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A study of the prevalence and clinical significance of venom-specific IgE

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The prevalence of unrecognized Hymenoptera-venom sensitization, assessed by venom skin tests (VSTs) in adults with no history of adverse reactions to sting, has been as high as 12% in previous epidemiologic studies. To assess further the clinical importance of positive VSTs in such individuals, we skin tested 33 subjects stung in the field during the preceding 12 months without reaction, and 33 persons who denied being stung in the preceding 3 years. Among the recently stung group, 12/33 had at least one positive VST ($\geq 2+$) at 1.0 $\mu\text{g/ml}$, whereas 5/33 had positive VST at 0.1 $\mu\text{g/ml}$. In contrast, only 2/33 nonstung subjects had positive VST at 1.0 $\mu\text{g/ml}$, and none were positive at 0.1 $\mu\text{g/ml}$. To estimate, prospectively, the sensitization rate after insect stings, we studied a third group of 11 nonsensitive patients with negative skin tests to Hymenoptera. After a deliberate in-hospital honeybee sting, only 1/11 developed a persistently positive honeybee VST. From among the three groups, we then performed nine sting challenges in eight patients with positive VSTs, and all stings were tolerated without significant reaction. We also measured IgE antibodies to Hymenoptera venoms in random blood bank donors. During April to May, 2/216 sera contained elevated venom-specific IgE antibodies, whereas 14/201 sera collected from October to November contained elevated venom-specific IgE antibodies. We conclude that a small but appreciable portion of the population has venom-specific IgE antibodies and that the prevalence is seasonably variable. Our data indicate that persons recently stung without significant reaction contribute to this group but that only a small portion of this group is at risk for a systemic reaction with a future sting. (J ALLERGY CLIN IMMUNOL 1988;81:77-82.)

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Estimates of the incidence of Hymenoptera-sting sensitivity, as determined by clinical history alone, have ranged from 0.4% to 0.8% of the general population.^{1,2} In a more recent cross-sectional survey by Golden et al.³ of a stratified random sample of employees at a Maryland manufacturing company, there was a 4% prevalence of previous systemic allergic sting reactions by history. Additionally, in 147 employees without a previous history of a systemic or large local reaction after a sting, >12% had a positive VST.³ In a health survey involving 3439 persons

Abbreviations used

VST:	Venom skin test
HB:	Honeybee
W:	Paper wasp
YJ:	Yellow jacket
YH:	Yellow hornet
WFH:	White-faced hornet

screened for venom sensitivity by specific IgE immunoassay, 16% had a positive result (RAST score ≥ 2).⁴ In a study of 86 adult male office workers, Herbert and Salkie⁵ found elevated serum IgE levels to either YJ or HB venom in 10 individuals (12%) who gave no history of insect sting reactions. Finally, in a study of nine insect-sting fatalities in North Carolina, Hoffman et al.⁶ noted that in only two of the cases was there a history of a previous generalized reaction to insect stings. All decedents were sensitized to venom, however, since venom-specific IgE antibodies were documented by immunoassay on a post-mortem blood specimen.

Collectively, the above information indicates that there exists a small, but appreciable, population of patients who are sensitized to Hymenoptera venom but who have a negative history for a significant sting reaction. Data of Hoffman et al.⁶ document that in some cases such patients may proceed to have a lethal sting. The current study was undertaken to assess the prevalence of venom sensitization in healthy mid-western blood donors and in respondents to a newsletter advertisement. We postulated that individuals recently stung uneventfully may become sensitized, with demonstrable positive VSTs and elevated levels of venom-specific IgE antibodies by immunoassay. Finally, we determined the clinical significance of positive VSTs or immunoassay results by administering deliberate Hymenoptera-sting challenges.

MATERIAL AND METHODS

Patients

Blood bank group. Sera were obtained from 417 random blood bank donors, either during April to May ($N = 216$) or during October to November ($N = 201$). Individuals with elevated venom-specific IgE antibody levels were contacted and interviewed concerning previous Hymenoptera stings. Skin testing was performed in most of these patients.

