

Demonstration of IgE and IgG antibodies against venoms in the blood of victims of fatal sting anaphylaxis

Donald R. Hoffman, Ph.D., Catherine L. Wood, M.D., Ph.D., and
Page Hudson, M.D. Greenville and Chapel Hill, N. C.

Nine people died from insect sting anaphylaxis in North Carolina from 1979 to 1981. Postmortem blood specimens from eight of these subjects were analyzed for IgE and IgG antibodies against venoms. All eight were RAST positive to at least one of the venoms. IgE and IgG anti-venom levels were comparable to those of a group of untreated sting-allergic individuals. RAST to venoms was also performed on several control groups of sera and from 3% to 50% positive RAST results were found. The highest incidence was in rural North Carolina outdoor workers. The incidence of positive RAST results in the sting-death group was significantly different from that in the control groups. This is the first demonstration of IgE antibodies against venoms in the sera of victims of fatal anaphylaxis from stings and adds further evidence for the role of IgE in sting anaphylaxis. (J ALLERGY CLIN IMMUNOL 71:193, 1983.)

It has been estimated that there are 40 to 50 deaths per year in the United States from anaphylactic reactions to Hymenoptera stings.^{1, 2} This is only a small percentage of the several million people who are allergic to stings, but it is the cause of a great deal of anxiety to many of these individuals. Several investigators have reported series of sting deaths.¹⁻⁶ The data reported include suspected insects, clinical cause of death, autopsy results, and other historical information. The overwhelming majority of cases reported had had no diagnostic testing to verify that they were sensitive to insect venom. In addition, no postmortem studies were performed to demonstrate IgE antibodies against the suspected venom.

In this article we report on a series of Hymenoptera venom anaphylactic deaths in which postmortem blood specimens were tested for the presence of IgE

and IgG antibodies against Hymenoptera venoms. This is the first report demonstrating the presence of IgE antibodies against the appropriate venom in the sera of individuals who died from sting-induced anaphylaxis.

MATERIALS AND METHODS

Specimens

Blood was obtained at time of autopsy or examination by the medical examiner and was mailed to our laboratory. Some specimens were collected as serum and immediately forwarded; others were collected as whole blood in sodium fluoride (blood alcohol specimens) and were stored for as long as 6 mo before arrival in our laboratory. Additional specimens were obtained at time of autopsy from cases of sudden unexpected death. The origins of other control specimens are described in the text.

Methods

The RAST was performed on each specimen for all five common venoms by the method previously described by our laboratory.⁷ IgG anti-venom antibodies were measured by a solid-phase heterogeneous ELISA assay described previously.⁸

From the Department of Pathology and Laboratory Medicine, East Carolina University School of Medicine, Greenville, and Office of the Chief Medical Examiner, Department of Human Resources, State of North Carolina, Chapel Hill, N. C.

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Reprint requests to: Donald R. Hoffman, Ph.D., Department of Pathology and Laboratory Medicine, East Carolina University School of Medicine, Greenville, NC 27834.

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Abbreviations used

RAST: Radioallergosorbent test

ELISA: Enzyme-linked immunosorbent assay

TABLE I. Historical and clinical data on sting-death patients from North Carolina 1979-1981

Subject No.	Age (yr)	Sex	Date	Emergency treatment	Previous history	Time from sting to death	Clinical symptoms	Autopsy
3838	62	M	7/79	Epinephrine	Yes	2 hr	Shock	Laryngeal edema
5390	67	M	7/80	No	Yes	30 min	Respiratory failure	Mild heart disease
7693	63	M	6/81	Epinephrine	No	25 min	Unknown	Pulmonary edema and congestion, sting site
8340	55	M	8/81	No	No	Minutes	No blood pressure	Laryngeal edema, sting site, emphysema
8397	31	M	9/81	No	No	Less than 30 min	Respiratory failure	Not done
8413	73	M	9/81	No	Large local	25 min	Cyanotic, asystolic	No findings
8706	51	M	10/81	No	No	30 min	Collapse	Not done
9035	45	M	12/81	No	No	Less than 30 min	Angioedema, burning, felt sick	General edema, sting site, cardiomegaly, atherosclerosis
GDSN	31	M	6/81	No	No	Less than 1 hr	Seizure, respiratory failure	Not done

