

Insect-venom allergy in Greek adults

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Relatively few studies have investigated the prevalence of insect-sting allergy and the results of diagnostic procedures in unselected populations. The prevalence of insect-sting reactions and of venom sensitization in Greece is unknown. We report the results from a stratified random sample of 480 subjects (404 men, 76 women), aged 20–60 years. They all belonged to the ground personnel of the Hellenic Air Force. A detailed history particularly focused on the reactions to Hymenoptera stings was taken in all subjects. Intradermal skin tests (concentration: 1 µg/ml) with three venoms (honeybee, paper wasp, common wasp) were performed. The prevalence of venom sensitization (one or more positive skin tests) was 32.7%. Sensitization appears to be more common (2.69 times) in those living in rural areas than in those living in the capital (Athens). The prevalence of systemic reactions was 3.1% (86.7% of them had positive skin tests). Large local reactions were reported by 4.6% of the subjects (77.3% of them had positive skin tests). Asymptomatic sensitization (positive skin tests to venoms) was observed in 28.7% of subjects with no history of an allergic sting reaction. We concluded that the prevalence of Hymenoptera allergy and venom sensitization in Greece is rather high compared to that of other countries.

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Allergic reactions to insect stings represent a major medical problem (1). Several deaths per year have been recorded in the USA and Europe (2–4). The mortality rate varies from 0.09 to 0.45 deaths per million inhabitants per year, but true mortality rates may be higher (5, 6). Most patients with severe reactions had no warning of their sensitivity. Most patients who died from insect-sting anaphylaxis had not had generalized allergic reactions in the past (2). Venom immunotherapy is now considered a safe and highly effective treatment, preventing death, recurrence, and fear of recurrence while keeping risk low during and after therapy (1, 7). Therefore, it is important to identify those who are at risk.

The prevalence of insect-sting allergy can be determined from anamnestic data or from the results of diagnostic tests. Relatively few studies have investigated the results of sensitization to Hymenoptera venoms and the prevalence of allergic reactions to stings in unselected populations. In the literature in the USA and Europe (among children and adults), the incidence of systemic reactions varied from 0.35% to 5% (1, 5, 6).

In Europe, Hymenoptera venom allergy is most often caused by stings from honeybees (*Apis*

mellifera) and wasps (e.g., *Vespula vulgaris* [common wasp] and the genus *Polistes* [paper wasp]) (7). Since there were no data on Hymenoptera allergy in Greece, the principal aim of this study was to estimate the prevalence of sensitization to Hymenoptera venoms and to identify those at risk of developing a systemic allergic reaction if restung by a bee or wasp.

Material and methods

From October 1991 to April 1992, 480 people (404 men and 76 women), aged 20–60 years, were studied. The mean age of men was 34.2 ± 8.9 years and that of women was 27.8 ± 7.1 years. All subjects were members of the ground personnel (career officers) of the Hellenic Air Force. Their examination took place during the scheduled, biannual medical checkup at the Department of Periodic Medical Examination at the Air Force General Hospital of Athens. In the present study, we included all subjects scheduled to be examined every second day, in order that their selection should be completely random. They were all living in various parts of Greece under similar socioeconomic conditions.

Questionnaire

All subjects, under the supervision of, and in cooperation with, an allergologist, completed a printed questionnaire which included:

- 1) demographic data (age, sex, place of origin, and place of residence)
- 2) questions regarding past or present beekeeping
- 3) previous Hymenoptera (bee and wasp) stings and nature of the reactions elicited.

According to the history of allergic reactions to Hymenoptera stings (we followed the method of Müller [8], with modifications), subjects were divided into the following groups:

Group 1) No reaction or small local reaction group (swelling with diameter ≤ 10 cm, at the site of the sting, lasting no more than 24 h). In this group, people who could not remember clearly the nature of the reaction caused by the sting, but who could assure us that they did not experience severe or intense symptoms, were included as well.

Group 2) Large local reaction group (swelling with diameter >10 cm at the site of the sting lasting more than 24 h).

Group 3) Systemic or anaphylactic reaction group (grades I–IV). These patients developed either a mild systemic reaction with symptoms of the skin (generalized urticaria, itching, and angioedema), gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain), constriction in the chest, and dizziness (grades I and II), or a severe systemic reaction with any of the above symptoms (grades I and II) plus two or more of the following symptoms – dyspnea, wheezing, stridor, dysphagia, dysarthria, hoarseness, weakness, confusion, feeling of impending disaster, fall in blood pressure, collapse, loss of consciousness, and cyanosis (grades III and IV) – within 45–60 min after the sting.