Advertisement group. A second study group contained 66 individuals from a total of 68 who responded to an advertisement placed in our institutional newsletter soliciting volunteers stung within the past year (but not within the past month) or volunteers not stung within the previous 3 years. None of these patients had a history of a systemic or a large local reaction to Hymenoptera stings, and none

had venom or whole body extract immunotherapy. All individuals who had been stung were questioned about the circumstances of the sting, including the number of stings, the presence of a visible nest, and the presence of a stinger at the sting site. In addition, subjects were asked to identify the culprit insect from preserved Hymenoptera specimens provided. These subjects had VSTs with HB, W, and vespid (YJ, YH, and WFH) venoms and had serum drawn for measurement of venom-specific IgE antibodies. Those subjects with positive VSTs were then requested to undergo deliberate insect-sting challenges.

Control group. This group contained 11 persons with no history of insect-sting reactions and negative VSTs with all five Hymenoptera venoms. All individuals had deliberate sting challenges with a live HB, after which VSTs were repeated 1, 4, and 6 weeks after the sting. Additional HB-sting challenges were performed in patients with persistent positive HB VSTs.

Skin tests. Commercially available HB, W, YJ, YH, and WFH venoms (Hollister-Stier Laboratories, Spokane, Wash.) were used for intradermal testing at concentrations of 0.1 and 1.0 $\mu\text{g}/\text{ml}$. Sufficient extract was injected to produce a wheal 5 mm in diameter; wheal-and-flare diameters were measured in 15 minutes and were graded according to the method of Norman,⁷ with a 2+ or greater reaction considered positive. Repeat VSTs were placed 4 months after the initial evaluation in the recently stung subjects whose VSTs were initially positive.

IgE antibodies. Individual venom-specific IgE antibodies were measured by radioimmunoassay with solid-phase allergens prepared by reacting HB venom (Sigma Chemical Co., St. Louis, Mo.) or YJ, YH, or WFH venoms (Vespa Laboratories, Spring Mills, Pa.) with CNBr-activated Sepharose 4B particles.⁸ Approximately 20 to 40 mg of venom protein was reacted with 30-ml packed volumes of Sepharose 4B. Wasp venom-specific IgE antibodies were measured with a solid-phase allergen prepared by adsorbing W venom (Vespa Laboratories) to Immulon II microtiter plates (Dynatech Corp., Alexandria, Va.) (100 μl of a 10 $\mu\text{g}/\text{ml}$ solution per well).⁹ Results were expressed as percent radioactive counts bound compared to counts bound by serum from a normal control individual. Values $>300\%$ than values of a negative control serum were considered positive.

Sting challenges. Sting challenges were performed in an outpatient setting as previously described.¹⁰ Subjects were stung on the upper arm with an insect to which the subject had a positive VST, and if multiple positive VSTs were noted, the VST producing the largest wheal and flare determined the insect used for the challenge.

Informed consent. Written, informed consent was obtained from all patients undergoing skin testing and/or deliberate insect-sting challenge. This study was reviewed and approved by the Mayo Institutional Review Board.

RESULTS

Blood bank group

Of 417 blood bank sera, 216 were obtained from April to May before the stinging-insect season in our

TABLE I. Results from VSTs and clinical history in blood bank donors having elevated venom-specific IgE antibody levels in October to November

Subject No.	Insect/IgE antibody level (% negative control)	Positive VSTs		History
		0.1 µg/ml	1.0 µg/ml	
1	YJ/470	YJ	YJ, WFH	No sting recalled
2	HB/2037	—	HB	No sting recalled
3	HB/354	HB	HB	No sting recalled
4	YJ/314	—	W	Recent sting; no reaction
5	YJ/865	YJ, WFH	W, vespids	Recent sting; no reaction
6	WFH/423	W, vespids	All	Systemic reaction 14 yr previously; angioedema and loss of consciousness
7	YJ/464	W, vespids	W, vespids	Systemic reaction 6 yr previously; dizziness and loss of consciousness
8	HB/986	HB, W, YJ, YH	All	Recent sting; large local reaction
9	HB/350	HB	HB	No sting recalled
10	HB/479; YJ/660	All	All	Stung 4 yr previously; large local reaction
11	WFH/446	—	HB	Recent sting; no reaction
12	YH/484	ND	ND	Recent sting; no reaction
13	HB/985	ND	ND	Unknown
14	HB/856	ND	ND	Unknown

