

Received: 2002.10.28
Accepted: 2003.10.23
Published: 2004.07.02

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

Prevalence of Hymenoptera venom allergy and its immunological markers current in adults in Poland

Marita Nittner-Marszalska^{ABDEFG}, Jerzy Liebhart^{ABCEFG}, Ewa Liebhart^{BC}, Anna Dor^{BC}, Rafał Dobek^{BCE}, Andrzej Obojski^{BC}, Wojciech Mędrala^{BC}

Department of Internal Diseases and Allergology, Medical University of Wrocław, Poland

Source of support: Departmental sources.

Summary

Background:

The prevalence of insect venom allergy is still being assessed. The aim of our study was to estimate, on the basis of an interviewer-administered questionnaire survey, the frequency of post-sting allergic reactions and venom sensitization.

Material/Methods:

The study was performed within the framework of the ECRHS. A random sampling of 3000 persons was selected from among 68,000 persons living in the area of Wrocław, Poland. Of the 2050 persons responding to a mailed screening questionnaire, 169 were randomly selected to complete a questionnaire designed only for insect allergy detection. Venom skin test and sIgE assessment were performed on 146 and 132 patients, respectively.

Results:

Allergic post-sting symptoms were found in 20.7% of surveyed patients. Large local reactions (LLs) occurred in 11.8% and systemic reactions (SYSs) in 8.9% of the study population. SYS was most often manifested by urticaria (4.7%). The frequencies of SYS II, III and IV were 1.8%, 1.8%, and 0.6%, respectively. Only LLs were more frequent in subjects with other allergic diseases ($p=0.03$). The presence of positive skin tests and/or sIgE in serum were 42.8% of subjects with LL, 53.3% with SYS, and 17.1% of "asymptomatic" patients. No significant differences were found between these groups regarding venom skin test results and sIgE serum concentrations. Occurrence of sIgE to bee venom was frequently associated with the presence of sIgE to timothy grass.

Conclusions:

Insect venom allergy and asymptomatic venom sensitization in adults are common in Poland. Only some venom allergy cases are IgE dependent.

key words:

insect allergy • epidemiology • prevalence of insect allergy • venom • honeybee • wasp • skin test

Full-text PDF:

http://www.MedSciMonit.com/pub/vol_10/no_7/3235.pdf

Word count:

2958

Tables:

4

Figures:

—

References:

17

Author's address:

Marita Nittner-Marszalska, Department of Internal Diseases and Allergology, Medical University of Wrocław, Traugutta 57/59, 50-417 Wrocław, Poland

BACKGROUND

The results of several epidemiological studies of the frequency of Hymenoptera allergy that have been published in Europe and the USA so far are ambiguous [1–12]. Moreover, these epidemiological studies do not usually assess clearly the frequencies of various forms of hyperresponsiveness, i.e. severe systemic anaphylaxis and other forms of allergic response. The issue in question has not been analyzed in detail in Polish studies so far.

The frequency of insect allergy may be evaluated by means of cross-sectional studies (based on anamnestic data) and/or skin test results and specific IgE serum concentration assay. In the majority of epidemiological studies, the prevalence of insect allergy is evaluated by means of a cross-sectional technique utilizing self-completed questionnaires, which is a commonly accepted diagnostic method. Published questionnaire surveys have revealed that a large local reaction (LL) occurs in 2.3% to 18.9% of the population and a systemic reaction (SYS) in 0.4% to 7.5% [1,2,4,5,11,12]. Such studies are influenced by several factors, including methodological issues (questionnaire overall design, method of responding: the subject unaided or with medical professional/physician assistance) and demographic factors (gender, age, educational level, profession, etc.). The evaluated population samples are usually heterogeneous with regard to gender, age, and intensity of exposure and are therefore difficult to compare. Moreover, respondents' related reactions are probably allergic only in part; while some proportion of symptoms may be non-allergic.

Another group of epidemiological studies is based on the results of immunological assays, skin tests, and serum-specific IgE concentrations in evaluated populations. However, the diagnostic value of these tests in the evaluation of the frequency of insect allergy is limited [13]. The presence of antigen-specific antibodies only proves venom sensitization, which is not always associated with clinical symptoms. The cases of "asymptomatic sensitization" are characterized by an unclear clinical prognosis. These patients are postulated to be at greater risk of developing an allergic reaction with a subsequent insect sting than are healthy subjects.

