

IgE antibodies to Hymenoptera venoms in the serum are common in the general population and are related to indications of atopy

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Determination of Hymenoptera venom (HV)-specific serum IgE antibodies is a useful diagnostic method in patients with systemic anaphylactic reaction (SAR) to Hymenoptera stings. In a general population cohort, we determined the prevalence of SAR and HV-specific IgE antibodies and assessed parameters associated with the latter. A total of 277 voluntarily participating inhabitants of rural Bavaria (Germany) (232 adults, mean age 38.0 years; 45 children, mean age 8.4 years) were investigated for a history of atopic disease or SAR to insect stings; in 258 of these, total IgE and specific IgE antibodies to HV (*Apis mellifera*, *Vespula vulgaris/germanica*) and four common aeroallergens (birch pollen, grass pollen, house-dust mite, and cat dander) in the serum were determined. Nine (3.3%) subjects reported SAR to insect stings. In 27.1% of the sera, specific IgE antibodies to HV were found, to bee venom in 24.8%, and to wasp venom in 8.5% ($P < 0.0001$). Of those exhibiting HV-specific IgE, 7.1% reported SAR to insect stings. A personal history of atopic disease (hay fever, asthma, or atopic eczema) was present in 16.7%, specific IgE to common aeroallergens was found in 32.6%, and total IgE > 100 kU/l was found in 22.5%. Specific serum IgE to HV was significantly associated with male sex (female vs. male, OR = 0.47; CI 0.25–0.86), young age (children vs. adults, OR = 2.80; CI 1.25–6.28), a history of SAR to insect stings (OR = 4.16; CI 1.15–15.03), total sIgE > 100 kU/l (OR = 3.88; CI 1.98–7.60), and specific IgE antibodies to three of the four aeroallergens (grass pollen, OR = 7.24 CI 3.66–14.38; birch pollen, OR = 3.67 CI 1.54–8.81; and house-dust mite, OR = 4.61 CI 2.08–10.32). It is concluded that immunologic sensitization to HV is common in the general population and is associated with atopy-related humoral IgE hyperresponsiveness.

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Hymenoptera venom (HV) allergy is one of the classical IgE-mediated allergic diseases. Among these, it is of particular importance, as reactions may be severe and life-threatening. Up to 5% of the population are reported to have experienced systemic sting reactions (1). In Germany, predominantly reactions to stings of the honeybee (*Apis mellifera*) and certain wasps (*Vespula germanica* or *V. vulgaris*) are of clinical relevance. For West Germany, up to 15 fatalities from insect stings per year have been reported to the vital statistics authorities within the last decade (2). This would account

for an incidence of one death per 4.5 million residents per year. However, in view of misclassification and recall bias, it is believed that the actual frequency of death is much higher. For various European countries and the USA, mortality rates between 0.09 and 0.45 per year/1 000 000 have been reported (3–5).

The diagnosis of anaphylactic HV allergy is based on the history and the finding of IgE-mediated sensitization by skin tests and *in vitro* methods (RAST or equivalent test). However, the diagnostic value of the determination of venom-specific IgE

antibodies in the serum is restricted by the fact that up to 24% of the general population (6–9) and up to 50% in selected cohorts (10) have been shown to exhibit such antibodies. Parameters associated with, or possibly even determining, the development of IgE antibodies to HV in such a high proportion of the population have not yet been evaluated.

We had the opportunity to investigate an unselected population in a rural area of Bavaria (Germany) and to correlate historical data on reactions to insect stings with indications of immunologic sensitization to venoms. Particularly, the relationship of the presence of HV-specific IgE antibodies to indications of atopy was evaluated.

Material and methods

Subjects

The study was carried out in a village and a small town in southeastern, rural Bavaria between December 1990 and February 1991. The study was initiated by the local authorities because of public concern about possible adverse health effects due to exposure to emissions from a small galvanizing plant in the village. The analysis of the body burden of relevant pollutants, however, yielded no striking results overall and particularly no differences between the populations of the village and the small town. Therefore, because both locations are rural areas in Bavaria, all data were merged for further analysis. After public announcement in the local press, 277 inhabitants participating voluntarily were included. The participants were not aware of the details of the allergologic investigation before enrollment. Formal written consent was obtained from all subjects or their guardians. A total of 123 female and 109 male adults aged 15–80 years (mean age 38.0 years) and 45 children (22 girls, 23 boys) aged 2–14 years (mean age 8.4 years) were investigated.

