

A prospective study of the natural history of large local reactions after Hymenoptera stings in children

Large local reactions are a frequent occurrence after insect stings. We prospectively studied the demography, immunology, and significance of these reactions in the pediatric age group. Most children (83%) who have had large local reactions have positive skin test results to one or more venoms. Elevated amounts of venom-specific IgE antibody are usually present. Over 3 to 5 years, allergic sensitivity declines, as evidenced by less positive skin test results and lower levels of antivenom IgE antibodies. Most significantly, of 113 repeat stings, only 2% resulted in a systemic reaction. (J PEDIATR 104:664, 1984)

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THE PATHOPHYSIOLOGY, IMMUNOLOGY, and treatment of systemic reactions to insect stings, which are estimated to occur at a rate of between 0.4% to 4% in the general population,^{1,2} have been the subject of most of the recent research efforts in Hymenoptera sensitivity. Large local reactions occur much more commonly, perhaps in as many as 17% of the population.³ These reactions consist of extensive and persistent swelling at the site of the sting; infrequently, an area the size of an entire extremity may be involved. The likelihood of a sting resulting in a systemic reaction in a patient who has had a large local reaction has been reported to be as high as 33%, with 15% of these reactions being severe.⁴

In this prospective study, we characterized large local reactions in a pediatric population with regard to demog-

raphy, degree of allergic sensitivity, and risk of subsequent systemic reactions.

METHODS

One hundred twenty-five children, aged 2 to 17 years, with a history of a prior large local reaction after a Hymenoptera sting were referred to the Allergy Clinic at The Good Samaritan Hospital between November 1978 and October 1981. A large local reaction was defined as induration measuring >5 cm in diameter and persisting for longer than 24 hours in the absence of any concomitant symptoms or signs of a systemic reaction. The initial evaluation consisted of a thorough medical and allergic history, with emphasis on all prior insect sting reactions, a physical examination, venom skin testing, and the measurement of venom-specific IgE antibodies. We tried to include children with milder reactions that might not otherwise have brought them to the attention of an allergist.

Venom skin testing. Honeybee, yellow jacket, yellow hornet, white-faced hornet, and *Polistes* (wasp) venoms, supplied by Pharmacia Diagnostics (Piscataway, N.J.), were applied and measured in the standard fashion⁵; a 2+ reaction (wheal size, 5 × 5 mm or greater) was considered positive. The minimum concentration of venom required to elicit a positive reaction was scored as follows: 1 point for

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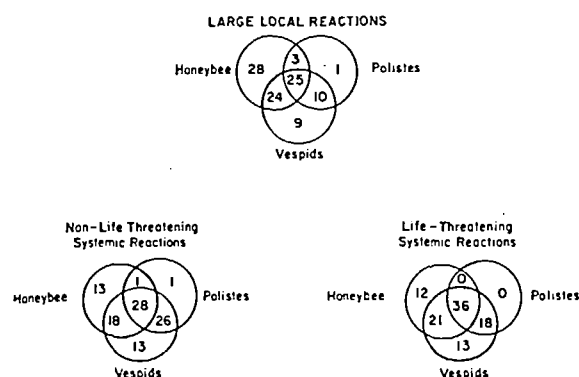


Fig. 1. Distribution of venom skin sensitivity by percent in children with large local reactions, non-life-threatening systemic reactions, and life-threatening systemic reactions.

1+ at 1.0 $\mu\text{g/ml}$, 2 points for 2+ at 1.0 $\mu\text{g/ml}$, 3 points for 1+ at 0.1 $\mu\text{g/ml}$ and 2+ at 1.0 $\mu\text{g/ml}$, 4 points for 2+ at 0.1 and 1.0 $\mu\text{g/ml}$, and so on, to a maximum of 7 points. Because samples of the initial venoms used were not available, comparison of simultaneous skin tests with early lots versus recent lots was not possible. However, on the basis of enzymatic assays for hyaluronidase and phospholipase activity, the potency of recent venom lots has been equivalent to that of those used for initial skin testing and treatment (data on file, Pharmacia Diagnostics). We have, moreover, assayed several different lots by histamine release and found them to be identical.

Antibody measurements. IgE antibodies against yellow jacket venom and honeybee venom were measured by a RAST technique previously described and are expressed in nanograms per milliliter.^{6,7}

Study protocol. Patients were evaluated annually with an interval medical and sting history, physical examination, venom skin tests, and venom-specific IgE antibody determinations. In addition, detailed accounts of the results of accidental stings were recorded promptly after the stings. A non-life-threatening reaction was defined as a systemic anaphylactic reaction with only cutaneous symptoms (erythema, pruritus, urticaria, or angioedema). A life-threatening reaction was defined as a systemic reaction that included laryngeal, respiratory, or cardiovascular symptoms.

