

ORIGINAL ARTICLE

Outcomes of Allergy to Insect Stings in Children, with and without Venom Immunotherapy

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ABSTRACT

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BACKGROUND

Children are thought to “outgrow” the allergy to insect stings, but there are no reports documenting the natural history of this reaction. We studied the outcome of allergic reactions to insect stings in childhood 10 to 20 years afterward in patients who had not received venom immunotherapy and in those who had been treated.

METHODS

Between 1978 and 1985, we diagnosed allergic reaction to insect stings in 1033 children, of whom 356 received venom immunotherapy. We conducted a survey of these patients by telephone and mail between January 1997 and January 2000, to determine the outcome of stings that occurred in the period from 1987 through 1999.

RESULTS

Of the 1033 patients, 512 patients (50 percent) responded, with a mean follow-up period of 18 years, a mean duration of venom immunotherapy of 3.5 years in treated patients, and an incidence of stings of 43 percent. Systemic reactions occurred less frequently in patients who had received venom immunotherapy (2 of 64 patients, or 3 percent) than in untreated patients (19 of 111 patients, or 17 percent; $P=0.007$). Patients with a history of moderate-to-severe reactions had a higher rate of reaction if they had not been treated (7 of 22 patients, or 32 percent) than if they had received venom immunotherapy (2 of 43 patients, or 5 percent; $P=0.007$). In patients who had been treated and who had a history of mild (cutaneous) systemic reaction (i.e., one with only cutaneous manifestations), none of the 21 subjects who received stings had a systemic reaction.

CONCLUSIONS

A clinically important number of children do not outgrow allergic reactions to insect stings. Venom immunotherapy in children leads to a significantly lower risk of systemic reaction to stings even 10 to 20 years after treatment is stopped, and this prolonged benefit is greater than the benefit seen in adults.

MOST CHILDREN RECEIVE STINGS BY hymenopterans during the years of outdoor play. A history of systemic allergic reaction appears in the medical records of at least 0.8 percent of children, but the true prevalence among the pediatric population is likely to be higher and fatal reactions have been reported.^{1,2} In 1974, we reported the use of purified-venom immunotherapy in the treatment of a child³; four years later, a controlled trial of venom immunotherapy was reported.⁴ The unique features of allergy to insect stings in children led to our 1990 report showing that the majority of affected children have mild systemic allergic reactions to stings and do not require venom immunotherapy.^{5,6}

The perception among parents and physicians is that children generally “outgrow” this allergy, although no formal evidence in support of this hypothesis has been reported. This perception implies that virtually all children who have had systemic allergic reactions to stings will not have severe reactions when they are older and therefore do not need venom immunotherapy for protection. Our primary aim in the present study was to discover whether outgrowing the allergy to insect stings is common in children. Although the clinical outcome of a course of venom immunotherapy has been described in adults, there have been no long-term studies in children; our secondary aim was therefore to study the long-term outcome of the therapy in children. This information could be useful in the decision to discontinue venom immunotherapy.⁷ Here we report follow-up information on more than 500 children with a history of allergic reaction to insect stings who received stings in the 6 to 32 years after their first reaction.

METHODS

PATIENT POPULATION

Between 1978 and 1985, we diagnosed allergy to insect stings of varying severity in 1033 children, from among whom we recruited subjects for a prospective study of children with mild (cutaneous) systemic allergic reactions (those with primarily cutaneous manifestations) who received or did not receive venom immunotherapy. The design of the study and the patient population have been described previously^{5,6}; the study included randomized treatment as well as the observation of patients who refused randomization. Additional patients who did not undergo randomization were included in an interim

report on the nine-year follow-up (through 1987) of the outcome of field stings.⁸ The current survey of long-term outcomes included patients who had been enrolled in the previous study (1978 to 1982) as well as other children with a history of moderate-to-severe systemic allergic reactions and large local reactions who had been evaluated at our center during the period from 1978 to 1985 (Table 1). Here we present our observations of children who received stings after our previous survey, which was completed in 1987. The data reflect outcomes 6 to 32 years after the patient’s initial allergic reaction. None of the stings reported were laboratory challenge stings.

SURVEY

The long-term observation of the outcomes of insect stings received at intervals was approved by the joint committee on clinical investigation, the institutional review board of the Johns Hopkins Medical Institutions; subjects, their parents, or both gave written informed consent. The respondents included in the study were always the patients, and not their relatives. The telephone survey was the primary tool of the study. We used, with minimal modification, a brief list of standard questions that we have used as a tool to screen for allergic reactions to insect stings during the past 25 years. Initial ef-

Table 1. Allergy to Insect Stings Studied in 1033 Children at Johns Hopkins Medical Institutions, 1978–1987.