Methods

Interview. All subjects (or, if necessary, their guardians) were interviewed personally with a structured questionnaire. The personal and family history of atopic diseases (atopic eczema, hay fever, asthma) was taken. The participants were also asked whether they had developed systemic symptoms after bee or wasp stings.

In vitro tests. Blood samples were obtained from 224 adults and 34 children. Specific serum IgE antibodies to bee (*A. mellifera*) and wasp (*V. vulgaris*, *V. germanica*) venoms were determined by the radioallergosorbent test (Pharmacia RAST[®], Uppsala, Sweden) according to the instructions of the manufacturer; results are given in classes from 0 to 4. Total IgE was determined by the

Nephelometer 100[®] (Behring, Marburg, Germany). Specific IgE antibodies to four aeroallergens (grass pollen, birch pollen, house-dust mite [*Dermatophagoides pteronyssinus*], and cat dander) were measured in the serum by a fluorescence enzyme immunoassay (CAP-RAST[®] Pharmacia, Uppsala, Sweden), as described by the manufacturer; concentrations of specific IgE antibodies are given in classes from 0 to 6.

Statistical analysis. Data were analyzed with the epidemiologic software EPI INFO[®] (Questionnaire Processing Programs, Version 5, Epidemiology Program Office, Centers for Disease Control, Atlanta, GA, USA). Bivariate analysis was done by the chi-square test. Odds ratios (OR) are given together with the 95% confidence intervals (CI).

Results

Frequency of atopic diseases

Among the 277 subjects investigated, there was a personal history of at least one of the atopic diseases in 16.4% (children 15.6%, adults 16.6%): 12.0% (4.4%/13.5%) reported hay fever, 5.1% (11.1%/3.9%) atopic eczema, and 3.7% (0/4.4%) asthma. A family history (parents, siblings, children) of atopic diseases was present in 22.3% (24.4%/21.8%).

Systemic anaphylactic reaction to insect stings

Nine subjects (3.3%; five males, four females) had a history of systemic anaphylactic reaction (SAR) (urticaria, generalized pruritus, shortness of breath, etc.) after a bee or wasp sting. No further diagnostics had yet been performed in these subjects with regard to these events.

Five of the individuals with systemic sting reactions had specific IgE antibodies to bee venom and two of these also to wasp venom. Details are given in Table 1. One of these insect venom-allergic subjects reported an atopic disease (allergic rhinitis). The statistical analysis indicates a relevant correlation of a history of SAR to insect stings and a finding of venom-specific IgE antibodies ($P=0.03$; OR 4.16, CI 1.15–15.03).

Total IgE

Total IgE levels in the serum could be determined in 258 subjects and ranged from <2 to 719 kU/l. Levels above 100 kU/l were found in 58/258 (22.5%) serum samples (children 23.5%, adults 22.3%, no significant difference).

Specific IgE antibodies in the serum

Specific IgE antibodies to any of the aeroallergens tested were found in 32.6% of the 258 sera tested

Table 1. Characteristics of subjects with previous SAR to insect stings

Patient no.	Sex	Age (years)	Specific bee/wasp (RAST class)	Serum IgE antibodies to grass/birch/mite/cat (CAP class)	Total serum IgE (kU/l)	History of atopic diseases
1	F	48	0/0	0/0/0/0	68	No
2	M	48	1/0	0/0/0/0	12	No
3	M	40	1/0	0/0/0/0	35	No
4	F	32	2/0	2/0/0/0	219	No
5	M	67	1/2	0/0/0/0	50	No
6	F	64	0/0	0/0/0/0	124	Hay fever
7	F	51	0/0	0/0/0/0	5	No
8	M	35	3/2	0/0/2/0	9	No
9	F	53	0/0	0/0/2/0	35	No

(children 38.2%, adults 31.7%). In detail, specific IgE antibodies to grass pollen were found in 23.3% (35.3%/21.4%), to birch pollen in 10.9% (8.8%/11.2%), to house-dust mite in 13.6% (8.8%/14.3%), and to cat dander in 6.2% (5.9%/6.3%) (Fig. 1).

Specific IgE antibodies to bee or wasp venom were present in 70 of 258 sera (27.1%; children 47.0%, adults 24.1%). Most subjects had antibodies only to bee venom (18.6%; 32.4%/16.5%), 2.3% (2.9%/2.2%) only to wasp venom, and 6.2% (11.8%/5.4%) to both venoms (Fig. 2). Most positive results were RAST class 2. Details of the RAST class distributions are given in Fig. 3.