RESULTS

Demography. In 105 (84%) of the 125 patients evaluated for sting-induced large local reactions, results of one or more venom skin tests were positive. The mean age (Table I) of this group was 10.1 ± 0.3 years, slightly higher than the mean age (8.1 ± 0.8 years) of the 20 children who had negative skin test reactions. There were no significant

Table I. Demography of large local reactions in children

	Positive venom skin test reaction	Negative venom skin test reaction
Number	105	20
% Male	57	48
Age (yr)		
Mean	10.1 ± 0.3	8.1 ± 0.8
Range	2.5 to 17.0	2.1 to 15.5
Prior large local reaction (%)	65	50
Atopic history (%)		
Personal	38	45
Family	68	70
Family history of Hymenoptera reaction		
Large local reaction	26	40
Systemic reaction	20	25

differences between the groups with regard to the proportion with large local reactions prior to the recent reaction that led to allergy clinic referral, personal or family atopic history, and personal or family history of adverse Hymenoptera reactions.

Venom skin tests. Twenty-eight percent of children with large local reactions were sensitive only to honeybee venom (Fig. 1). An additional 52% of the group had sensitivity to honeybee venom in conjunction with other venom sensitivities. The increased frequency with which isolated honeybee sensitivity occurred in large local reactors (28% as compared to 13% in mild systemic reactors and 12% in more severe systemic reactors) was significant at $P < 0.005$. The proportion of patients with honeybee sensitivity, alone or in combination with other venom sensitivities, was also significantly greater in large local reactors (80%) than in mild systemic reactors (60%, $P < 0.001$) or severe systemic reactors (69%, $P < 0.05$).

Twenty-five percent of large local reactors had skin test scores of 1, indicating a low degree of skin reactivity; only 10% of systemic reactors had this low score (Fig. 2). Similarly, only 15% of large local reactors had scores of 6, whereas nearly 40% of the systemic reactors had this high level of skin reactivity. A rank-order analysis of these data, performed using the Mann-Whitney U test, demonstrated that positive skin test results were elicited with lower concentrations of venom in the systemic reaction group as compared with the large local reaction group for each venom type (honeybee, $P < 0.02$; vespid, $P < 0.001$; *Polistes* (wasp), $P < 0.001$).

The most current venom skin test results were compared with those performed at the beginning of the study. The interval between data ranged from 1 to 5 years (mean 2.2 ± 0.1 years). A "change" in skin test sensitivity was defined as at least a 10-fold difference in the lowest venom

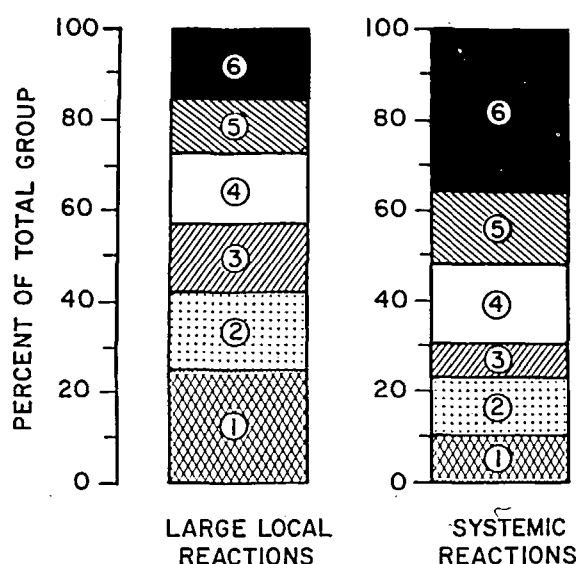


Fig. 2. Degree of vespid skin sensitivity in children with large local reactions and systemic reactions. Numbers 1 to 6 refer to skin test score (see text and Table I). Skin test scores of ≥ 6 are considered as 6 for the purposes of this figure.

concentration that elicited a 2+ skin test response. Separate comparisons for honeybee and vespid venoms were made for each patient, with the vespid score obtained by following the most positive of yellow jacket, hornet, or wasp venoms. Of 53 children who had initial positive vespid skin test responses, 32 (60%) had decreased skin test sensitivity with time (Table II). Patients who avoided stings were more likely to have a decrease in sensitivity than those who were stung ($P < 0.008$). No significant differences were found between the stung and unstung patients with regard to decreases in skin test sensitivity to honeybee venom (Table III). Again, of 58 children who had initial positive honeybee skin test reactions, 35 (60%) had decreased with time (Table III).

Venom-specific IgE antibody measurements. Five (16%) of 32 children with positive yellow jacket venom skin tests at the time of the initial evaluation had undetectable amounts of yellow jacket venom IgE antibody. The rate of RAST-negative positive skin test reactions ranged from 15% to 20%, for honeybee and yellow jacket venom, respectively.

