

Insect venom allergy: a prospective case study showing lack of correlation between immunologic reactivity and clinical sensitivity

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This case report demonstrates the lack of correlation between clinical sensitivity to insect venoms and immunologic reactivity as indicated by the presence of venom-specific IgE. A 20-yr-old venom collector was monitored over a 3-yr period with measurements of venom-specific IgE (skin test and RAST) and venom-specific IgG. In the first year of venom collection, multiple stings were tolerated with no reaction. In the second season, she had an anaphylactic reaction after a yellow jacket sting. Subsequently, there was a rising titer of serum yellow jacket and bee venom-specific IgE and positive skin-test reactions. In the third season, yellow jacket, hornet, and bee venom skin tests remained positive and serum IgE antibody titers remained elevated. Stings from all three insects were tolerated with no reaction. Throughout the 3-yr course, serum venom-specific IgG remained low and unchanged. The factors other than IgE-modulating clinical anaphylaxis, perhaps responsible for this clinical and immunologic dichotomy, are unknown. These observations add a further complication to the choice of patients for venom immunotherapy. (J ALLERGY CLIN IMMUNOL 68:406, 1981.)

The use of pure insect venoms for the diagnosis and treatment of stinging insect hypersensitivity has uncovered complexities of the relationship between immunologic reactivity, as indicated by the presence of venom-specific IgE, and clinical sensitivity. Several observations have already indicated that the presence of venom-specific IgE, as measured by skin test or in the serum by the RAST, does not necessarily indicate that an anaphylactic reaction will occur with subsequent exposure to venom.¹⁻³ This observation has great significance in appreciating the natural history of this disease process and the suggested effects of any immunotherapeutic regimen.

This lack of clinical and immunologic correlation is conclusively demonstrated in this prospective study of an individual who collected insect venoms. During the course of her occupation, she did develop a systemic sting reaction. Despite the persistent presence

of venom-specific IgE, further stings were tolerated without difficulty. Her immunologic response, measured prior to and after the sting reaction, and clinical exposure are the subjects of this case report.

METHODS

Serum venom-specific IgE (RAST)

Specific IgE antibodies to bee, yellow jacket, and hornet venoms were measured by the RAST, as previously described.⁴ One milligram of venom protein was used to couple to 200 cyanogen bromide-activated discs. Results are expressed as percent of net binding of a serum pool from ragweed-sensitive patients to ragweed discs. A net binding to the venom disc >10% was regarded as significant. The background activity bound when normal human serum was assayed was 0.7% for ragweed discs and varied between 0.7% and 1.5% of the total activity added for the venom discs. The maximal binding of the ragweed standard went up to 15% of the total activity.

Serum venom-specific IgG (radioimmunoassay)

Serum venom-specific IgG was determined by a solid-phase radioimmunoassay using ¹²⁵I-labeled protein A.⁵ The same venom-coupled discs used for the IgE antibody assay were used. A serum with a high titer of yellow jacket venom-specific IgG and another serum with high-titered bee venom-specific IgG were used as positive standards. Fifty microliters of a 1:50 dilution of the standard serum or

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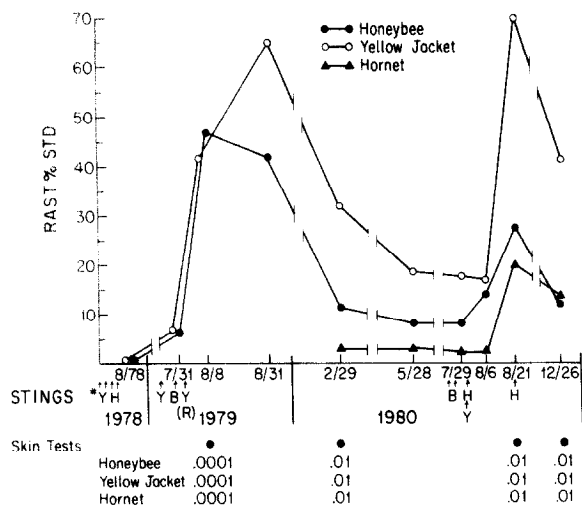