Parameters correlated with the presence of specific IgE antibodies to Hymenoptera venoms

The presence of specific IgE antibodies to HV was negatively correlated with female sex, 44/127 males (34.6%) and 26/131 females (19.8%) exhibiting positive findings (OR=0.47, CI 0.25–0.86). Children (16/34, 47.1%) more often had specific IgE antibodies to HV than adults (54/224, 24.1%) (OR=2.80,

CI 1.25–6.28). Demonstration of specific IgE to HV by RAST was not related to a positive history for a single atopic disease or for at least one of the atopic diseases.

Elevated IgE levels (>100 kU/l) were found to be strongly associated with specific IgE antibodies to HV (OR=3.88, CI 1.98–7.60).

With respect to specific serum IgE antibodies to aeroallergens, demonstration of specific IgE to HV was significantly correlated with the presence of specific IgE to grass pollen (OR=7.24, CI 3.66–14.38), birch pollen (OR=3.67, CI 1.54–8.81), and house-dust mite (OR=4.61, CI 2.08–10.32), but not with the presence of specific IgE to cat dander.

Table 2 gives details of the correlations between specific IgE antibodies to HV and various parameters.

Discussion

Definite figures on the frequency of HV allergy in the general population are not yet available. It can be estimated best by a personal interview, which is

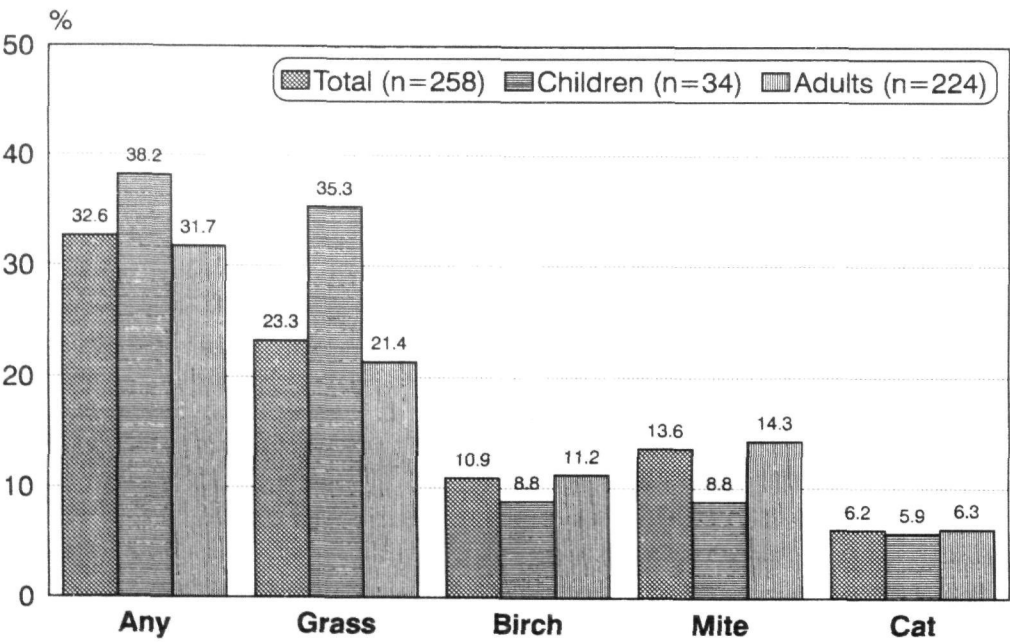


Fig. 1. Frequency of specific IgE antibodies to four common aeroallergens (grass pollen, birch pollen, house-dust mite [*D. pteronyssinus*], cat dander).