The geometric mean* yellow jacket IgE antibody level in the 32 individuals with positive yellow jacket venom skin test reactions was 9.5 ng/ml (7.4 to 12.3 ng/ml) at the time of diagnosis (Table III). This had decreased to 4.6 ng/ml (3.5 to 6.0 ng/ml) when measured 2 to 3 years later. Children who avoided intercurrent stings experienced a

Table II. Changes in vespid and honeybee skin sensitivity in children with large local reactions

	Stung		Not stung		Total	
	n	%	n	%	n	%
Vespid						
Increased	7	24	1	4	8	15
No change	10	35	3	13	13	25
Decrease	12	41	20	83	32	60
Total	29		24		53	
Honeybee						
Increased	4	13	0	0	4	7
No change	9	29	10	37	19	33
Decreased	18	58	17	63	35	60
Total	31		27		58	

decline in the amount of venom-specific IgE antibody in their sera ($P < 0.002$), whereas no significant decline (paired *t* test) occurred in 19 stung patients (Table III).

The initial geometric mean honeybee IgE antibody level in 42 children was 5.7 ng/ml (4.3 to 7.5 ng/ml, which decreased to 2.9 ng/ml (2.2 to 3.8 ng/ml) (Table III). Again, unstung children showed a decline in the amount of venom-specific IgE antibody in their sera ($P < 0.003$), whereas no significant decline occurred in 27 stung patients.

Consequences of subsequent stings. One hundred thirteen stings in 54 children resulted in one potentially life-threatening systemic reaction (mild to moderate laryngeal edema), one non-life-threatening systemic reaction, 43 (38%) large local reactions, and 68 (60%) normal reactions. In many instances, the insect responsible for the sting was not known. However, 53 stings occurred in which the insect was positively identified or the child had a skin test positive reaction to all insect groups (honeybee, vespid, and *Polistes*), making any sting relevant. The stings that met these criteria resulted in a similar distribution of sequelae (one non-life-threatening systemic reaction, 22 large local reactions, and 30 normal reactions). Eleven of 12 stings that would be expected to be tolerated with impunity (the culprit was identified and the patients had negative skin test reactions to the venom of that insect) resulted in normal reactions. The other patient developed a large local reaction after the sting.

Sting outcome patterns in individual patients were examined. Thirty-five of the 54 stung patients received only one sting, with a 70%:30% distribution of normal reactions/large local reactions. The 19 patients who received multiple stings over time showed all types of patterns, including normal reactions, large local reactions, and various proportions of each consequence. The two patients who sustained systemic reactions also had a normal reaction to an intercurrent sting.

*Geometric mean antibody level = (Geometric mean - SEM) - (Geometric mean $\pm$ SEM).

Table III. Changes in yellow jacket and honeybee venom-specific IgE antibody level (ng/ml)

	Stung		Not stung		Total	
	Mean*	Range	Mean	Range	Mean	Range
Yellow jacket						
At diagnosis	8.7	6.2 to 12.3	11.2	7.8 to 16.2	9.5	7.4 to 12.3
After 2 to 3 yr	6.2	4.1 to 9.3	2.9	2.2 to 3.8	4.6	3.5 to 6.0
Paired <i>t</i> test	<i>P</i> = NS <i>n</i> = 19		<i>P</i> = <0.002 <i>n</i> = 13		<i>P</i> = <0.005 <i>n</i> = 32	
Honeybee						
At diagnosis	5.4	3.9 to 7.4	6.3	3.7 to 10.6	5.7	4.3 to 7.5
After 2 to 3 yr	3.6	2.7 to 5.0	2.0	1.2 to 3.2	2.9	2.2 to 3.8
Paired <i>t</i> test	<i>P</i> = NS <i>n</i> = 27		<i>P</i> = <0.003 <i>n</i> = 15		<i>P</i> = <0.003 <i>n</i> = 42	

*Geometric mean = (Geometric mean - SEM) - (Geometric mean + SEM).

The most recent presting venom skin test score and venom-specific IgE level for stings with known culprits were evaluated to determine whether they might aid the physician in predicting sting outcome. Neither measure of allergic sensitivity proved helpful in this endeavor.