Type of Reaction and Group	No. of Patients	No Venom Immunotherapy	Venom Immunotherapy
Mild (cutaneous) systemic*	462	352	110
Patients enrolled, 1978–1982†			
Randomized		61	45
Not randomized		113	23
Additional patients (not randomized) enrolled, 1978–1985‡		178	42
Moderate-to-severe systemic	345		
Patients (not randomized) advised to undergo venom immunotherapy		99	246
Large local	226		
No venom immunotherapy		226	0

* In mild systemic (cutaneous) reactions, signs and symptoms are limited to the skin (urticaria and angioedema).

† These patients were studied by Valentine et al.⁶

‡ These patients were studied by Schuberth et al.⁸

forts were made to contact the family of a patient or the patient at the last known telephone number or by searching telephone-number databases. Of 1033 patients, 405 were reached by telephone. A final effort to contact the remaining 628 patients was made by forwarding the survey questionnaire to them through the Social Security Administration. The 107 patients who returned the questionnaire were then contacted by telephone to review and confirm their responses. A total of 512 patients were included in the survey.

This study identified and described the outcome of stings received by patients since 1987. The severity of the original reaction was determined by the investigator from the description in the medical records, and not by a new inquiry. Interviewers were not assigned to review the records of the original reaction and were unaware of the patients' original reactions. Interviewers were asked to confirm the details of the treatment and so were not blinded to this information. For the 521 subjects who could not be contacted, data from the National Death Index were obtained to determine whether any had died and the cause of any deaths.

REACTIONS

Patients were asked to describe their reactions and were provided with a standard list of questions about symptoms, the time course of the reaction, and treatment. Allergic reactions were graded according to severity. Large, local reactions caused an induration larger than 12 cm (5 in.) in diameter, with the size peaking within 24 to 48 hours after the insect sting and the reaction resolving within five days or more. Mild (cutaneous) systemic allergic reactions involved urticaria, angioedema, or both distant from the site of the sting but with no involve-

ment of other organ systems. Moderate systemic allergic reactions usually included signs and symptoms of a cutaneous reaction as well as discomfort in the throat or chest, mild symptoms of airway obstruction, light-headedness, and dizziness or mild hypotension. A severe systemic allergic reaction involved marked respiratory distress, severe dizziness, and marked hypotension or unconsciousness, or both, in addition to the signs of a cutaneous systemic reaction.

Mean values are shown with the standard deviation (\pm SD). The comparison of rates of reaction among patients who had received or had not received venom immunotherapy and the comparison of rates of reaction among patients with a history of mild or moderate-to-severe systemic allergic reaction were performed with the use of Fisher's exact test, and for each comparison the P values are two-sided.

RESULTS

We were able to contact 512 of the 1033 patients (50 percent), who agreed to complete the survey questionnaire (Tables 2 and 3). We were able to contact 46 percent of patients who had received venom immunotherapy and 53 percent of those who had not ($P=0.05$). Similarly, we were able to contact 54 percent of the patients with a history of mild (cutaneous) systemic allergic reactions and 44 percent of those with moderate-to-severe reactions ($P=0.005$). Those we contacted did not differ from those we were not able to contact with respect to age at original reaction and time between the original reaction and the survey.

Among the 512 patients, the mean age was 8 ± 3 years at the time of the first allergic reaction to an in-

Table 2. Stings and Systemic Reactions According to Type of Original Reaction and Presence or Absence of Prior Venom Immunotherapy, 1987–1999.

Patients	Systemic Reaction		Large Local Reaction
	No Venom Immunotherapy	Venom Immunotherapy	No Venom Immunotherapy
Contacted — no./total no.	239/451	163/356	110/226
Stung — no. (%)	111 (46)	64 (39)	44 (40)
With systemic reaction — no. (%) [†]	19 (17)*	2 (3)*	3 (7)

* The rate of systemic allergic reaction was significantly lower among patients with systemic allergic reactions who had received venom immunotherapy than among those who had not received venom immunotherapy ($P=0.007$).

