

Association of features of atopy and diagnostic parameters in hymenoptera venom allergy*

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In a total of 525 patients with hypersensitivity reactions to hymenoptera stings diagnostic parameters of hymenoptera venom (HV) allergy (severity of reactions, skin test threshold and RAST for bee and vespid venoms) were investigated for their relationship to the following indicators of atopy: positive history of atopic diseases, elevated (≤ 100 kU/l) total serum IgE and positive prick test reactions to common inhalant allergens (CIA) (grass pollen, cat epithelium, house dust mite). There was a conclusive history of atopic disease in 25 %, a total serum IgE ≥ 100 kU/l in 48 %, and at least one positive reaction to CIA in 53 %. Total IgE ≥ 100 kU/l correlated with a higher frequency of RAST classes ≥ 2 ($P < 0.01$) and with less severe reactions to hymenoptera stings ($P < 0.05$). In the presence of at least one positive reaction to CIA, there were more frequently skin test thresholds ≤ 10 μ g/ml ($P < 0.05$) and RAST classes ≥ 2 ($P < 0.01$) for HV than in CIA prick test negative individuals. There was no significant relationship between the other pairs of parameters evaluated. Thus, reactivity to HV in diagnostic tests is increased in the presence of certain indicators of atopy. This has to be considered in the interpretation of skin test and RAST results obtained with HV.

Key words: atopy; hymenoptera venom allergy; inhalant allergens; RAST; skin test; total serum IgE.

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Atopy is a genetically determined state of reactivity characterized clinically by the tendency to develop a typical form of eczema ("atopic eczema") and/or allergic, IgE-mediated mucosal disorders (rhinoconjunctivitis, bronchial asthma). The most prominent pathophysiological feature of atopy is an increased IgE immune response against common environmental allergens. This constitutes the pathophysiological basis of atopic allergic rhinoconjunctivitis and bronchial asthma.

However, allergic diseases of the immediate type can occur also in non-atopic individuals. Bee or vespid venom hypersensitivity, which mostly is IgE-mediated, represents a paradigm of such a condition: determination of the frequency of atopy in hymenoptera venom (HV) allergy has led to divergent results with a minimum of 11 % (13) and maximum of 66 % (20) of the patients being regarded atopic, and thus a substantial part of the study populations was always found to be non-atopic. As the constitutionally increased IgE immune response in atopy may influence the reactivity at skin testing and RAST, we have done a retrospective study on a large number

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Table 1.

Severity scale for grading of anaphylactic/anaphylactoid reactions (after 18)

Severity grade	Skin	Gastrointestinal tract	Respiratory tract	Cardiovascular tract
I	pruritus flush urticaria angioedema	no symptoms	no symptoms	no symptoms
II	pruritus flush urticaria angioedema (not mandatory)	nausea cramping	rhinorrhea hoarseness dyspnea	tachycardia drop of RR arrhythmia
III		full shock		
IV		cardiac and/or respiratory arrest		

of unselected patients with hypersensitivity reactions to insect stings in order to determine the relationship of parameters of atopy to diagnostic parameters of HV allergy.

PATIENTS AND METHOD

A total of 525 patients (245 males, 280 females) aged 4 to 78 years (mean: 33.1 ± 0.7 years) presented for diagnostic evaluation of hypersensitivity reactions to hymenoptera stings. There had been systemic symptoms in 492 patients and large local reactions in 26 patients; the reaction type was not reported in 7 cases. Information about the time interval

since the latest hypersensitivity reaction was available in 471 patients: in 42.9 % the interval was less than 6 months, in 28.4 % between 6 and 12 months, in 11.7 % between 1 and 2 years, and in 17.0 % 2 years or more.

Systemic reactions were graded according to the scale given in Table 1 (after 18).