ND = Not done; — = negative.

area (Rochester, Minn.). Only two of the 216 sera contained elevated venom-specific IgE antibodies. One individual in whom IgE-specific antibodies were found to YH did not respond to our inquiry letter. The other individual was subsequently interviewed, skin tested, and had a sting challenge. This subject had been stung by an unknown insect approximately 3 years previously and experienced a large local reaction. Her serum contained elevated venom-specific IgE antibodies to YJ. The VST demonstrated positive reactions only to the vespid venoms at concentrations of 0.1 µg/ml and 1.0 µg/ml. A subsequent YJ-sting challenge produced no systemic or large local reaction.

In contrast, of the 201 sera collected from October to November, 14 sera contained elevated venom-specific IgE. Twelve of these subjects were available for interviews, and 11 subjects were available for skin testing. VSTs and IgE antibody results are presented in Table I. Two subjects reported large local reactions 4 months and 4 years before testing, and two subjects reported systemic reactions after previous stings occurring 6 and 14 years before testing. Four other subjects had been stung uneventfully in the 4 months preceding the blood sampling, and the remaining four subjects did not recall a sting in recent years. All 11 patients who were skin tested demonstrated positive reactions to at least one venom at the 1.0 µg/ml test

concentration. In nine of these 11 patients, the same insect venom to which the patient demonstrated elevated IgE antibodies also produced a positive VST. Multiple positive VSTs were observed mostly in the patients with histories of systemic or large local reactions to stings. None of the 14 patients had a subsequent deliberate insect-sting challenge because vespids were not available at that particular time of year.

Newspaper advertisement group

Of the 66 newspaper advertisement volunteers enrolled, 33 had been stung without reaction during the previous 8 months (four persons had received multiple stings), but none of the stings occurred in the preceding 4 weeks. These patients ranged in age from 7 to 68 years (mean = 28 years); only two patients were less than 18 years of age. The remaining 33 patients denied being stung during the previous 3 years. Their ages ranged from 18 to 55 years (mean = 31 years). Ten of the 33 previously stung individuals were able to identify the culprit insect after viewing preserved insect specimens. The identification in these cases was consistent with that suggested by historical information.

Skin tests

At VST concentrations of 0.1 µg/ml, five of 33 subjects recently stung had 2+ or greater positive

TABLE II. Results from VSTs, specific IgE antibody levels, and sting challenges in newspaper advertisement volunteers who were available for study and who had at least one positive VST

Subject No.	Field sting†	Positive VSTs				Insect/elevated IgE antibody level (% negative control)		Sting challenge
		Initial		Repeat*		Initial	Repeat	
		0.1 µg/ml	1.0 µg/ml	0.1 µg/ml	1.0 µg/ml			
Individuals recently stung								
1	INP	YJ	W, YJ	YJ	W, YJ	WFH/524	WFH/344	YJ
2	INP	YJ	Vespids	YJ	Vespids	YJ/318 YH/491	YJ/275 YH/439	YJ
3	INP	—	W, YJ, WFH	—	W, YJ	—	—	W, YJ
4	W	—	W	—	W	—	—	W
5	INP	—	YJ	—	YH	—	—	YJ
6	INP	—	W	—	W, YJ	W/308	W/348	W
7	INP	Vespids	Vespids	Vespids	Vespids	—	—	ND
8	INP	YJ	YJ	YJ	YJ	—	—	ND
9	HB†	—	HB	—	—	—	—	ND
10	YJ, HB†	—	YJ	—	YJ, HB	—	—	ND
11	HB	—	HB	—	—	—	—	ND
12	INP	YJ, WFH	W, YJ, WFH	ND	ND	—	—	ND
Individuals not recently stung								
1		—	Vespids	ND	ND	—	—	YJ
2		—	HB	ND	ND	—	—	ND

ND = Not done; INP = identification not possible; — = negative.

*Tests repeated 4 months after initial visit.