FIG. 1. Relationship of insect stings to serum venom-specific IgE titers and venom skin-test reactivity. Insect stings are depicted (arrows) below the time course. Asterisk (1978) indicates multiple yellow jacket and hornet stings. The systemic reaction (*R*) occurred on July 31, 1979. Skin-test reactions are indicated in $\mu\text{g}/\text{ml}$ of venom. Serum venom-specific IgE titers (RAST) are expressed as percent of a positive standard.

the test sera in borate-buffered saline containing 0.2% ovalbumin and 1% Tween were added to each tube containing a venom-coupled disc. After incubation for 2 hr at room temperature, the discs were washed three times in buffered saline. Fifty microliters containing 50 ng of radiolabeled protein A were then added. After a 90-min incubation at room temperature the discs were washed three times with buffered saline and the radioactivity bound was determined in a gamma counter. The background activity for normal human sera was about 1% of the total activity added. The binding of the standard serum at a 1:50 dilution was about 13% of the total activity. Results are expressed in arbitrary units, based on the percent net binding of the total activity. All serum samples were assayed for venom-specific IgE and IgG at the same time.

Skin testing

Intradermal skin tests were performed with serial dilutions of yellow jacket, hornet, and bee venoms obtained by electrical stimulation⁶ and on one occasion, with venoms obtained by venom sac extraction, purchased from a commercial source (Pharmacia Laboratories, Piscataway, N. J.). Freshly prepared dilutions of venoms were prepared prior to testing. For testing, venom concentrations ranged from 1 $\mu\text{g/ml}$ to 0.0001 $\mu\text{g/ml}$; 0.02 ml was injected intradermally into the upper arm. Normal saline diluent with 0.2% human serum albumin and histamine were used as controls.

CASE REPORT

Clinical history and immunologic studies

J. D., a 20-yr-old nonatopic woman, was initially seen during the summer of 1978, at which time she worked as a

venom collector. This was her first year in that occupation. Venoms from honeybees and vespids were collected by the method of electrical stimulation. She had been stung several times in childhood without any difficulty.

Her clinical course and immunologic studies are depicted in Fig. 1. During 1978, she experienced numerous yellow jacket and hornet stings without adverse reactions. Serum analysis in August 1978 showed undetectable levels of bee and yellow jacket venom-specific IgE.

In the summer of 1979, she resumed venom collecting. In mid-July 1979, she had one uneventful yellow jacket sting. On July 27, she was stung on the arm by a honeybee and had a slight local reaction. On July 31, she had one yellow jacket sting on her right arm. Within a few minutes she developed an acute anaphylactic reaction characterized by generalized hives and facial swelling. There were no cardiovascular or respiratory symptoms. The acute symptoms were treated with epinephrine and antihistamines and she recovered uneventfully. A serum sample taken at the time of the acute reaction showed low titers of bee and yellow jacket venom-specific IgE. Approximately 1 wk later, there was a marked rise in these antibody titers (yellow jacket venom RAST, 42%; bee venom RAST, 47%). Skin testing done at this time showed fairly marked immediate skin reactions to 0.0001 $\mu\text{g}/\text{ml}$ of honeybee, yellow jacket, and hornet venoms (collected by electrical stimulation). A further serum sample 1 mo after the systemic reaction showed a continued rise in the yellow jacket venom-specific IgE titer (yellow jacket venom RAST, 65%; bee venom RAST, 42%).

After the systemic reaction, she was advised to avoid insect collection and was retired to the laboratory. There was no further venom exposure during the 1979 season.