Skin-testing procedure

Skin tests with venoms from honeybee, common wasp (*Vespa*), and paper wasp (*Polistes*) were performed in all subjects. Dilutions of purified venoms (Pharmalgen, ALK, Denmark) in a concentration of 1 $\mu\text{g}/\text{ml}$ were used. Skin tests were performed always by the same investigator, always in the morning, by the intradermal method, in the interior surface of the forearm with a tuberculin syringe of 1 ml. A volume of 0.02 ml was injected intradermally. A negative (diluent) and a positive

control (histamine, 0.1 mg/ml) were placed concurrently with each set of venom skin tests. Skin tests were read after 20 min and were graded according to the system of Norman (9). Reactions graded as 2+ (wheal 5–10 mm, erythema 21–30 mm), 3+ (wheal 5–10 mm or with pseudopods, erythema 31–40 mm or >40 mm), and 4+ (wheal >15 mm or with many pseudopods, erythema 31–40 mm or >40 mm) were considered positive.

Statistical analysis

The data of the subjects examined were analyzed with the aid of a computer. For the significant and nonsignificant correlations between the parameters examined, both the chi-square method (Mantel-Haenszel stratification method) and the chi-square test were employed (10).

Results

Of the 480 subjects, 20 (4.2%) reported that they were or had been beekeepers. According to their history, of the 480 subjects, 443 (92.3%) reported that Hymenoptera stings caused no reaction or only a small local reaction (this group included 52 who did not remember in detail what happened after the sting, but were sure that no severe reaction had been elicited), 22 (4.6%) reported that the sting caused a large local reaction, and the remaining 15 (3.1%) reported that the sting resulted in a systemic reaction (Table 1). In the last group, six subjects reported mild systemic reactions (grades I and II) with mainly skin manifestations, and the remaining nine, symptoms of multiple systems (severe systemic reactions, grades III and IV).

Of the 480 subjects, 404 were men (84.2%) and 76 were women (15.8%). Of the 404 men, 138 (34.2%) had positive skin tests to one or more Hymenoptera venoms and of the 76 women, 19 (25%) proved to be venom positive. As a whole, 157 subjects (32.7%) had positive skin tests to at least one venom and 323 subjects (67.3%) had negative skin tests to venoms (Table 2). The difference in prevalence of positive skin tests between

Table 1. Insect-sting allergy by clinical history

History	Subjects examined (n = 480)	
	n	%
No reaction	443	92.3
Large local reaction	22	4.6
Systemic reaction (grades I and II)	6	1.2
Systemic reaction (grades III and IV)	9	1.9

Table 2. Skin-test results with insect venoms, according to age and sex. Influence of sex in sensitization to Hymenoptera venoms (positive skin tests) by elimination of confounding effect of age: χ^2 (Mantel-Haenszel) = 1.89, $P=0.17$. Influence of age in sensitization to Hymenoptera venoms (positive skin tests): $\chi^2=28.5$, $P=0.00008$

Age (years)	Men		Women		Total	
	<i>n</i>	No. positive (%)	<i>n</i>	No. positive (%)	<i>n</i>	No. positive (%)
20-24	60	17 (28.3)	34	8 (23.5)	94	25 (26.6)
25-29	76	25 (32.9)	17	5 (29.4)	93	30 (32.2)
30-34	88	45 (51.1)	14	4 (28.5)	102	49 (48)
35-39	60	22 (36.7)	6	0 (0)	66	22 (33.3)
40-44	64	24 (37.5)	2	1 (50)	66	25 (37.9)
45-49	36	5 (13.9)	2	1 (50)	38	6 (15.8)
>50	20	0 (0)	1	0 (0)	21	0 (0)
Total	404	138 (34.2)	76	19 (25)	480	157 (32.7)

the two sexes was not statistically significant. The influence of sex in the sensitization to Hymenoptera venoms, by elimination of the confounding effect of age, was tested by the chi-square method (Mantel-Haenszel stratification method); $\chi^2=1.89$, $P=0.17$. The distribution of subjects with positive skin tests by age showed a statistically significant difference ($\chi^2=28.5$, $P=0.00008$) (Table 2). Of the 480 subjects, 396 (82.5%) lived in rural areas and 84 (17.5%) in Athens. Of the 396 subjects living in rural areas, 142 (35.8%) had positive skin tests (one or more) to Hymenoptera venoms. Of the 84 subjects living in Athens, 15 (17.8%) had positive skin tests (one or more) to Hymenoptera venoms. The difference was statistically significant. The influence of the place of origin on the sensitization to venoms, by elimination of the confounding effect of age, was tested by the chi-square method (Mantel-Haenszel stratification method), $\chi^2=9.96$, $P=0.002$. The odds ratio value was 2.69 with a confidence interval of 95% (1.14-5.01).