†Field sting determined by history and by identification from preserved Hymenoptera specimens. Patients 9 and 10 had received multiple HB stings.

skin tests, and all subjects were reactive to vespids (Table II). Twelve subjects demonstrated a 2+ or greater positive skin test at a venom concentration of 1.0 µg/ml. Among these individuals, five were reactive to one or more vespids, three were reactive to one or more vespids and W, two were reactive to W alone, and two individuals were reactive to HB alone. The remaining 21 subjects had negative VSTs and were not retested. However, all positive VSTs were repeated at 4 months after initial evaluation (Table II). Two subjects who initially had positive HB VSTs (Nos. 9 and 11) were skin test negative on repeat testing. No patient lost skin test reactivity to vespid or W venoms during this interval. On repeat testing, subject No. 10 was also positive to HB, and subject No. 6 was also positive to YJ. Both of these tests had been positive at 1+ on initial evaluation.

Of the 33 individuals who had not been stung recently, only two had positive skin tests at venom con-

centrations of 1 µg/ml, with one individual reactive to all three vespids and with the second individual reactive only to HB (Table II). None of these 33 patients had a positive VST at 0.1 µg/ml. Neither of these two individuals had repeat VSTs.

IgE antibodies

Venom-specific IgE antibodies were elevated in only three of the recently stung subjects (Table II). In two of the three subjects, corresponding VSTs were also positive, whereas in the third subject, IgE antibodies were elevated to WFH and VSTs were positive to W and YJ. None of the 33 subjects in the nonstung group had elevated IgE antibodies.

Sting challenges

Seven sting challenges were performed in six volunteers from the recently stung group. Two of the seven challenges were performed with an insect to

which the subject had a positive VST at 0.1 $\mu\text{g/ml}$, and the remaining five challenges were performed with an insect to which the individual had a positive VST at 1.0 $\mu\text{g/ml}$. One of the two subjects with positive VST in the nonstung group volunteered for a sting challenge. Despite the positive VST, all sting challenges were tolerated without systemic or large local reactions.

Control group

Of the 11 subjects with initially negative HB VSTs who had HB-sting challenges, two had positive HB VSTs 1 week after the challenge. One of the two patients subsequently had a negative HB VST at 4 and 6 weeks after the challenge, whereas the second subject had a persistent positive HB VST. This subject then had a second HB-sting challenge and tolerated it without reaction.

DISCUSSION

The results indicate that up to 7% of blood donors will have venom-specific IgE antibodies, as measured by immunoassay, during the late summer and fall. To qualify as blood donors at our institution, individuals must be in good general health and satisfy many other criteria and, thus, are probably representative of the healthy adult population in Rochester, Minn. The 7% prevalence figure for venom sensitization is likely a minimal estimate because the blood donors were screened by venom RAST, a less sensitive procedure than venom skin testing,¹¹ which was used by Golden et al.³ in their study. Considering differences in criteria for positivity of VSTs and venom RAST assays, as well as geographic and climatic differences, the 7% prevalence estimate for venom sensitivity in our study is comparable to that found in other published studies.^{3, 5, 6} In this study and other published studies, however, the prevalence rate for venom sensitization is higher than the proportion of persons with histories of allergic reactions to stings (<1% to 6%).¹⁻⁵ This implies that in many subjects without a history of generalized reactions to Hymenoptera stings, elevated venom-specific antibodies may be transient and/or clinically irrelevant.

The second phase of the study involving the advertisement group and control group was undertaken to evaluate these possibilities. Most persons stung by Hymenoptera will sustain only pain and mild erythema at the sting site. We subsequently assessed whether subjects recently stung with such a normal reaction would have different immunologic responsiveness (as determined by VSTs and *in vitro* immunoassays) than subjects not stung in the past 3 years. It is evident that most subjects with histories of systemic reactions

after Hymenoptera stings will have elevation of venom-specific IgE, as determined by skin testing and immunoassay.¹²⁻¹⁵ However, even in this group, the presence of venom-specific IgE antibodies is indicative of clinical sensitivity only in 40% to 60% of subjects studied.^{10, 15} The presence of these IgE antibodies therefore does not equate with clinical sensitivity.