Further evaluation was carried out in February and May of 1980. Skin tests in February showed continued but diminished sensitivity to the three insect venoms, with reactivity to 0.01 $\mu\text{g/ml}$. Reactions with the three commercial venoms were present at concentrations of 0.1 $\mu\text{g/ml}$. Titers of serum bee and yellow jacket venom-specific IgE continued to fall. However, the yellow jacket venom titer did remain elevated (RAST 20%, May 1980). After a thorough discussion, she desired to continue as a venom collector during the 1980 season. Emergency medication was kept on hand at all times; venom immunotherapy was not given. During the summer of 1980, she had several honeybee stings, several hornet stings, and one yellow jacket sting, all without adverse reaction. On July 24 and 25, she had honeybee stings on her arm and foot, with only slight local reactions. Serum was taken on July 29 and showed persistence of the mild elevation in titers of bee and yellow jacket venom-specific IgE. On July 31, 1980, 2 days later, she was stung by a bald-faced hornet twice, on the arm and shoulder, and once on the knee by a yellow jacket. Blood taken 1 wk later on August 6, 1980, showed a slight rise in bee venom-specific IgE. On August 20, 1980, she was stung by a bald-faced hornet, with no reaction. Blood taken 1 day later on August 21, showed a marked rise in the titer of yellow jacket venom-specific IgE, with small but significant rises in bee and hornet venom-specific IgE (yellow

TABLE I. Levels of serum yellow jacket- and bee venom-specific IgG over the 2-yr period*

Date	Venom-specific IgG (units - % STD)	
	Yellow jacket	Honeybee
8/18/78	3.1	3.4
7/31/79 (sting reaction)	2.3	2.9
8/31/79	3.9	4.4
5/28/80	2.3	3.4
8/21/80	3.9	4.9
12/16/80	4.4	3.2

STD = standard.

*There were no significant changes in these antibody titers.

jacket venom RAST, 70%; bee venom RAST, 27%; bald-faced hornet venom RAST, 20%). Skin testing at this time showed the same degree of sensitivity found in February 1980.

Final skin tests and serum analysis in December 1980 showed a decline in the serum antibody levels, with persistent skin-test reactivity.

Because it is possible that a clinical anaphylaxis could have been dampened by the presence of venom-specific IgG, this assay was also carried out (Table I). Low titers of yellow jacket and bee venom-specific IgG were present throughout the time course from 1978 to 1980. Insect sting exposure did not influence these titers.

DISCUSSION

This case report with prospective immunologic evaluation shows the lack of correlation between immunologic reactivity and clinical sensitivity. After tolerating a number of stings uneventfully, this individual had a systemic reaction from a yellow jacket sting in late July 1979. Subsequently, she developed rising titers of yellow jacket venom- and bee venom-specific IgE. Throughout the next summer she retained evidence of immunologic reactivity, as indicated by continued significant skin-test reactions and elevated titers of serum venom-specific IgE. Despite antibody persistence, further stings by a yellow jacket, honeybees, and hornets were tolerated uneventfully. Both yellow jacket and hornet stings occurred at a time when venom-specific IgE was demonstrable by skin tests and RAST. Neither sting resulted in a systemic reaction but both led to rising antibody titers.

Her clinical protection cannot be attributed to the presence of venom-specific IgG. This antibody was present in low titer throughout her clinical course and did not change prior to or after the sting reaction.

It is interesting to speculate on the reason for the rise in bee venom-specific IgE, which occurred on two occasions. Both times she had been stung by a honeybee several days prior to stings by yellow jackets. In all probability, the rising titer of bee venom-specific IgE was the result of the bee sting, although there could have been some cross-sensitivity with yellow jacket venom.

The presence of IgE antibodies without clinical sensitivity adds a major complication to the problem of evaluation of patients who have had previous systemic reactions. The study performed at Johns Hopkins,¹ which showed the clinical efficacy of venom therapy, supports this observation. In this report, 40% of the patients with past histories of systemic reactions and positive skin tests and who received placebo and whole-body extract, failed to react when subsequently challenged with venom. Similarly, studies at the Mayo Clinic² showed that patients with positive skin tests failed to show signs of anaphylaxis after in-hospital intentional re-stings. Additional data relating to the lack of correlation between immunologic reactivity and systemic sensitivity come from patients with large local reactions. These patients often have high antibody titers without signs of generalized clinical sensitivity.³ It would appear that factors other than the presence of venom-specific IgE contribute to the occurrence of clinical anaphylaxis. Elucidation of these factors that apparently influence or modify clinical anaphylaxis, should lead to better selection of patients who require venom immunotherapy and perhaps to guidelines for the duration of such therapy.

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