[†] Percentages are of those who were stung.

sect sting and 21 ± 5 years at the time of the most recent reaction. The mean time to follow-up between the original reaction and the survey was 18 ± 5 years, and the mean interval between the original reaction and the most recent known sting was 13 ± 4 years. Age at the first systemic reaction did not differ significantly between patients who responded to the questionnaire (7.85 ± 2.8 years) and those who could not be contacted (7.84 ± 3.2 years), between those who had received stings (7.88 ± 3.1 years) and those who had not (7.84 ± 3.2 years), or between those who had received venom immunotherapy (8.3 ± 3.1 years) and those who had not (7.8 ± 3.2 years). None of the patients who had received venom immunotherapy were still receiving it at the time of the survey. The duration of therapy was less than 3 years in 38 percent of patients, 3 to 4 years in 35 percent of patients, and 5 or more years in 27 percent of patients, with a mean duration of treatment of 3.5 years.

Among patients who had received venom immunotherapy, there was no significant difference in the duration of the treatment between patients we were able to contact and those we were not able to contact, nor was there a difference in the duration of treatment between those who had received stings and those who had not. Among those who had received treatment, in 14 patients the sting occurred 1 to 5 years after venom immunotherapy was stopped, in 18 patients 6 to 10 years afterward, in 25 patients 11 to 15 years afterward, and in 6 patients 16 to 20 years afterward. The mean time to follow-up was the same for treated and untreated patients.

Of the 512 patients contacted, 43 percent received insect stings during the summers of 1987

through 1999. The rate of stings was similar between treated patients (64 of 163 patients, or 39 percent) and untreated patients (111 of 239, or 46 percent; $P=0.22$) (Table 2), and similar between those who had mild (cutaneous) systemic allergic reactions (110 of 250, or 44 percent) and those who had moderate-to-severe systemic allergic reactions (65 of 152, or 43 percent; $P=0.92$) (Table 3). Of 110 patients with large local reactions, 44 (40 percent) received subsequent stings (Table 2). Among untreated patients, systemic reactions occurred in 4 of 19 patients (21 percent) who received stings 6 to 10 years after the original reaction, in 8 of 43 patients (19 percent) who received stings 11 to 15 years afterward, in 5 of 34 patients (15 percent) who received stings 16 to 20 years afterward, and in 2 of 15 patients (13 percent) who received stings more than 20 years afterward. The frequency of systemic allergic reactions among untreated patients declined slowly over the 20-year period of observation, but this trend was not statistically significant. The distribution of intervals between the original reaction to an insect sting and a recent sting was similar in treated and untreated patients (data not shown).

The incidence of systemic allergic reactions was lower ($P=0.007$) among children who had received venom immunotherapy (2 of 64 patients, or 3 percent) than among those who had not (19 of 111, or 17 percent) (Table 2). Among patients with large local reactions, 3 of 44 children (7 percent) who received stings had a systemic allergic reaction. Among untreated patients with a history of mild (cutaneous) systemic allergic reactions, 12 of the 89

Table 3. Stings and Systemic Reactions during the Current Study (1987–1999), According to the History of Treatment and the Severity of Original Reactions (1978–1985).

Patients	Mild (Cutaneous) Systemic Reaction		Moderate-to-Severe Systemic Reaction	
	No Venom Immunotherapy	Venom Immunotherapy	No Venom Immunotherapy	Venom Immunotherapy
Contacted/contact attempted — no./total no.	193/352	57/110	46/99	106/246
Stung — no. (%)	89 (46)	21 (37)	22 (48)	43 (41)
With systemic reaction — no. (%)	12 (13)	0*	7 (32)†	2 (5)‡

* Among patients with mild (cutaneous) systemic reactions to insect stings, $P=0.12$ for the comparison between those who had not received venom immunotherapy and those who had received venom immunotherapy.

† Among patients who did not receive venom immunotherapy, $P=0.05$ for the comparison between those with mild (cutaneous) systemic reactions to insect stings and those with moderate-to-severe reactions.

‡ Among patients with moderate-to-severe reactions to insect stings, $P=0.007$ for the comparison between those who had not received venom immunotherapy and those who had received venom immunotherapy.

children (13 percent) had a subsequent systemic allergic reaction (Table 3). Among patients with previous moderate-to-severe systemic allergic reactions who had not received venom immunotherapy, 7 of 22 (32 percent) had a subsequent systemic allergic reaction. This rate, even in so small a number of subjects, is greater than the rate observed in untreated patients with mild (cutaneous) systemic allergic reactions ($P=0.05$). Among patients with a history of mild (cutaneous) systemic allergic reactions who received venom immunotherapy, none of the 21 who subsequently received an insect sting had a systemic allergic reaction. Among those with a history of moderate-to-severe systemic allergic reactions, only 2 of 43 patients (5 percent) had a subsequent systemic allergic reaction — a rate of reaction lower than that among untreated patients ($P=0.007$) (Table 3). Among patients with a history of mild (cutaneous) systemic allergic reactions who had not received venom immunotherapy, the rate of reaction was zero, which was not significantly different from the relatively low rate of reaction among untreated patients ($P=0.12$) (Table 3).