DISCUSSION

Large local reactions, which are more extensive and persist longer than the usual swellings expected after Hymenoptera stings, resemble the late cutaneous response of Umemoto et al.⁸ and the late-phase reaction of Solley et al.,⁹ which have been shown to be IgE mediated. In support of the allergic cause of most of these reactions, we found that a high proportion (84%) of children who have had large local reactions have positive venom skin test reactions. In fact, this incidence of positivity is almost as high as the 89% figure we have found in children with sting-induced systemic reactions.¹⁰

Previous reports have found a lower rate of venom sensitivity in large local reactors. Albrecht et al.⁴ found that 68% of 40 patients had at least one positive venom skin test reaction; however, the highest concentration of venom extract used for skin testing was only 0.1 µg/ml (10-fold lower than the accepted guidelines). Green et al.,¹¹ found that about half of a group of 22 patients, ranging in age from 4 to 74 years, with large local reactions had venom-specific IgE antibodies, detected by either the venom skin test or RAST (40% of the venom skin test results were positive). The lower occurrence of positive venom skin tests in their patients as compared with ours may be related to several factors: (1) Our study involved only children, who might have a higher rate of skin sensitivity to venoms than do adults. This seems unlikely, however, because we find that adults with large local reactions have nearly the same rate (80%) of positive venom skin test reactions as do children (Golden DBK: Personal communication). (2) Green et al. prepare their own venoms for testing purposes, and it is unknown how

their venoms compare in allergenicity to those obtained from the usual commercial sources. (3) As in the Albrecht report, the highest tested venom concentration was 0.1 µg/ml. (4) The 40% figure stated in their report is derived from an analysis inherently different than that used in our study. Inasmuch as allergy to one type of Hymenoptera (honeybee or vespid [yellow jacket or hornet], or *Polistes*) is sufficient to make a diagnosis of insect sting allergy, our data are reported as the proportion of patients with one or more positive venom skin test reactions. Green et al., in contrast, evaluated 21 patients for positive or negative skin test results individually to the venoms of each of three types of Hymenoptera (honeybee, yellow jacket, and hornet) and reported that 25 (40%) of 63 skin test results were positive. In fact, 11 of 21 patients had at least one positive skin test reaction, giving, by our criteria, a 52% rate of venom skin sensitivity, a figure that more closely approaches the proportion we found.

Examination of the distribution of positive venom skin tests disclosed a higher prevalence of honeybee sensitivity in large local reactors than in systemic reactors. A possible explanation for this observation is that the usual site of a honeybee sting is the unshod foot, and dependent regions of the body may be more likely to accumulate fluid, resulting in the manifestations of a large local reaction.

The proportion (60%) of children with large local reactions in whom skin sensitivity decreased by at least a factor of 10 was similar to that found in children with systemic reactions (58%).¹² Unstung children were significantly more likely to experience a decline in venom skin tests and underwent a significantly greater fall in venom-specific IgE antibody as compared with stung children. Thus, intercurrent stings slowed the loss of allergic sensitivity.

Albrecht et al.⁴ have reported that one third of patients with large local reactions are at risk for developing a systemic reaction after a subsequent sting. These figures, however, are artificially elevated by the retrospective

nature of the study and by the bias generated by the inclusion of persons who, at the time of the analysis for a systemic reaction, reported that they had had previous large local reactions. Individuals who have sustained a systemic reaction are much more likely to seek the care of a physician than those who have only had large local reactions. This factor results in an unknown denominator (i.e., how many individuals with large local reactions do not subsequently develop systemic reactions), and therefore tends to falsely elevate risk predictions. Our prospective study resolves some of this uncertainty. We found that two of 113 (2%) stings in children with previous large local reactions resulted in systemic reactions. The degree of allergic sensitivity measured either by venom skin tests or specific IgE antibody levels that existed prior to subsequent stings was not predictive of sting outcome.

Knowledge of the natural history of a disease aids greatly in the analysis of the risk-benefit equation for various treatment modalities. Venom immunotherapy, which has proved efficacy for the prevention of subsequent systemic reactions in patients with histories of a systemic reaction and positive venom skin test results, has been proposed for treatment of large local reactors also. The use of venom injections in large local reactors might be contemplated to prevent progression to systemic reactions and to prevent subsequent sting-induced large local reactions. In view of the natural history of large local reactions in children, the risk of subsequent systemic reactions is low and therefore does not argue favorably for the use of a protracted and expensive treatment regimen.

No studies have been performed to document the efficacy of venom injections in the amelioration or prevention of subsequent large local reactions. Data from the treatment of mild *systemic* reactions in children suggest that it would probably prove effective for this purpose. We found, in a different study, that in addition to lowering the systemic reaction rate, large local reactions after subsequent stings occurred less frequently in patients given treatment (5% versus 33%; $P < 0.001$).¹³ This decrease in the occurrence of large local reactions was accompanied by a significant increase in venom-specific IgG antibody levels, a fact that effectively rules out a role for IgG in the

pathogenesis of these types of reactions. However, to administer venom immunotherapy in individuals who have had only large local reactions does not seem indicated, and we recommend that these individuals not receive such therapy.

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