
Reaction time	30 min or less	25
	more than 30 min	15
Time interval between last sting and examination	1 year or less	18
	1-3 years	13
	more than 3 years	9
Culprit insect	bee only	21
	bee and/or yellow jacket	14
	yellow jacket only	5

* Large: exceeding 10 cm in diameter and 24 hr in duration but less than very large.

† Very large: exceeding one large joint (wrist, elbow, shoulder, ankle, knee, hip) or swelling of the face or head on both sides of the median line.

solutions were discarded after 1 week. Injections were started by the intracutaneous application of 0.01 ml of the concentration 10^{-6} mg/ml of either venom. The dose was then increased at intervals of 30 min until a weal of at least 5 mm in diameter with erythema resulted. A test was considered to be positive if such a reaction was observed at a concentration of 10^{-4} mg/ml or less (Patrizzi *et al.*, 1979).

Serological investigations

Total IgE-antibodies were estimated by the Phadebas IgE PRIST (Pharmacia Diagnostics AB, Uppsala, Sweden), specific IgE antibodies against BV and YJ by the Phadebas RAST. Experimental YJ discs were kindly supplied by Dr L. Yman, Pharmacia Diagnostics AB, Uppsala, Sweden. IgG antibodies to BV phospholipase A were measured as described previously (Müller, Johansson & Streit, 1978) by a technique based on the adsorption of IgG to a sepharose protein A complex followed by the addition of ^{125}I -labelled antigen.

Statistical methods

See Abrecht & Eichler (1980).

Results

Analysis of case histories

Of the 277 patients with systemic reactions fifty-nine (21%) had experienced one or several SLRs before their first SR. The severity of the first SR in these fifty-nine patients is given in Table 1. The difference between the incidence of the four grades of

SR following a SLR was not significant. One hundred and forty-two (51%) of all the patients with SR had reactions of grade III or IV at their first sting. In thirty (50%) of the fifty-nine patients with SLR preceding the first SR this was of grade III or IV.

In the total of 317 patients 224 single episodes of SLR were reported: 138 in fifty-nine patients with SLR previous to SR, seven in seven patients with SLR after SR and seventy-nine in forty patients with SLR only. Of these 224 episodes of SLR 177 were followed by another sting and in fifty-nine cases (33%) a systemic reaction developed. Of these SR 15.3% were of grade IV. The probability of experiencing a life-threatening reaction when restung after a SLR can thus be estimated to be approximately 5%. Of the children up to 14 years 30% presented a history of SLR before the first SR compared to 16% of the adults. The difference was statistically significant ($P < 0.02$). No correlation between the incidence of SLR previous to SR and a personal or familial history of atopy was found and the incidence of SLR previous to SR was the same in bee- and yellow jacket-sensitive patients.

Examination of forty patients with severe local reactions

Seven (18%) of the forty patients had a history of atopy. In four of them total serum IgE levels of 100 i.u./ml or more were found and in the remaining three, levels between 20 and 100 i.u./ml. Of the thirty-three non-atopic patients eight (24%) had serum IgE levels below 20 i.u./ml, eleven (33%) between 21 and 100 i.u./ml and fourteen (43%) 100 i.u./ml or more.

The results of the estimation of specific IgE antibodies against BV and YJ in the serum of patients with SLR are given in Table 3. About two thirds of the patients clinically sensitive to only one insect had specific IgE antibodies to the venom of the culprit insect and about one third to that of the other insect. In the patients of the intermediate group who reported to be sensitive to stings of both bees and yellow jackets or who could not identify the stinging insect, BV-specific IgE was detected even more frequently than in the BV-sensitive patients and YJ-specific IgE in about the

Table 3. Specific IgE antibodies to bee venom (BV) and yellow jacket venom (YJ) in forty patients with severe local reactions to Hymenoptera stings

Culprit insect	Number of patients	RAST score										Number of patients positive with at least one venom (%)	
		With bee venom						With yellowjacket venom					
		0	1	2	3	4	Per-centage positive	0	1	2	3		Per-centage positive
Bee only	21	7	2	7	3	2	67	13	4	3	1	38	15 (71)
Bee and/or yellow jacket	14	3	4	6	0	1	79	9	2	1	2	36	11 (79)
Yellow jacket only	5	3	0	2	0	0	40	2	0	3	0	60	3 (60)
Total	40	13	6	15	3	3	68	24	6	7	3	40	29 (73)

The Phadebas RAST was performed following the method of Pharmacia Diagnostics, Uppsala, Sweden. The classification of the results in score 0 to 4 for each sample was attained by comparison of the count-rate with reference sera.

Table 4. Specific IgG antibodies to bee venom phospholipase A in forty patients with severe local reactions to Hymenoptera stings compared with values of patients with systemic reactions, beekeepers and non allergic controls

Population	Number of patients	Serum IgG against BV-PLA in percentage of beekeeper reference					Mean value (geometrical)
		0-50	51-100	101-500	501-1000	> 1000	
Patients with SLR to							
BV only	21	14	0	7	0	0	44.67
BV and/or YJ	14	7	6	1	0	0	33.59
YJ	5	5	0	0	0	0	12.04
All patients with SLR	40	26	6	8	0	0	33.52
Patients with SR to BV	40	21	5	11	3	0	145.1
Beekeepers	40	8	0	16	13	3	459.9
Non allergic controls	25	23	2	0	0	0	14.9

The adsorption of IgG to a sepharose protein A complex was measured by addition of ^{125}I -labelled phospholipase A and expressed in percent (%) of a reference serum of a bee keeper.

same frequency than in bee-sensitive patients. Twenty-nine (73%) of all the patients had specific IgE antibodies to at least one of the two venoms.