Of the 157 subjects with positive skin tests, 96 (61.1%) showed monosensitivity (positive skin tests to one venom only) and 61 (38.9%) polysensitivity (positive skin tests to more than one venom). The results of positive skin tests to venoms are analyzed in Table 3. Of the 480 subjects, 59 (12.3%) were positive to bee venom, 60 (12.5%) to *Polistes* venom, and 115 (23.9%) to *Vespula* venom. Table 4 presents the relationship between the clinical history of Hymenoptera stings and skin tests. Of the 443 subjects with no history of a reaction, 127 (28.7%) had positive skin tests (asymptomatic sensitization). Of the 22 subjects with large local reaction, 17 (77.3%) had positive skin tests. Of the 15 subjects with systemic reaction, 13 (86.7%) had positive skin tests. Positive skin tests to Hymenoptera venoms were significantly more frequent in subjects who had systemic reactions

Table 3. Positive skin tests to Hymenoptera venoms (bee, *Polistes*, *Vespula*)

Hymenoptera venom Species	Subjects with positive venom	
	Skin tests (<i>n</i> =157)	
	<i>n</i>	%
Bee	25	15.9
<i>Polistes</i>	15	9.5
<i>Vespula</i>	56	35.7
Bee plus <i>Polistes</i>	2	1.3
Bee plus <i>Vespula</i>	16	10.2
<i>Polistes</i> plus <i>Vespula</i>	27	17.2
Bee plus <i>Polistes</i> plus <i>Vespula</i>	16	10.2

Table 4. Correlation of venom skin tests and clinical history of sting reactions

History	Venom skin tests			
	Positive		Negative	
	<i>n</i>	%	<i>n</i>	%
No reaction (<i>n</i> =443)	127	28.7	316	71.3
Large local reaction (<i>n</i> =22)	17	77.3	5	22.7
Systemic reaction (<i>n</i> =15)	13	86.7	2	13.3

(86.7%) and large local reactions (77.3%) than in subjects who had no reaction (28.7%) (chi-square test, $P<0.05$).

Table 5 presents the results of insect-sting allergy by clinical history and by venom skin testing in the adult population sample studied. Of the 480 subjects, 316 (65.8%) had no reaction and negative skin tests, 127 (26.5%) had no reaction and positive skin tests, five (1%) had large local reactions and negative skin tests, 17 (3.6%) had large local reactions and positive skin tests, two (0.4%) had systemic reactions and negative skin tests, and 13 (2.7%) had systemic reactions and positive skin tests.

Discussion

The objective of this report was to describe the epidemiology of immediate hypersensitivity to Hymenoptera sting and venoms in an adult population sample from Greece.

The overall prevalence of sensitization (positive skin tests to one or more of the three Hymenoptera venoms used) in Greek adults is relatively high compared to that from other studies (11-15). In Switzerland, Müller et al. (11) reported positive RAST against bee venom in 12% of 52 nonallergic (controls) blood donors studied. In an extensive study in Australia, Stuckey et al. (12) observed that 542 out of 3439 subjects had positive RAST to bee

Table 5. Insect-sting allergy by clinical history and venom skin tests

History	Venom skin tests	Subjects examined (n = 480)	
		n	%
No reaction	Negative (-)	315	65.8
No reaction	Positive (+)	127	26.5
Large local reaction	Negative (-)	5	1
Large local reaction	Positive (+)	17	3.6
Systemic reaction	Negative (-)	2	0.4
Systemic reaction	Positive (+)	13	2.7