Data from the newspaper advertisement group suggest that a recent field sting is associated with a skin sensitization rate of 15% at a venom test concentration of 0.1 $\mu\text{g/ml}$ and a skin sensitization rate of 36% at a venom test concentration of 1.0 $\mu\text{g/ml}$. Eight sting challenges were tolerated without reaction in seven patients in the newspaper advertisement group, all of whom had positive VSTs. In addition, persistently positive HB VSTs (both at 0.1 and 1.0 $\mu\text{g/ml}$) were found in one of 11 normal control subjects (9%) after deliberate HB stings in a hospital setting. This individual also tolerated a second HB-sting challenge without reaction 6 weeks later. Thus, nine sting challenges were tolerated without reaction in eight patients who had a negative history of a significant reaction to a sting but who had positive VSTs. Although the number of patients undergoing deliberate insect-sting challenges was too small to establish a precise estimate of risk for subsequent systemic reactions, this risk is probably low (<10% to 15%). The difference in VST positivity rates (15% to 36% in the recently stung members in the newspaper advertisement group versus 9% in the deliberately stung control group members) may be due in part to a greater propensity by vespid venoms for sensitization or in part to the imprecision of the latter figure because of the relatively smaller number of normal control subjects stung. Moreover, the sensitization rate in children may differ from that in adults, although the relatively small number of children in the newspaper advertisement group did not permit us to address this issue. Support for the hypothesis that vespid venoms are more apt to sensitize than HB venom is provided by data from Hoffman et al.,⁶ who reported a sensitization rate of only 6% in 16 patients recently stung by HB without generalized reactions, and by data from Jarisch et al.,¹⁶ who found elevated IgE antibodies to HB venom phospholipase A in 26 of 250 (10.4%) plasma donors. Our own data demonstrate that skin reactivity to W or vespid venoms tends to persist for longer periods than does skin reactivity to HB venom. Also, two subjects in the newspaper advertisement group with positive skin tests had multiple stings, which may increase the chances for sensitization.

An additional finding in this study was that there was a higher rate of positive VSTs in individuals with-

out a history of sting reaction with a venom concentration of 1.0 $\mu\text{g/ml}$ versus 0.1 $\mu\text{g/ml}$. This information is consistent with that of Patrizzi et al.¹⁷ who performed prick and intracutaneous HB VSTs in 20 nonatopic subjects and in 15 atopic subjects with pollinosis, 31 of whom had sustained previous HB stings without significant reaction. Nine subjects had positive HB VSTs at a concentration of 1.0 $\mu\text{g/ml}$, whereas only one of 35 subjects had positive HB VSTs at 0.1 $\mu\text{g/ml}$. In addition, Georgitis and Reisman,¹⁸ using commercially available Hymenoptera venoms, have reported that 26 of 56 (46%) insect-nonallergic patients exhibit positive VSTs at a concentration of 1.0 $\mu\text{g/ml}$. The above studies suggest that there is an appreciable rate of clinically irrelevant positive VSTs (eg., positive VSTs without history of systemic sting reaction) obtained at 1.0 $\mu\text{g/ml}$. The situation is clouded, however, since Hunt et al.¹⁹ have reported that in 30 subjects with a history of a systemic reaction to a sting, 100% had positive VSTs at 1.0 $\mu\text{g/ml}$, whereas only 77% had positive VSTs at 0.1 $\mu\text{g/ml}$. Thus, although a high percentage of potentially clinically irrelevant positive VSTs will be obtained at 1.0 $\mu\text{g/ml}$, sensitization will not be demonstrated in nearly 20% of patients with a history of a systemic reaction if VST is confined to lower venom concentrations. This overlap in VST reactivity between insect sting-allergic and nonallergic populations has been pointed out previously²⁰ but is still not appreciated by many clinicians. The above findings emphasize the importance of a detailed history in the evaluation of all patients with suspected Hymenoptera sensitivity. In summary, we have demonstrated that after an uneventful sting, some subjects may become sufficiently sensitized so as to develop a positive VST, but such VSTs cannot be used to predict a future systemic reaction. In addition, we have demonstrated that, although there are a significant number of individuals in a blood donor population with elevated venom-specific IgE, only a minority of these patients will have a history of previous systemic reactions to Hymenoptera stings. The significance of elevated specific IgE in patients with a negative history is not completely known, but negative sting challenges in small numbers of these patients in our study suggest that such elevations are usually not of clinical significance.

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