The aim of our study was to estimate, on the basis of an interviewer-administered questionnaire survey, the frequency of post-sting allergic reactions and of the various clinical manifestations of Hymenoptera venom allergy in a population sample examined within the framework of the European Community Respiratory Health Survey (ECRHS) in Wrocław, Poland. A secondary aim was to estimate the presence of immunological markers of sensitization. We also aimed to evaluate the frequency of asymptomatic sensitization.

MATERIAL AND METHODS

Study sample

The study was performed within the framework of the European Community Health Survey (ECRHS). A random sample of 1,500 males and 1,500 females, aged 20–44 years, was selected from the general population of around 68,000 persons living in the area of Wrocław, Poland. Overall, 2,050 subjects responded to a mailed screening qu-

estionnaire enquiring about allergic diseases, asthma, and rhinitis (response rate: 68%). Of these, 169 randomly selected individuals (72 males, 97 females) agreed to participate in Stage I, involving an additional questionnaire (see below) designed for insect allergy detection. The respondents filled in the questionnaire aided by an allergologist. None of these patients had ever undergone venom immunotherapy.

In Stage II, 146 of the 169 subjects had skin tests with a panel of inhalant allergens and venom performed; 132 also had immunological blood tests done.

Skin testing

Skin testing was done on the volar side of the forearm with a distance of 5 cm between points as a skin-prick test with a panel of the standard inhalant allergen extracts: *Dermatophagoides pteronyssinus*, cat, *Alternaria alternata*, *Cladosporium herbarum*, timothy grass, birch, *Parietaria judaica*, olive, and ragweed (Allergopharma). The positive control was histamine 10 mg/ml soluprick. A positive skin test result was defined according to the recommendations of the European Academy of Allergy and Immunology.

Intradermal skin tests with insect venoms (bee, wasp) were performed by injection of 0.02 ml of the respective venoms (Pharmalgen common wasp, Pharmacia AB, Uppsala, Sweden) in concentration 10^{-4} g/l, and were paralleled with a negative (diluent) and positive (histamine) control. Test results were considered positive when the longest wheal diameter was greater than 5 mm after 15 minutes. Skin test results are expressed as the mean value of the sum of the two diameters of the wheal.

Specific IgE determination

Bee and wasp venom-specific serum IgE antibodies were assessed by the commercially available Phadezym CAP (Pharmacia, Fine Chemicals, Uppsala, Sweden). The test was performed according to the recommendations of the manufacturer. All tests were duplicated and their results are given in kU/l.

Classification of allergic reactions

The severity of allergic reaction was estimated according to the Mueller classification (15). The patients who in Stage I answered with "yes" to questionnaire question 17 were classified as the LL group. The SYS I group was comprised of patients who answered "yes" to question 18, the SYS II group of patients who answered "yes" to questions 18 and 19 or only 19, the SYS III group of patients who answered "yes" to questions 18 and/or 19 and 20, and the SYS IV group of patients who answered "yes" to questions 18 and/or 19 and/or 20 and 21. In the case of simultaneous occurrence of LL and SYS reactions (SYS I, II, III, or IV), the patients were classified according to the more severe reaction, that is SYS.

Statistical analysis

The frequencies of manifestations of Hymenoptera venom allergy and its immunological markers as well as 95% confi-

Table 1. Incidence of Hymenoptera post-sting allergic reactions in the evaluated population by means of the questionnaire survey.

Type of allergic reaction	N (%)	95%CI
All local and systemic post-sting allergic reactions	35 of 169 (20.7)	14.6–26.2
Local reactions	20 of 169 (11.8)	6.9–16.7
Systemic reactions	15 of 169 (8.9)	4.6–13.2
Systemic I	8 of 169 (4.7)	1.5–7.4
Systemic II	3 of 169 (1.8)	0.0–38
Systemic III	3 of 169 (1.8)	0.0–38
Systemic IV	1 of 169 (0.6)	0.0–1.8

dence intervals were calculated. Comparisons of some parameters between selected subgroups were performed by means of the Chi-squared test and odds ratio indices.