TABLE II. RAST results for sting-death victims

Subject No.	Probable insect	RAST (percent binding minus nonspecific)*				
		B	YJ	YH	WFH	PW
3838	PW	1.9	4.6	3.5	4.1	3.8
5390	YJ†	0	2.2	0.7	3.9	4.1
7693	PW	0	1.6	0.8	0.7	4.7
8340	YJ	0	10.5	4.2	1.1	0
8397	YJ	3.2	7.4	2.4	1.1	1.3
8413	YJ, multiple	0.8	1.8	0.6	0	0.7
8706	YJ, multiple	0	3.0	2.6	0	2.2
9035	YJ or PW	0	0.7	0	0.5	1.8

B = honeybee; YJ = yellow jacket; YH = yellow hornet; WFH = white-faced hornet; PW = paper wasp.

*Positive was defined as twice nonspecific binding (0.5% for bee, 0.7% for vespids). Ranges observed after nonfatal reactions 0 to 58.2% binding. The RAST values for the sting-death group are not significantly different from the RAST results from non-fatal reactors tested 6 mo or more after the last sting episode.

†Victim was stung uneventfully 10 days before.

Summaries of the historical and clinical data for all nine subjects are given in Table I. The victims were all men, ages 31 to 73 yr. Two had previous histories of systemic reactions, and one had a previous history of a large local reaction. Two were treated with epinephrine. One patient had previously received whole-body extract immunotherapy (3838), but therapy had been discontinued for several years. All died within 2 hr of the sting, seven of the nine within 30 min. Autopsies were performed on six subjects, yielding relevant findings in four cases. Clinical findings before death were reported in eight cases and were variable. Occupations included construction workers, farm workers, church caretaker, and retired. One of the victims was stung while in an automobile, another while opening a garage.

The RAST results are shown in Table II, along with the insect implicated by history. In all eight cases the suspected insect was either yellow jacket or paper wasp. All eight victims' blood specimens gave positive RAST results to at least one of the suspected insect venoms. Five blood specimens were negative to honeybee and two were negative to paper wasp; all eight were positive to yellow jacket venom. As a control, a similar blood specimen from a patient who died from penicillin anaphylaxis was tested and found to be negative to all five venoms and positive to penicilloyl. IgE antibodies against the appropriate venom were demonstrated in the blood specimens from all of the victims of fatal sting anaphylaxis.

IgG antibody levels to yellow jacket and paper wasp venom were measured for all eight blood specimens. Levels ranged from 0.10 to 0.58 ELISA units with a mean of 0.34 and a standard deviation of 0.20.

Patient data

Information concerning patient histories, circumstances of death, and autopsy findings was supplied by the Office of the Chief Medical Examiner for North Carolina. In several cases additional information was obtained from the regional medical examiners or victims' physicians.

RESULTS

Nine victims were reported to have died from sting anaphylaxis in North Carolina from 1979 to 1981. Blood specimens were obtained from eight of these.

TABLE III. Venom RAST in various populations

Group	Venoms tested	Percent positive
Randomly selected adults, Nebraska (n = 112)	B, YJ	3
Pollen-allergic, California (n = 10)	B, YJ, YH, WFH, PW	10
Normal bee sting reaction (n = 16)	B	6
Recent systemic to bee (n = 44)	B	96
Recent large local to bee (n = 40)	B	80
Sting fatality, North Carolina (n = 8)	B, YJ, YH, WFH, PW	100
Sudden death, rural North Carolina (n = 10)	B, YJ, YH, WFH, PW	50

B = honeybee; YJ = yellow jacket; YH = yellow hornet; WFH = white-faced hornet; PW = paper wasp.