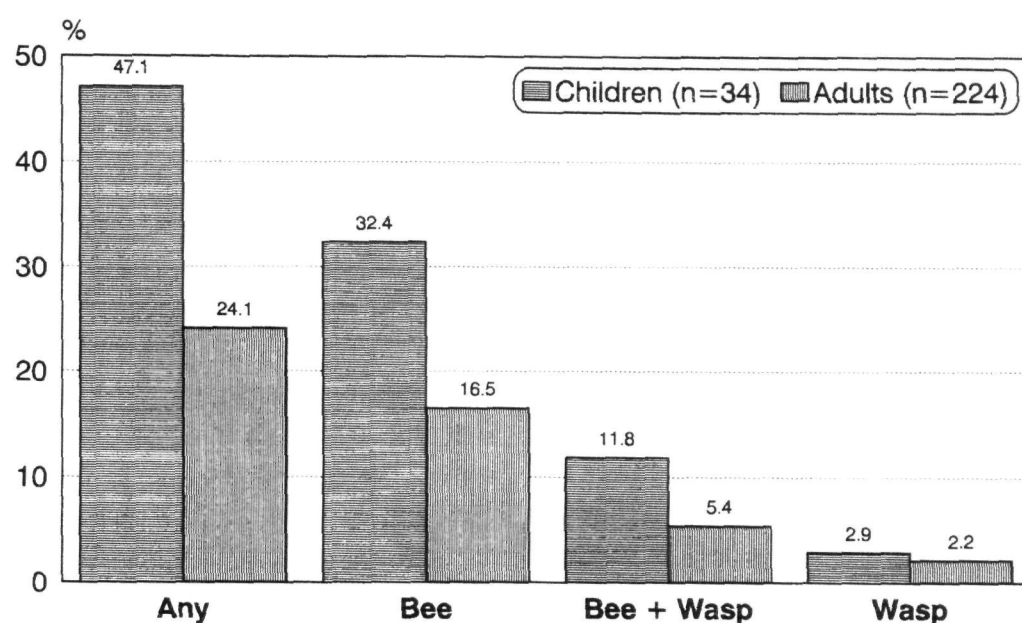


Fig. 2. Frequency of specific IgE antibodies to bee or wasp venom.

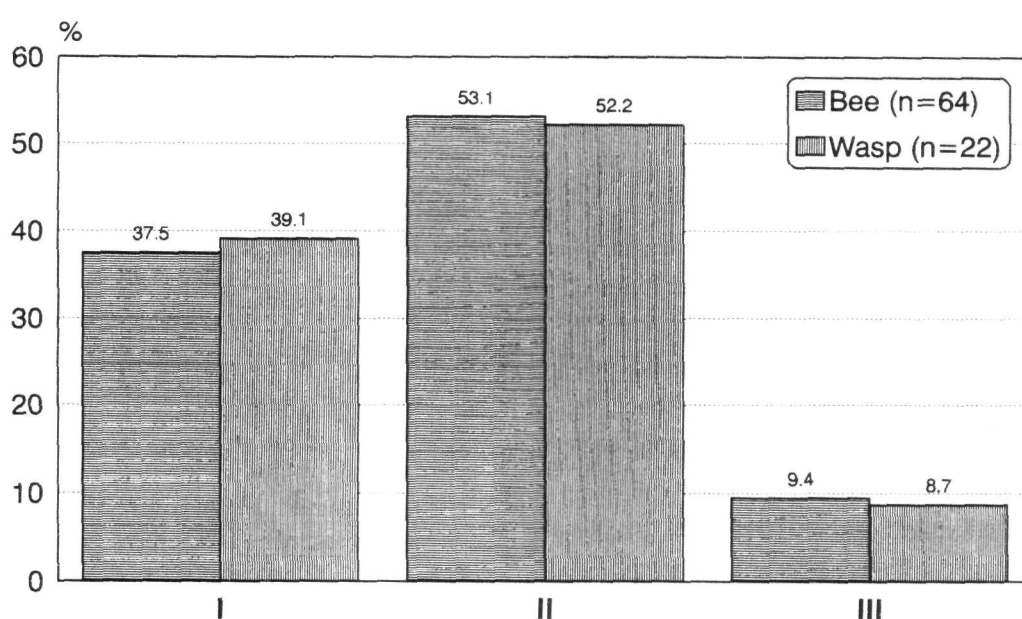


Fig. 3. Distribution of specific IgE antibodies to bee or wasp venom in RAST classes I, II, and III.