RESULTS

Allergic post-sting symptoms were found in 20.7% of Stage I surveyed individuals (Table 1). The frequencies of LL and SYS reactions were 11.8% and 8.9%, respectively (8.3% reported local and systemic symptoms occurring concurrently). The systemic reaction was most often manifested with urticaria (SYS I: 4.7%). The frequency of the SYS II reaction was 1.8%, SYS III 1.8%, and SYS IV only 0.6%.

The clinical pattern of systemic reactions included one main symptom characterizing a class of systemic responses in 14/15 subjects, two symptoms in 1/15, three in 3/15, and four in 1/15 (main symptoms: urticaria, angioedema, dyspnoe, and consciousness disturbances). 88 of the 169 evaluated subjects (52.1%), reported other allergic diseases besides insect allergy. 81 (47.9%) did not report any allergic manifestation. The allergic post-sting systemic symptoms were not reported more frequently by subjects with concomitant allergic diseases than by others without any allergic history (Table 2). We noted, however, a statistically significant difference in the frequency of LL reactions, which were more prevalent in subjects with coexisting allergy ($p=0.032$) (Table 2).

Table 3 presents a comparison of sting allergic case histories with skin test and specific serum IgE results. No link was found between diagnostic test results and the intensity of clinical manifestations.

Stage II of the study revealed a positive venom skin test result and/or the presence of serum sIgE antibodies in 42.8% LL subjects and in 53.3% SYS subjects (Tables 3 and 4). All of the patients had been stung within the last 5 years.

A large group of patients who entered both stages of the study and did not report any post-sting allergic symptoms had positive skin tests and/or specific IgE results. In 25/146 (17.1%) of these asymptomatic patients we found positive skin tests to

one of the venoms. In turn, specific IgE antibodies, in class II or higher, were present only in 40% of the asymptomatic patients with positive venom skin tests (10/25).

The intensities of intradermal reactions to venoms, expressed as the mean value of the sum of the two diameters of the wheal, in asymptomatic subjects compared with those in patients who reported post-sting allergic symptoms did not show statistically significant differences ($p=0.43$). No significant differences were found between these two groups with regard to specific IgE antibody serum concentrations ($p=0.34$).

In the group of patients with positive venom skin test results, the relationship was examined between bee or wasp skin test and sIgE results and the results of skin test and sIgE assays performed with a set of aeroallergens. A significant relationship was found only between sIgE against bee venom and timothy allergens. Bee venom allergic subjects manifested allergy to timothy significantly more frequently ($p=0.008$) in the sIgE test; (OR =3.34; 95% CI =1.52–7.33).

DISCUSSION

The results of the study, based on a retrospective analysis of post-sting reactions by means of questionnaires (completed with the assistance of an allergologist), suggest that in the examined population of volunteers, 11.8% gave a history of isolated large local reactions and 8.9% of systemic reaction to an insect sting. Among systemic reactions, the most frequent included mild urticaria and angioedema, while anaphylactic shock was the rarest manifestation. These results correspond with the outcome of our previous study, in which 28.9% of 881 persons who responded to the same questionnaire (completed without a physician's assistance) reported allergic reactions to stinging insect venom (16% local reactions and 12.9% systemic reactions) [4]. A comparison of the results based on the self-completed questionnaire and the ones based on the questionnaire completed with a physician's assistance shows an overestimation in the former case.

These results are difficult to compare with other authors' studies, mainly due to methodological differences. The list of case histories based on epidemiological studies is rather long [1,2,4–12]. The frequency of venom systemic reactions ranges from 0.4% (US Rhode Island Study performed on 4992 boy scouts aged 11–16), through 3.1% (USA industrial workers), to about 5.5% in the population of blood donors in Switzerland and 7.5% in the population in Turkey [2,5,7]. The frequency of local symptoms has been reported to be as high as 18.6% [2]. Two of the cited studies, performed by Stuckey et al. and Golden et al. in a way similar to ours (questionnaire filled in with a physician's assistance), report lower ratios of systemic reactions (2.7% in a population of 3439 inhabitants of Buselton; 3.3% in a population of 269 industrial workers in the USA) with a similar incidence of local symptoms (18.6%) [2,9]. Unfortunately, the questionnaires applied in the above studies have not been published and it is therefore not possible to compare questions defining local or systemic reactions, which might have an influence on the studies' results. Moreover, there were obvious inconsistencies between the demographic characteristics of the evaluated samples.