Specific IgG-antibodies against BV-phospholipase A (Table 4) were found in the serum of some of the patients who incriminated the bee or bee and/or yellow jacket as the culprit insect, but in none of those who reported reactions to yellow jacket stings only. Mean IgG levels were lower than in patients with SR but higher than in non-allergic controls.

Results of skin tests are given in Table 5. Positive results were again found in about two thirds of the patients with the venom of the culprit insect and one third with the

Table 5. Skin tests with bee venom and yellow jacket venom in forty patients with severe local reactions to Hymenoptera stings

Culprit insect	Number of patients	Skin test positive at 10 ⁻⁴ mg/ml or less				Positive with at least one venom	
		With bee venom		With yellow jacket venom			
		No.	(%)	No.	(%)	No.	(%)
Bee only	21	12	(57)	7	(33)	13	(62)
Bee and/or yellow jacket	14	10	(71)	4	(29)	10	(71)
Yellow jacket only	5	2	(40)	3	(60)	4	(80)
Total	40	24	(60)	14	(35)	27	(68)

other venom. Twenty-seven patients or 68% had positive skin tests to at least one venom. Positive results with either RAST or skin tests were found in thirty-two or 80% of the patients.

Corresponding positive or negative results were observed in fifty-seven of the eighty paired tests performed (71%). In thirteen cases RAST results were positive and skin tests negative and in ten skin tests positive and RAST negative. Discordant results were found in 23% of the tests with BV and in 35% of those with YJ.

No correlation was observed between serological or skin test results and age of the patient, history of atopy, extension of SLR, reaction time, and interval between last sting and examination.

Discussion

About one fifth of our 277 patients with systemic reactions to Hymenoptera stings reported severe local reactions to previous stings. This incidence is somewhat higher than that observed by other authors (Hoffman, 1978; Mueller *et al.*, 1975). This may be due to a slightly different definition of the severe local reaction. In contrast to Mueller *et al.* (1975) we did not find a higher incidence of severe systemic reactions (grade III and IV) in our patients with preceding SLR than in all our patients with SR. The probability to develop a life threatening reaction when restung after a SLR was calculated to be about 5%, which is quite low.

In 80% of the forty patients with SLR only hypersensitivity to either bee venom or yellow jacket venom was demonstrated by RAST or skin tests. Using RAST only, Hoffman (1977) found venom specific IgE in sixteen of seventeen and Kleinhans (1977) in seven of nine patients with SLR only. Green, Reisman & Arbesman (1979) studied a group of twenty-two patients with SLR to Hymenoptera stings and found positive results with either RAST or skin tests in thirteen (59%). Thus there is no doubt that the majority of severe local reactions to Hymenoptera stings are allergic in nature and mediated by IgE-antibodies. Possible reasons for a failure to detect IgE antibodies to venoms in these patients are: (1) spontaneous desensitization following the last sting could have occurred; (2) the patient could have misidentified the stinging insect and the appropriate venom was not available for testing; and (3) SLR may be due in some instances to infection or to local toxicity. As previously reported (Müller *et al.*, 1978), somewhat better results were found with BV than with YJ as the antigen also in this study. One reason for the difference may be that bee sting allergy is much more frequent in Switzerland than yellow jacket allergy. Most of the patients who were unable to identify the stinging insect were therefore probably sensitive to bees. Alternatively BV was collected by electrostimulation whereas YJ was extracted from venom sacs and may also contain some body proteins (Reisman *et al.*, 1979). The YJ used in this study is thus probably the less potent antigen than the BV.

Results of RAST and skin tests showed a fair correlation. In contrast to the results found in patients with SR (Patrizzi *et al.*, 1979) we did not observe more favourable results with skin tests than with RAST in patients with SLR. Local factors preventing the development of a SR in spite of the presence of specific IgE antibodies may also interfere with immediate type skin test reactions. On the other hand it is conceivable that in patients with SR, positive skin tests and negative RAST the allergy is mediated by short term skin-sensitizing IgG antibodies (Parish, 1970). These specific IgG antibodies would be able to induce SR and positive skin tests but not SLR.

The distribution of IgG antibodies to BV-phospholipase A was similar in patients

with SLR and with SR to bee stings, the mean values were, however, lower in patients with SLR. The serological pattern regarding IgE and IgG antibodies was therefore not significantly different in patients with SLR and with SR to Hymenoptera stings. In a more detailed serological study (Hoffman, 1978), using different BV-antigens—phospholipase A, hyaluronidase, mellitin and acid phosphatase—could not find different antibody patterns in patients with SLR and SR to bee stings. Therefore local rather than serological factors are probably decisive for the development of either a SLR or a SR in patients allergic to hymenoptera venoms.

Conclusions

(1) Severe local reactions (SLR) to Hymenoptera stings (bee and yellow jacket), exceeding 10 cm in diameter and 24 hr in duration, are most often of an allergic nature and mediated by IgE-antibodies to venom proteins.

(2) The risk to develop a life threatening systemic reaction when restung after a SLR is relatively low.

(3) There is therefore no general indication for a hyposensitization therapy with venoms in patients with SLR in contrast to patients with systemic reactions of grade III or IV. This form of treatment may, however, be advisable in single patients with repeated episodes of extensive SLR, whose allergy is proven by skin tests or RAST and who are at a high risk of being restung, such as beekeepers or their family members.

(4) All patients with SLR should be instructed how to avoid stinging insects. They should also be given antihistaminics and corticosteroids and take these medications immediately when restung. In contrast to severe systemic reactions, where adrenalin kits should be given, we do not advocate the prescription of these kits for patients with SLR.

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