We compared the severity of reaction to recent insect stings with that of the original reaction 10 to 20 years earlier among the patients in the survey. Among those with a history of moderate-to-severe systemic allergic reactions, in 15 of 22 patients (68 percent) who had not received venom immunotherapy and had recently received stings there were no systemic allergic reactions, in 1 patient there was a less severe systemic allergic reaction, in 6 the systemic allergic reactions were similar to the original reactions, and in none was the reaction worse than earlier. No severe reactions occurred. Among patients with a history of mild (cutaneous) systemic allergic reactions, in 77 of the 89 patients (87 percent) who had not received treatment and had recently received stings there were no systemic allergic reactions, in 6 there were subsequent mild (cutaneous) systemic allergic reactions, in 6 there were moderate systemic allergic reactions, and in none was there a severe reaction. In two patients who had received venom immunotherapy, who had a history of severe allergic reactions, and who had a reaction to a recent sting, the severity of the reaction was decreased to a reaction that was moderate. These two patients had been treated for three and a half years and four years, and venom immunotherapy had been stopped nine years and two years, respectively, before the recent stings. Thus, in 6 (3 percent) of 175 patients the reaction to a recent sting was more

severe than the original systemic allergic reaction; these 6 patients constituted 7 percent of the 89 patients who originally had mild (cutaneous) systemic allergic reactions. Data from the National Death Index indicated that 5 of the 520 patients we had not been able to contact had died between 1987 and the end of 2000, but none of the deaths were known to be due to an insect sting.

DISCUSSION

Our data show that although the majority of children do outgrow the allergy to insect stings, a systemic allergic reaction still occurred in almost one child in five who was stung up to 32 years after the original reaction. The frequency of systemic allergic reactions in patients who had not received venom immunotherapy declined slowly over time, but more than 20 years after the original reaction it was 13 percent. Thus, many affected children do not outgrow the allergy to insect stings. A further finding is that the benefit of venom immunotherapy in childhood is remarkable in its duration. The risk of future systemic allergic reactions was greatest in children who had had moderate-to-severe systemic allergic reactions. The frequency of recurrence of systemic allergic reactions to a sting was reduced from 17 percent in patients who had not received venom immunotherapy (Table 2) to 5 percent in treated patients with previous moderate-to-severe reactions and to zero in treated patients with only previous mild (cutaneous) systemic reactions (Table 3). The significantly lower rate of reaction among treated children, even 10 to 20 years after treatment was stopped, provides some evidence of long-term immunomodulatory effects of allergen immunotherapy in children.

The relapse rate of 5 percent among treated children was lower than among adults, in whom the rate is reported to be more than three times as great.⁹ The comparison with adults also suggests that there is less reason to continue venom immunotherapy in children beyond three to five years, owing to the prolonged reduction in risk after treatment. Children who had a relapse after treatment originally had moderate-to-severe reactions — a finding suggesting that current guidelines recommending that adults with a history of extremely severe reactions should have prolonged venom immunotherapy may apply equally to children.

The severity of the initial reaction is of special prognostic value in children, as it is in adults. In pa-

tients with mild (cutaneous) systemic reactions who did not receive venom immunotherapy, we uncovered no subsequent severe systemic allergic reactions; systemic reactions occurred in such patients significantly less often than in untreated children who had originally had moderate-to-severe reactions (Table 3). Our results show that both the risk of allergic reaction to stings and the benefit of venom immunotherapy are greatest for the 40 percent of children with allergy to insect stings who originally had moderate-to-severe systemic reactions. These results also confirm that the 60 percent of affected children with only mild (cutaneous) systemic reactions have a very low risk of subsequent reactions and do not require venom immunotherapy.^{5,6} Although venom immunotherapy seems to have reduced the risk of subsequent reactions in patients with mild (cutaneous) systemic reactions, this reduction was not statistically significant, owing to the low rate of reaction even among untreated patients with such reactions.