Table 2. Incidence of post-sting allergic reactions in the populations of allergic and non-allergic subjects (by means of the questionnaire survey).

Type of reaction	Allergic subjects 88 of 169	Non-allergic subjects 81 of 169	OR 95%CI	χ ² P
Local	16 of 88 (18.2%)*	4 of 81 (4.9%)*	3.68; 1.09–13.65	4.56; 0.032
Systemic	6 of 88 (6.8%)	9 of 81 (11.1%)	0.61; 0.18–1.99	0.8–0.37
Co-occurrence of local and systemic	7 of 88 (8.0%)	7 of 81 (8.6%)	0.92; 0.28–3.08	0.02; 0.881

* the difference statistically significant

Table 3. Relation between history of allergic reaction and confirmation of presence of IgE specific wasp and bee venoms.

Type of reaction	Number of subjects	Positive ICT test and/or positive sIgE N (%)	Positive ICT test N (%)	Positive sIgE N (%)
Local	14	6 of 14 (42.8)	6 of 14 (42.8)	2 of 14 (14.2)
Systemic	15	8 of 15 (53.3)	7 of 15 (46.7)	3 of 15 (20.0)
		χ ² =0.11; p=0.74	χ ² =0.02; p=0.89	χ ² =0.02; p=0.71
		OR=0.8; 0.18–3.46 (95%CI)	OR=0.92; 0.2–41 (95%CI)	OR=0.71; 0.05–7.31 (95%CI)

ICT – intracutaneous test

Table 4. Summary of the study stages I and II.

Type of reaction	Subjects with a questionnaire-positive history of allergic reaction stage I N (%); 95%CI	Subjects with a positive history of allergic reaction participating in the study stage II N (%); 95%CI	Subjects with a history of allergic reaction and positive skin test and/or positive sIgE N (%); 95%CI
Local	20 of 169 (11.8); 6.9–16.7	14 of 146 (9.5); 4.7–14.3	6 of 146 (4.1); 0.9–7.3
Systemic	15 of 169 (8.9); 4.6–13.2	15 of 146 (10.3); 5.4–15.2.	8 of 146 (5.5); 1.8–9.2
Systemic I	8 of 169 (4.7); 1.5–7.9	6 of 146 (4.1); 0.9–7.3	2 of 146 (1.4); 0.0–3.3
Systemic II	3 of 169 (1.8); 0.0–3.8	3 of 146 (2.0); 0.0–4.3	3 of 146 (2.0); 0.0–4.3
Systemic III	3 of 169 (1.8); 0.0–3.8	2 of 146 (1.4); 0.0–3.3	2 of 146 (1.4); 0.0–3.3
Systemic IV	1 of 169 (0.6); 0.0–1.8	1 of 146 (0.7); 0.0–2.1	1 of 146 (0.7); 0.0–2.1

CI – confidence interval

The results of any cross-sectional questionnaire-based study probably overestimate the frequency of local allergic symptoms and, to some extent, also of the lower classes of systemic reactions. This may be due to an overstatement of the size or severity of the reaction by some of the subjects. It should be remembered that every survey of this type is based on the subjective feeling of the evaluated patient. Moreover, a questionnaire contains commonly accepted definitions of these reactions, which do not allow differentiation between allergic and toxic responses or a local reaction complicated by an infection. Therefore, such results may contain reports of both allergic and non-allergic reactions.