Table 2. Correlation of various parameters with presence of HV-specific IgE antibodies in serum

Parameter	Parameter		P value	Odds ratio	Confidence interval (95%)
	Present	Not present			
Male sex	34.6% (44/127)	19.8% (26/131)	0.008	0.47	0.25–0.86
Age (< 15 years)	47.1% (16/34)	24.1% (54/224)	0.005	2.80	1.25–6.28
Atopic eczema	25.0% (3/12)	27.2% (67/246)	0.865	0.89	0.18–3.78
Hay fever	30.3% (10/33)	26.7% (60/225)	0.661	1.20	0.49–2.85
Asthma	20.0% (2/10)	27.4% (68/248)	0.605	0.66	0.09–3.53
Any atopic disease	32.5% (14/43)	26.4% (56/215)	0.381	1.37	0.63–2.95
Specific serum IgE to					
Grass pollen	60.0% (36/60)	17.2% (31/198)	<0.001	7.24	3.66–14.38
Birch pollen	53.6% (15/28)	23.9% (55/230)	<0.001	3.67	1.54–8.81
<i>D. pteronyssinus</i>	57.1% (20/35)	21.5% (50/123)	<0.001	4.61	2.08–10.32
Cat dander	43.8% (7/16)	26.0% (63/242)	0.123	2.21	0.71–6.83
Total IgE > 100 kU/l	50.0% (29/58)	20.5% (41/200)	<0.001	3.88	1.98–7.60

more reliable than studies based on questionnaires, and thereby it is possible to distinguish large local from systemic reactions. For systemic reactions after insect stings, prevalences between 0.8% and 5.0% have been reported for the general population (1,

6, 7, 11, 12). In a questionnaire-based study involving 9930 subjects, 4.5% assessed themselves as being allergic to insect stings (13). In our study, we found strong evidence of prior systemic reactions in 3.3%. Selection bias with regard to the outcome

of interest seems to be unlikely in our study since the participants were not aware of the details of the allergologic investigation before enrollment. Interestingly, none of the HV-allergic subjects had undergone further diagnostic procedures or had received specific immunotherapy, indicating the need of more educational work in this field.

Specific IgE antibodies to insect venoms have been found in the general population in a much higher percentage. From the USA, Canada, Australia, or Switzerland, there have been reports of 12–18% positive RAST results with insect venoms (3, 6, 7, 9). This rate rises to 50% for more exposed populations; e.g., outdoor workers in rural North Carolina (10).

Our study yielded a high rate of 27.1% of subjects with specific IgE antibodies to HV in the serum. Only 7.1% of these gave a history of SAR to insect stings. The frequency of sensitization was higher for bee venom than for wasp venom (24.8% vs. 8.5%), in children than in adults (47.1% vs. 24.1%), and in males than in females (34.6% vs. 19.8%). The lower sensitivity of the RAST for specific IgE to wasp venom may partially account for the differences and might have led to an underestimation of the sensitization to wasp venom. In contrast to other reports (3, 6, 14), a history of SAR to insect stings was not more frequent in males than in females. However, the total number of subjects with SAR was small.

An increased percentage of atopics among patients with HV allergy has been reported, particularly in subjects exposed to insect stings more than the general population due to professional or recreational activities (7, 15, 16). Other studies did not identify among patients with HV allergy more atopics than in the general population (14, 17–20). It seems that a positive association between atopic diseases and HV allergy cannot be established in patients exposed to stings only occasionally. However, HV-allergic patients reacting to common aeroallergens in the skin prick test more frequently exhibit lower thresholds at skin testing with HV and higher levels of HV-specific IgE antibodies in the serum than subjects without such reactions to aeroallergens (19). In the present study, there also was no association between the presence of specific IgE antibodies to HV and a personal history of atopic diseases. However, an association between HV-specific IgE antibodies and specific IgE to grass pollen, birch pollen, and house-dust mite could be demonstrated. The further association between HV-specific serum antibodies and total IgE level probably can be explained by the fact that total IgE is constituted to a considerable extent by specific IgE antibodies.

The serologic findings indicate that the develop-

ment of HV-specific IgE antibodies is evidently determined by humoral IgE hyperresponsiveness on the basis of an atopic constitution. Additionally, there could be cross-reactivities between HV and common aeroallergens (1, 3, 21). This might be especially true for grass pollen, although our own preliminary investigations with these sera do not provide enough evidence to assume relevant cross-reactivity. The determination of HV-specific IgE antibodies remains a helpful tool especially in confirming the IgE mediation of a prior SAR to an insect sting, but isolated demonstration of specific IgE antibodies to HV must not be regarded as an indication of clinical hypersensitivity. The presence of HV-specific IgE antibodies in patients with suspected SAR to insect stings has to be interpreted in the context of all findings of the allergologic workup.

We conclude that the frequency in the general population of immunologic sensitization to HV, as recognized by the presence of serum specific IgE antibodies, is high and that there is an association between this phenomenon and atopy-linked humoral IgE hyperresponsiveness.

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