Skin testing was done on the ventral aspect of the forearms as modified prick test (using a blood lancet) or as intracutaneous test. Threshold skin prick testing with Reless® honey bee venom (*Apis mellifica*) and Reless® vespid venom protein (*V. germanica*, *V. vulgaris*) (Deutsche Pharmacia, Freiburg, Germany) was performed with incremental concentrations of 0.01, 0.1, 1.0, 10.0 and 100.0 µg/ml. Intracutaneous testing at concentrations of 0.1 and 1.0 µg/ml followed if the prick test with HV was negative. Prick testing with common inhalant allergens (CIA) was done with standard extracts of grass pollen, house dust mite (*D. pteronyssinus*) and cat epithelium (Bencard, Beecham-Wülfling, Neuss). A positive test result was defined as the presence of at least a 1+ reaction (prick test: wheal ≥ 2 mm, intracutaneous test: wheal ≥ 3 mm). At titrated skin testing, the lowest concentration causing a positive result was designated as the threshold concentration.

Specific IgE antibodies to bee or vespid venom were determined using the Phadebas® RAST (Pharmacia, Uppsala, Sweden).

Table 2.

Score system for evaluation of diagnostic parameters in HV allergy (modified after 24)

Parameter	0	Points	
		1	2
Reactions to hymenoptera stings	local	severity grade I	severity grades II-IV
Threshold concentrations in the skin	skin test	prick: 100 µg/ml	
test with HV	negative	IC: 0.1/1.0 µg/ml	prick ≤ 10 µg/ml
RAST classes for HV	0	1	2-4

Diagnosis of HV allergy was based on the score system shown in Table 2 (modified after 24). If the evaluation of each of the three diagnostic parameters yielded a score sum of ≥ 5 points, patients were judged to be allergic to the respective venom. If this was not the case for any venom, 4 points were sufficient for diagnosis. At ≤ 3 points diagnosis remained uncertain.

A conclusive history of atopy was defined by allergic rhinitis and/or bronchial asthma in the personal history of the patient or one of these conditions in the familial history (i.e. in consanguineous relatives) and additional signs of atopy (e.g. flexural eczema, stigmata of atopic diathesis) in the index case. If there were such conditions in the personal or familial history and the above-mentioned criteria were not fulfilled, the history of atopic diseases was regarded as questionable.

Total serum IgE was determined by the IgE PRIST® (Pharmacia, Uppsala, Sweden). Elevated values were defined as being ≥ 100 kU/l. A concentration of 100 kU/l can be regarded as an appropriate cut-off in all age groups except infants ≤ 5 years, who have somewhat lower IgE levels (26).

Analysis

According to the scheme given in Table 2 (after 24) two categories of parameters of HV allergy were discerned: local reactions, severity grade I / severity grades II–IV: less / more

severe reactions; prick test threshold > 10 $\mu\text{g/ml}$ / ≤ 10 $\mu\text{g/ml}$: lower / higher reactivity; RAST classes 0, 1 / 2–4: lower / higher reactivity. Standard statistical methods were used (19), P values of < 0.05 were regarded as significant. If necessary, correction was made for multiple testing. Mean values are given with the standard error of mean. Not all parameters were available for each patient; missing data were not due to patient selection.

RESULTS

History of atopic diseases

Eighty-five (25.4 %) of 335 patients had a conclusive, another 85 a questionable history of atopic diseases. When patients with a negative history of atopic diseases were compared with those with a conclusive history, there was no significant (χ^2 test) difference with regard to the frequency of more severe sting reactions (118/156 (75.6 %) vs. 60/85 (70.6 %)), a higher reactivity in the HV skin test (54/150 (36.0 %) vs. 29/84 (34.5 %)), nor a higher reactivity in the HV RAST (107/154 (61.5 %) vs. 63/84 (75.0 %)).

Total IgE.

An elevated level of total IgE was found in 192 (47.8 %) of 402 patients (for details see

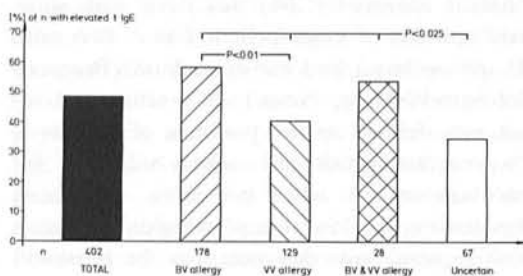


Fig. 1. Frequency of total serum IgE levels ≥ 100 kU/l in patients with hypersensitivity reactions to hymenoptera stings. BV: bee venom; VV: vespid venom.