Skin tests and serum-specific IgE assays were applied in the second phase of our study as diagnosis verification tools. The skin test was performed with insect venom at a concentration of 10⁻⁴ g/l (although we are aware that this venom con-

centration may produce “false negative” results in some insect-allergic patients; a concentration of 10⁻³ g/l involves the risk of a high percentage, as high as 46%, of “false positive” results in non-allergic patients). The presence of sIgE antibodies was found in 42.8% of the LL patients and 53.3% of the SYS patients. The nearly twice lower frequency of IgE-dependent post-sting reactions may be explained in a two-fold manner. The first seems to be an overestimation error of the survey study. However, the questionnaire serves as a screening device in epidemiological studies and is characterized by higher sensitivity than specificity. Supplementing the study protocol with skin tests and/or specific IgE evaluations allows a selection of patients with an IgE-dependent type of reaction. The group of subjects responding positively to survey questions contains some individuals with IgE-mediated and some with other than IgE-mediated reactions. Our knowledge of the latter pathomechanism of reactions is still insufficient, though the Gel-Coombs type III mecha-

nism has been postulated to play a role. Systemic reactions observed in patients with negative skin test results may indicate non-IgE-dependent reactions, i.e. anxiety, conditioned reflex, or toxic reactions. However, a negative skin test or negative specific IgE results need not exclude a role for these antibodies in the pathogenesis of previous reactions.

It is widely accepted that both tests results depend on the period of time that has passed since the incidence of symptoms and may turn negative a few years after the episode [13]. According to Golden et al, a negative skin test result does not exclude the possibility that a patient will experience another systemic sting reaction in the future [3]. In this study the frequency of systemic reactions after sting challenges was found in 22% of the patients manifesting no skin reaction to venom. Nevertheless, a positive result of one of these tests may occur in patients currently clinically reactive to venom and those without any post-sting symptoms as well. The latter group of patients, referred to as "asymptomatic sensitive", turned out to be numerous, constituting as much as 17.1% of our sample. It was very interesting that asymptomatic sensitive and symptomatic sensitive patient groups did not differ with respect to the immunological parameters examined, i.e. intensity of skin reactions to venoms and concentrations of serum sIgE antibodies. This only proves the well-known thesis questioning the prognostic importance of skin test results and sIgE assay for clinical symptom intensity.

The results of this part of our examination are consistent with other epidemiological studies in which the prevalence of positive venom skin tests "without clinical symptoms" has been estimated to be 15%. [2]. The prognosis in this group of subjects is unclear, though it is postulated that these subjects are predisposed to develop allergic symptoms in the future. It is also possible that these persons are sensitized transiently. Therefore, we planned to observe these persons within the framework of a cohort study. Studies performed by Jarish et al. revealed that a single insect sting causes specific sensitization in 14% of subjects not allergic to venom and in 31% after repeated stinging [14]. An insect venom allergic reaction occurs as a single lifetime event in 50–58% of cases, which suggests that the sensitization is not long lasting in most cases [15]. A disturbing finding, typical of the natural history of insect allergy, is that the majority of individuals with severe reactions had not had any episodes that might suggest the danger of future sensitization; moreover, most individuals who die of insect anaphylaxis did not have prior systemic allergic reactions.

In the present study there was no association between positive intracutaneous skin test results to insect venom and positive skin prick test results to aeroallergens, but there was a significant association between the presence of specific serum IgE to bee venom and to timothy allergens. In this respect, our results are similar to those of other authors who found an association between specific serum IgE to bee venom and grass pollen, birch pollen, and house dust mite [1,16,17].

CONCLUSIONS

Summing up, according to the epidemiological data obtained from our survey study, insect allergy is common in Poland, but it most frequently occurs in the form of mild skin symptoms. Only a half of the individuals reporting post-sting symptoms

manifested the presence of sIgE antibodies. Positive skin test results occurred both in persons manifesting clinical reactions to venom and, even more frequently, in individuals non-reactive to stinging. The latter group constitutes an intriguing phenomenon that requires a further investigation.

QUESTIONNAIRE

The following questionnaire designed especially for Hymenoptera venom allergy assessment was administered by physicians (allergologists), independently of the ECRHS Main Questionnaire.