venom (16%). Herbert & Salkie (13) studied 86 Canadian adults and found out that 12% of them had positive specific serum IgE antibodies to the venom of bee or vespids. Björnsson et al. (15) have reported that of the 1399 subjects examined in Sweden, 130 (9.3%) had specific bee or wasp (*Vespa*) venom IgE in serum. In the USA, Golden et al. (14) investigated 269 subjects (factory workers in Baltimore) and found that 47 (17%) had positive skin tests against bee and yellow-jacket venoms. It is obvious that the prevalence of sensitization to venom allergens in Greece is rather high when compared to that of other countries. This may be attributable to methodologic factors, but it may also represent a real phenomenon. Methodology has mainly to do with the kind of diagnostic tests employed for the detection of specific IgE antibodies to Hymenoptera venoms. Skin tests with Hymenoptera venoms and estimation of venom-specific serum IgE, antibodies are the most common diagnostic tests. For estimation of venom specific IgE, the commercial RAST is less sensitive than skin tests (14, 16, 17), especially in patients with previous allergic reactions to vespids (18). In this study, skin tests were the only diagnostic test, and three different venoms (from bee and two different wasps) were tested instead of bee venom only (11, 12) or bee venom and one wasp venom (13–15). For the skin tests, the concentration of 1 µg/ml was used. This concentration is considered sensitive enough to detect allergic patients, but, at the same time, it is considered of "borderline" sensitivity for the exclusion of subjects with no history of insect-sting allergy (5).

Another probable explanation of the higher prevalence of sensitization in Greek than in adults of other countries lies in the geographic and climatic factors of Greece. Climatic factors have an effect not only on lifestyle and clothing, but also on the living conditions of the various Hymenoptera species (5). In cold and wet climates, like that of Scandinavia, people are less exposed to Hymenoptera species than in central and southern Europe.

This is supported by the findings derived from mortality statistics (3). In a population study of venom allergy in adult Swedes, Björnsson et al. (15) estimated that the lowest prevalence of sensitization was recorded in their three most northern centers. The climate of Greece appears to be ideal for an increased degree of exposure to stings.

The degree of exposure is an important risk factor for sensitization to insect venoms and for developing Hymenoptera sting allergy. It is well known that beekeepers very often have allergic reactions to Hymenoptera stings (19, 20). In our study, beekeepers (active or in the past) represented a rather small portion (4.2%) of the population studied. The degree of exposure is also influenced by social and cultural factors in combination with climatic conditions. People living in rural areas or away from big cities are at greater risk than those living in cities (5). This is supported by the finding of this study on sensitization to venoms according to the place of origin. Subjects living outside Athens were at greater risk (2.69 times) of sensitization to Hymenoptera venoms than those living in Athens.

The prevalence of sensitization to Hymenoptera venoms diminished with increasing age. This became obvious beyond the age of 30–34 years. This observation may mean that older people get stung less often and therefore that the interval between the last sting and testing was longer than in younger patients. However, it could also mean that older people are less easily sensitized after a sting. Golden et al. (14) found that positive venom skin tests were more frequent in subjects aged 20–29 years than in older subjects (14). On the other hand, Björnsson et al. reported that the prevalence of specific IgE antibodies did not decline with age. Nevertheless, it is well known that IgE levels in adults decrease with increasing age (21, 22), and skin test reactivity (positivity) to inhalant allergens demonstrated a tendency to decrease between 20 and 60 years of age (22, 23). Venom skin tests and RAST were also more often positive in subjects with positive inhalant allergen skin tests (14, 15). This observation agrees with our results on the prevalence of sensitization to venoms in association with age.

Venom sensitization has been reported to be more common in men than in women (14, 15). In most studies of Hymenoptera sting allergy (sting anaphylaxis), men are more often affected than women (2, 24–27). This probably indicates that men are more exposed to insect stings than are women. This opinion is supported by the observation that the incidence of Hymenoptera sting allergy showed no differences in Boy and Girl Scouts of similar ages and degrees of exposure (28,

29). In our study, positive venom skin tests were more frequent in men than in women, but the difference was not statistically significant (Table 2).

Skin tests were positive to bee venom in 12.3% of subjects, to *Polistes* venom in 12.5%, and to *Vespula* venom in 23.9%. Golden et al. (14) studied 269 subjects and reported that some skin tests were positive to bee venom (5%) and yellow-jacket (*Vespula*) venom (14%). In each of the three parts of Sweden involved, the prevalence of specific serum IgE to wasp venom (*Vespula*) was higher than that of bee venom (15). This means that sensitization to *Vespula* venom was more frequently reported than to bee venom. Such differences probably reflect the degree of exposure and the living conditions of the various Hymenoptera species. Our study found positive skin tests to two or three venoms (38.9% of the 157 subjects with positive skin tests). Limited cross-reactivity has been thought to exist between bee venom and the various vespid venoms, whereas extensive cross-reactivity between major allergens has been demonstrated in many vespid venoms. Although weaker, cross-reactivity between *Vespula* and *Polistes* venoms does exist (5).