IgG antibody levels for 30 consecutive pretreatment sera from patients with systemic reactions to yellow jacket and/or paper wasp gave a range of 0.05 to 0.64 ELISA units with a mean of 0.28 ± 0.14 . The matched post-venom-treatment sera gave levels from 0.21 to 1.10 ELISA units with a mean of 0.50 ± 0.22 . The IgG levels from the sting-death cases were similar to those seen in untreated venom-allergic patients.

There are very limited data available on the incidence of venom allergy and IgE antibodies against venoms in unselected populations. Golden et al.⁹ recently reported that of 187 random subjects 4% had histories of systemic reactions, 17% had histories of large local reactions, and over 12% of those with no history of an adverse reaction to a sting had a positive venom skin test. RAST results were similar. A study from Alberta¹⁰ showed that 3% of office workers gave histories of previous sting reaction and that 12% of those without a previous history were RAST positive to either honeybee or yellow jacket venoms. Some studies from our laboratory are presented in Table III. A group of randomly selected adults from Nebraska showed 3% RAST-positive results when RAST was performed with bee and yellow jacket. A group of inhalant allergy patients from northern California showed 10% of patients positive to at least one of the five venoms. A group of patients who had recently been stung by honeybees and experienced only a normal reaction was 6% RAST positive. Patients with recent large local reactions to bee were 80% RAST positive and those with recent systemic reactions were 96% RAST positive. A group of 10 sera were obtained at autopsy from cases of sudden unexpected death in rural eastern North Carolina. Half of these sera were RAST positive to at least one of the five venoms. Eight of these individuals had been employed in either farming, logging, or construction. Medical examiner investigation and autopsy results indicated that all of these patients died from trauma or disease; in no case was insect anaphylaxis a reasonable possibility for cause of death.

The RAST results for the sting-death victims were compared by means of a chi-square test with the results for the various negative control populations. The 100% positive result for eight specimens was different at a significance level of $p < 0.01$ for all of the control groups except the rural sudden unexpected death group, where $p = 0.07$. This strongly suggests that the results are significant.

DISCUSSION

Although a fatal outcome to a sting is a relatively rare occurrence, the possibility generates a great deal of anxiety among those persons who are sting allergic. In a medical-legal sense, verification of sting anaphylaxis can be important, since it is considered to be a form of accidental death as opposed to a natural cause. This can be very important to the victims' survivors in that they may receive payment from accidental death policies and from double indemnities for accidental death, which are part of many life insurance policies.

IgE antibodies against the appropriate venom or venoms were found in all of the postmortem blood specimens obtained from victims of fatal sting anaphylaxis. This incidence was statistically significant when compared with all control groups, except one composed of cases of sudden unexpected death in rural eastern North Carolina males, where $p = 0.07$. Levels of IgG antibodies against venoms and IgE/IgG ratios were comparable to those seen in untreated venom-allergic individuals.

All of the cases that were referred to us had clearcut histories of a sting, and death occurred within 2 hr after the sting. The incidence of IgE antibodies in the general population without previous history of sting reactions may be much higher than has been estimated in the past. This incidence appears to be as great as 50% in rural southern males employed in outdoor occupations and a level of 12% has been reported for office workers from western Canada.¹⁰ This high incidence of positive RAST results makes it impossible to use postmortem serologic analysis to assign venom

anaphylaxis as a cause of death in cases without supporting historical and autopsy findings.

This is the first report of the detection of IgE antibodies against venoms in the blood of victims of fatal sting anaphylaxis. These findings lend further support to the large amount of evidence indicating that IgE antibodies play an essential role in sting anaphylaxis.¹¹ The serologic studies did not show any significant differences in either IgE or IgG levels between specimens from fatal and nonfatal reactors. RAST appears to be a useful test for confirming histories of fatal anaphylaxis. The IgE antibodies appear to be able to survive in unseparated blood with sodium fluoride preservative for 6 mo at refrigerator temperature before being assayed. A serum specimen should be promptly drawn and sent for analysis or stored frozen for the most reliable results. The community of medical examiners and pathologists should be made aware of the usefulness of RAST for helping to confirm a postmortem diagnosis of anaphylaxis.

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