1. Questionnaire number
2. First name, surname, address:
3. Age
4. Sex: a) male b) female
5. Do you live in a) a big city b) a town c) in the country
6. Do you live in: a) mountains b) highlands c) lowlands
7. Have you, currently or within the last 10 years, occupationally or as a hobby, done any of the following: a) bee keeping b) farming c) gardening d) none
8. Do you suffer from bronchial asthma? a) yes b) no
9. Do you suffer from allergic perennial rhinitis? a) yes b) no
10. Do you suffer from hay fever? a) yes b) no
11. Do you suffer from drug allergy? a) yes b) no
12. Do you suffer from food allergy? a) yes b) no
13. Do you suffer from allergic skin diseases? a) yes b) no
14. Have you ever been stung a) yes b) no
15. How many times have you been stung by the same insect species (bee, yellow jacket, hornet)? a) once b) a few times (2–5) c) many times (more than 5) d) never
16. Being stung by an insect, did you notice a swelling at the site of the sting? a) yes b) no
17. Being stung by an insect, did you notice a swelling with a diameter of more than 10 cm, lasting over 24 hours? a) yes b) no
18. Being stung by an insect, did you notice urticaria on the whole body? a) yes b) no
19. Being stung by an insect, did you have swelling of the face, tongue or lips? a) yes b) no
20. Being stung by an insect, did you experience difficulties of breathing, dyspnoea? a) yes b) no
21. Being stung by an insect, have you ever lost consciousness? a) yes b) no
22. Did the allergic symptoms show for the first time? a) in childhood b) between 10–30 years of age c) between 30–40 years of age d) later e) no allergic reaction has ever occurred

REFERENCES:

1. Novembre A, Cianferoni A, Bernardini R et al: Epidemiology of insect venom sensitivity and its correlation to clinical and atopic features. *Clin Exp Allergy*, 1998; 28: 834–38
2. Golden DBK, Marsh DG, Kagey-Sobotka A et al: Epidemiology of insect venom sensitivity. *JAMA*, 1989; 262: 240–44
3. Golden DBK, Kagey-Sobotka A, Norman PhS et al: Insect sting allergy with negative venom skin test responses. *J. Allergy Clin Immunol*, 2001; 107: 897–901
4. Nittner-Marszalska M, Liebhart J, Malolepszy J: Results of research on the prevalence of allergic reaction to hymenoptera venom in south-west Poland. *Pol Arch Wewn*, 1998; 100: 245–51
5. Kalyoncu AF, Demir AU, Ozcan U et al: Bee and wasp venom allergy in Turkey. *Ann Allergy Asthma Immunol*, 1997; 78: 408–12

6. Bjornsson E, Jansson C, Plaszke P, Norman E et al: Venom allergy in adult Swedes: a population study. *Allergy*, 1995; 50: 800-5
7. Settipane GA, Boyd GK: Prevalence of bee sting allergy in 4992 Boy Scouts. *Acta Allergol*, 1970; 25: 286-91
8. Settipane GA, Newstead GJ, Boyd GK: Frequency of Hymenoptera allergy in an atopic and normal population. *J Allergy Clin Immunol*, 1972; 50: 146-50
9. Stuckey M, Cobain T, Sears M et al: Bee venom hypersensitivity in Busselton. *Lancet*, 1982; 2: 41
10. Charpin D, Birnbaum J, Vervloet D: Epidemiology of hymenoptera allergy. *Clin Exp Allergy*, 1994; 24: 1010-15
11. Grigoreas Ch, Galatas ID, Kiamouris Ch et al: Insect venom allergy in Greek adults. *Allergy*, 1997; 52: 51-57
12. Herbert FA, Salkie MI: Sensitivity to Hymenoptera in adult males. *Ann Allergy*, 1982; 48: 12-13
13. Zora JA, Swanson MC, Younginger JW: A study of the prevalence and clinical significance of venom-specific IgE. *J Allergy Clin Immunol*, 1988; 81: 77-82
14. Jarish R, Zajc J, Buzath A et al: The risk of sensitisation of nonallergic persons to bee venom. *Arch Dermatol Res*, 1982; 273: 173
15. Muller UR: Clinical presentation and pathogenesis. Epidemiology. In: Muller UR *Insect sting allergy: Clinical picture, diagnosis and treatment*. Stuttgart, New York: Gustav Fisher, 1990; 52-65
16. Schafer T, Przybilla B: IgE antibodies to hymenoptera venoms in the serum are common in the general population and are related to indications of atopy. *Allergy*, 1996; 51: 372-77
17. Przybilla B, Ring J, Grieshammer B: Association of features of atopy and diagnostic parameters in hymenoptera venom allergy. *Allergy*, 1991; 46: 570-76