In the patients with isolated mild (cutaneous) systemic reactions who did not receive venom immunotherapy, the frequency of a new systemic allergic reaction that was worse than the original reaction appears to be higher than was described in the earlier reports on this population. The report by Valentine et al.⁶ was on a prospective study in which very few patients were lost to follow-up; this was also the case in an interim report from a study by Schubert et al., in which 2 of 44 systemic reactions (4.5 percent) were moderate in severity during the first nine years of observation.⁸ In our retrospective survey, we may have overestimated the frequency of reactions that increased in severity, because patients with minimal or no reaction to recent stings may be less likely to respond to a survey than those with more severe reactions, and because reactions recalled for the survey after many years may seem, in retrospect, to have been more severe than they were. Although the chance that children with mild (cutaneous) systemic reactions will have subsequent moderate systemic allergic reactions is not quite as low as initially estimated by the insect-allergy group at Johns Hopkins, our results support the recommendation that venom immunotherapy is not required for such patients, especially since none in our studies have yet had a severe reaction.

Among the patients with large local reactions, the observed rate of systemic allergic reactions of 7 percent is consistent with the previously reported rates of 4 percent and 10 percent in adults and chil-

dren, respectively.^{10,11} However, it was surprising to find that this risk has remained unchanged over a period of 10 to 20 years. The systemic allergic reactions reported by the patients in these studies were mild in one case and moderate in three cases, and none were severe.

There are two reports on the long-term outcome after venom immunotherapy was stopped. Lerch and Muller described 200 patients 11 to 78 years of age who had a total of 123 stings within five to seven years after treatment was stopped and among whom the rate of reaction was 12 percent.¹² We described 50 adults who were stung within 5 to 13 years (mean, 9) after stopping venom immunotherapy among whom the rate of reaction was 10 percent.⁹ The current study shows a prolonged clinical benefit of venom immunotherapy in a large cohort of affected children, even more than 10 years after stopping treatment.

There are shortcomings inherent in retrospective surveys such as ours. The first one is the potential for self-selection bias among the subjects. Among those who responded, the frequency of receiving venom immunotherapy was lower than among those who did not respond, suggesting that among the respondents the rate of reaction to stings was higher. However, among respondents to the survey, the frequency of moderate-to-severe systemic allergic reactions was lower, suggesting a lower rate of reaction. At worst, this result may have led to a slight underestimation of the rate of reaction among treated patients with a history of moderate-to-severe reaction.

A second potential limitation is the possibility that stings that caused minimal or no reaction were underreported, leading to a slight overestimation of the rate of reaction. An underestimation of the rate of reactions was due to the fact that some field stings are caused by insects of a species different from the one to which the patient is allergic. The reporting of stings and reactions could also have been affected by differences in expectations and the degree of fear among respondents: patients who had received venom immunotherapy might play down a reaction, whereas untreated patients might have greater concern. However, this was not the case in recent studies of the quality of life among patients with an allergy to insect stings.^{13,14} On the one hand, patients who choose to remain untreated usually do not expect a severe reaction and tend to play down their reactions. On the other hand, those who choose to undergo treatment often do so despite having rela-

tively mild reactions, because they have more concern about the possibility of a life-threatening reaction.

There were no severe reactions reported in this survey, and no patients died as a result of an allergic reaction to an insect sting, as determined from data in the National Death Index. The natural history of allergy to insect stings would predict fewer than one fatal reaction in 500 untreated children with this allergy over a 20-year period. A fatal reaction to a sting after venom immunotherapy was stopped is also exceedingly rare but has been reported.¹⁵ This should not lead to the conclusion that treatment should be continued indefinitely in all cases but, rather, should be taken to indicate that high-risk patients should be identified.¹⁶

Although the majority of children with allergy to insect stings do not have allergic reactions when they are older, a clinically important number of children do not outgrow this allergy. The long-term risk of a systemic allergic reaction to a sting among pa-

tients who do not receive venom immunotherapy is significantly higher in those with a history of moderate-to-severe reactions than in those with strictly mild (cutaneous) systemic reactions. Venom immunotherapy in children results in a significantly lower risk of systemic reactions even 10 to 20 years after therapy is stopped, and this prolonged benefit is greater than that seen in adults. Venom immunotherapy should be recommended for children with moderate-to-severe reactions, but there is little need for such therapy in patients with milder reactions, in whom the risk of a severe reaction is less than 5 percent (and possibly less than 1 percent, since none occurred in such patients in this study).

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