The number of subjects reporting anaphylactic or systemic reactions was also consistent with the high rate of sensitization. We found one of the highest rates reported in the literature, although there is a wide variation (6). Other authors reported the prevalences of systemic reactions in children to be, variously, 0.4% (29), 0.35% (28), and 0.8% (30). The prevalence of systemic sting reactions was 1.3% in Switzerland (31), 2.7% of the general population in Australia – of these, 1.3% had positive RAST (12) – 1.2% in the Canadian population (13), 3.3% of industrial workers in the USA – of these, 1.8% had positive venom skin tests (14) – 0.9% in southeast France (32), and 1.5% in three areas in Sweden – of these, 0.6% had positive RAST (15).

The prevalence of insect-sting allergy can be determined not only from the results of diagnostic tests, but also from the anamnestic data. History by itself is not always reliable because it is based on subjective evaluations. The way the case history is taken is very important. Usage of simple questionnaires may underestimate the percentage of allergic reactions to Hymenoptera stings, in contrast to questionnaires completed under medical supervision. Differences in interpretation of an insect-sting reaction (criteria) can also have an effect. All the above, in combination with other factors (population studied, degree of exposure, and age), seem to play an important role in the relatively wide variation of the results obtained in previous studies (11–15, 28–31). In this material,

13 subjects reported systemic reactions to insect stings and also had positive skin tests to venom. In subjects with systemic reactions after an initial sting, positive skin tests to venom or high levels of IgE venom-specific antibody levels have been thought to indicate the risk of systemic reactions to another sting (33). None of our subjects with systemic reactions had sought medical attention or advice. They were also informed for the first time of the advantages of venom immunotherapy. This finding is in keeping with that of other authors (14, 15, 34), indicating that proper information on insect sting allergy, for both doctors and the public, is critical.

Large local reactions were reported by 4.6% of the population. Other authors reported the prevalence of large local reactions to be, variously, 1.5% (31), 3.1% (12), 2.3% (13), and 18.6% (14). The wide variation in the results suggests that the criteria of a large local reaction vary from author to author (35–37) and are influenced by other factors (such as degree of exposure). Positive skin tests were present in 77.3% of the subjects with large local reactions and in 86.7% of the subjects with systemic reactions. According to other investigators, in 50–80% of subjects with large local reactions, skin testing and/or RASTs revealed the presence of specific IgE antibodies to venoms (35, 37, 38). This percentage was higher in patients who had systemic reactions (38–40). Golden et al. (14) reported that 22% of the subjects with large local reactions and 56% of patients with systemic reactions had positive venom skin tests. The wide variation of the results may, in part, be due to the long interval between stinging and testing (5). Golden et al. (14) estimated that a positive venom skin test or RAST was more frequent in subjects who had been stung within the last 3 years (35%) than in those stung more than 3 years before (20%).

Asymptomatic sensitization (positive venom skin tests) was observed in 28.7% of subjects with no history of allergic sting reaction (systemic or large local). Golden et al. (14) estimated that 15% of the subjects with negative history of venom allergy had positive skin tests. The results of this study were based on venom skin tests with concentrations similar to that used in our study (1 µg/ml). With the same concentration, 3–46% of control subjects with no previous history of insect-sting allergy had positive tests, according to other authors (39, 41–45). When the concentration of 0.1 µg/ml was used, this percentage was significantly lower (0–5%) (39, 41–45). Thus, Georgitis & Reisman (45) studied 56 subjects with no history of insect-sting allergy and reported that 46% of them had positive skin tests to Hymenoptera venoms

(concentration 1 µg/ml). This percentage dropped to 4% when a concentration of 0.1 µg/ml was used.

Positive venom skin-test results in subjects without history of allergic reactions to insect stings could be interpreted as subclinical sensitization to venoms. This subclinical or asymptomatic sensitization has been described also with aeroallergens (e.g., pollen or house-dust mite) (46, 47). The actual risk of systemic sting reaction in patients with asymptomatic venom sensitivity is unknown; it may be small but perhaps not negligible (48, 49). The identification of subjects liable to develop systemic sting reactions is of great importance, since most fatal sting reactions occur in patients who have never had an allergic sting reaction (2).

In conclusion, we found that the prevalence of Hymenoptera sensitization in Greece is much higher than that reported in studies from other countries. Allergic sensitization to Hymenoptera venoms was found in 32.7% of the population studied. Sensitization is more common (2.69 times) in those living in rural areas than those living in Athens. Systemic allergic reactions to insect sting was reported by 3.1% of the subjects, who never sought medical attention or advice. Large local reactions were reported by 4.6% of those examined. Asymptomatic sensitization (positive venom skin tests) was observed in 28.7% of subjects with no history of allergic sting reaction.

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