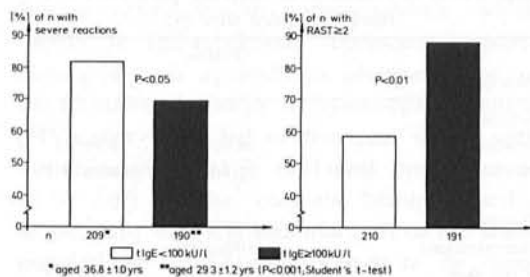


Fig. 2. Total serum IgE in patients with hypersensitivity reactions to hymenoptera stings: relationship to severity of reactions and reactivity in the RAST with bee venom or vespid venom.

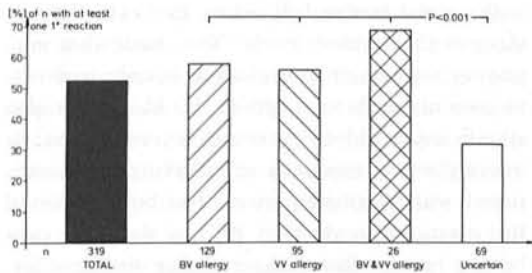


Fig. 3. Frequency of individuals with at least one 1+ skin prick test reaction to CIA in patients with hypersensitivity reactions to hymenoptera stings. BV: bee venom; VV: vespid venom.

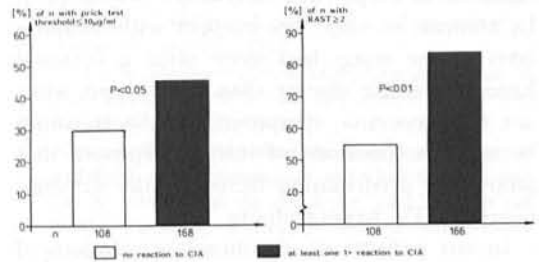


Fig. 4. Skin prick test reactivity to CIA in patients with hypersensitivity reactions to hymenoptera stings: relationship to reactivity in the prick test and RAST with bee venom or vespid venom.

Fig. 1). Compared with patients with total IgE levels < 100 kU/l, those with elevated IgE had a significantly ($P < 0.05$; χ^2 test) lower frequency of more severe sting reactions (171/209 (81.8 %) vs. 132/190 (69.5 %)) (Fig. 2). Simultaneously, patients with total IgE levels < 100 kU/l were significantly ($P < 0.001$; Student's *t* test) older than those with elevated IgE (36.8 ± 1.0 years vs. 29.3 ± 1.2 years). Compared with patients with total IgE < 100 kU/l, those with elevated levels exhibited significantly ($P < 0.01$; χ^2 test) more frequently HV RAST classes ≥ 2 to at least one of the HV (123/210 (58.6 %) vs. 168/191 (88.0 %)) (Fig. 2). No significant (χ^2) difference was found between patients with total IgE levels < 100 kU/l or ≥ 100 kU/l with regard to the frequency of a higher reactivity in the HV skin test (74/206 (35.9 %) vs. 83/190 (43.7 %)).

Skin test reactivity to CIA

Of 319 patients tested, 168 (52.7 %) had at least one 1+ reaction (for details see Fig. 3). Individuals who had negative reactions to all CIA tested exhibited a significantly ($P < 0.05$; χ^2 test) lower frequency of a higher reactivity in the HV skin test than those with at least one positive reaction to CIA (32/108 (21.6 %) vs. 76/168 (45.2 %)) (Fig. 4). Patients negative to CIA had a significantly ($P < 0.01$; χ^2 test) lower frequency of RAST classes ≥ 2 to at

least one of both HV compared with those with at least one 1+ reaction to CIA (59/108 (54.6 %) vs. 139/166 (83.7 %)) (Fig. 4). There was no difference in the frequency of more severe systemic reactions between patients not reacting to CIA and those who exhibited at least one 1+ reaction to CIA (76/107 (71.0 %) vs. 118/167 (70.7 %)).

DISCUSSION

Several investigators have determined the frequency of atopy among patients with hypersensitivity reactions to hymenoptera stings, reporting a wide range of values between 11 % and 66 % (3, 5, 11, 12, 13, 17, 20, 21, 27; Table 3). These findings were mostly based on history taking. Our results indicating that about 25 % of the patients have a conclusive and another 25 % a questionable history of atopic diseases, fit very well with the data found by others. It cannot be decided, however whether the percentage of individuals with a history of atopic diseases is higher among patients than in the general population, as a representative control group is difficult to obtain. The frequency of atopic diseases in the general population, as reported by others, was found to be 11 % (2) or 15 % (10), but among college students the prevalence of a history of asthma or allergic rhinitis was as high as 25 % (8). The prevalence of HV hypersensitivity was not found to be markedly increased in patients with atopic diseases (4) nor to be

different in atopic and non-atopic scouts (23). In contrast to this, bee-keepers with anaphylaxis to bee stings had more often a personal history of atopic disease than bee-keepers without such systemic symptoms (3). So it would be only in situations of intense exposure that atopy is a predisposing factor for the development of HV hypersensitivity.

In our patients no significant associations of the severity grade of reactions, skin test or RAST reactivity were found with regard to the presence or absence of a history of atopic disease. However, others have reported the occurrence of more severe sting reactions in patients with bronchial asthma compared with patients with allergic rhinitis or non-atopics (21, 22).

As elevated total serum IgE can be demonstrated in numerous non-atopic conditions, it is not an appropriate marker of atopy (16). Further, in patients with known IgE-mediated diseases total IgE is constituted to a considerable extent by allergen-specific IgE antibodies (7, 15). This can explain the significant association found between elevated total IgE and a high reactivity in the RAST with HV.

Sting reactions exceeding skin symptoms were significantly more frequent in patients

with a total serum IgE below 100 kU/l than in those with elevated levels. This somewhat surprising association presumably is only indirect, as patients with total IgE < 100 kU/l were also significantly older. A more severe course of anaphylactoid reactions in elderly people compared with younger patients has been reported for reactions to dextran (9), so that age may be the critical factor determining the severity.

Sensitization to CIA is a characteristic feature of atopy. About one half of our patients with HV hypersensitivity had at least one 1+ reaction to house dust mite, grass pollen or cat epithelium. Positive immediate skin test reactions to ubiquitous environmental allergens have been found in the general population in 16 % (14) to 64 % (25), in most investigations a frequency of about 30 % to 35 % was demonstrated (1, 6, 8). Although we had no control group, the data available do not suggest that reactivity to CIA is substantially increased in HV hypersensitivity.

Compared with patients with no reaction to CIA, those with at least one 1+ results more often exhibited a higher reactivity in the skin test and in the RAST with HV. The cause of this relation is probably the individual IgE immune response, leading to a higher or lower

Table 3.

Frequency of atopy in patients with hypersensitivity reactions to hymenoptera stings

Author	Patients		Method of evaluation
	Total (n)	Atopy (%)	
Mokry et al. 1985 (13)	142	10.8	PH
		22.0	FH
Settipane et al. 1980 (21)	587	22.3	PH
Chipps et al. 1980 (5)	44	22.7	PH
Yunginger et al 1978 (27)	27**	29.6	PH
Reisman et al 1979 (17)	50	30.0	-
Lockey et al. 1983 (11)	3202	31.0	-
Bousquet et al. 1982 (3)	105**	41.0	PH
Miyachi et al. 1979 (12)	34**	47.1	PH
		44.1	RAST*
Schwartz et al. 1970 (20)	41	65.9	PH/FH/skin tests*
This study	335	25.4/50.8	PH
			(conclusive/conclusive and questionable)
	319	52.7	skin tests*

PH = personal history; FH = family history; - = unknown.

*with ubiquitous environmental allergens.

**bee keepers/family members of bee keepers.

production of specific IgE antibodies to either allergen. Prick testing with CIA is a simple screening method to assess the IgE immune response, and it should be used in certain situations for critical evaluation of test results obtained with HV. For example, low reactivity to HV in patients with simultaneously negative reactions to CIA may reflect a weak IgE response and not, primarily, absence of a relevant sensitization to HV. This view is supported by the finding that patients who could not be assigned to a diagnostic group, showed significantly less frequently positive reactions to CIA than those in whom a diagnosis could be established (Fig. 3). Test reactions to HV should be interpreted cautiously, if at all, with regard to quantitative conclusions. Further prospective studies will have to clarify in more detail the interrelationship between hypersensitivity reactions to hymenoptera stings, IgE response to HV, and the atopic state.

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