

Risk assessment in determining systemic reactivity to honeybee stings in beekeepers

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Background: The use of laboratory tests as a reliable method for risk assessment in determining the systemic reactivity of beekeepers to honeybee stings has proven unsatisfactory.

Objective: This study was conducted to evaluate the usefulness of a structured questionnaire as a supplement to bee venom-specific IgE data in the prediction of systemic sting reactions of 78 beekeepers to honeybee stings.

Methods: Participants in previous studies completed a questionnaire concerning potential risk factors of systemic sting reactions. Serum bee venom IgE was measured by CAP-RAST. Skin prick tests were performed with standardized bee venom extracts prior to the beekeeping season. Venom challenges were performed using unintentional field stings. A new questionnaire concerning sting reactions during the recent beekeeping season was sent to the beekeepers after it had ended. A multiple logistic regression analysis was done to evaluate the influence of potential risk factors upon systemic bee sting reactions.

Results: Four variables were significant. The pre-season presence of serum bee venom-specific IgE at concentrations exceeding 1.0 kU/L increased the risk of systemic reactions 12-fold. The risk was 10-fold if nasal or respiratory symptoms had occurred while working at hives. When the years spent in beekeeping were fewer than eight the risk of systemic sting reaction was 9-fold, any previous systemic reaction increased the risk 8-fold.

Conclusion: The use of more detailed patient histories in combination with laboratory tests may markedly improve the reliability of risk assessment.

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INTRODUCTION

Systemic reactions to bee stings occur suddenly and may cause death in a small number of otherwise healthy subjects. Persons allergic to bee venom are most often beekeepers who face a high risk of being stung. Systemic reactions following bee stings have been reported in 14% to 42% of beekeepers,¹⁻³ while serum bee venom-specific IgE has been found in 42% to

79%.^{1,2,4,5} For comparison, the prevalence of systemic reactions to Hymenoptera stings among the general population ranges from 0.8% to 3.3%.⁶⁻⁸ Hymenoptera hypersensitivity was found in 21% of forestry workers, a group frequently stung by Hymenoptera.⁹

Although numerous studies have been published debating the use of immunologic variables in the prediction of reaction severity to sting challenges, the clinical use of risk assessment models is not established.^{10,11} To the best of our knowledge, studies of risk assessment that combine patient history and venom-specific IgE for predicting systemic sting reactions in beekeepers have not been published. The present study was designed to evaluate the usefulness of a structured questionnaire as a supplement to venom-specific IgE data in predicting systemic

reactions of beekeepers to accidental honeybee stings.

MATERIAL AND METHODS

The study population was formed on the basis of our preceding surveys of beekeepers in 1993 and 1994.^{12,13} The subjects completed a questionnaire concerning factors presumed to correlate with bee venom allergy.¹² Serum venom-specific IgE was measured by CAP-RAST (CAP). Skin prick tests were performed with standardized bee venom extracts.¹³ A new questionnaire concerning the presence of any systemic sting reactions that year—according to Müller's classification¹⁴—was mailed in October 1994 to 102 beekeepers following the beekeeping season. Venom challenge was performed using unintentional field stings. One of the 102 beekeepers had died, one did not respond and three had ceased beekeeping. Nineteen beekeepers were excluded from the study because they were not stung on bare skin by honeybees during the 1994 season.

The final study group consisted of 78 people. The ages of seven female and 71 male beekeepers ranged from 27 to 76 years with a mean of 51 years. They managed from one to 300 beehives (mean 28). Five of the subjects were professional beekeepers, 11 were farmers, and two were gardeners. For the remaining 60 subjects, beekeeping was a leisure pursuit.

Statistical Analyses

Statistical tests used were analysis of variance, Bonferroni's paired *t* test, the chi-square test and multiple logistic regression analysis. Differences were considered significant for $P < .05$. Initially, univariate relationships were investigated by obtaining the odds ratio (OR) of systemic sting reactions in 1994 for each of the independent vari-

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Table 1. Relationships Between Systemic Sting Reactions and Potential Risk Factors

	Systemic sting reaction in 1994		<i>P</i>	Odds Ratio (95% CI)
	Yes (n = 10) Number (%)	No (n = 68) Number (%)		
Bee venom CAP > 1.0 kU/L	9 (90)	24 (35)	.0011	16.50 (2.0–138.2)
Skin prick test +	7 (70)	32 (47)	NS	2.63 (0.7–9.4)
Atopy in history	5 (50)	19 (28)	NS	2.58 (0.7–9.9)
Systemic sting reaction in history	8 (80)	15 (22)	.0002	14.12 (2.7–73.7)
Large local reaction in history	7 (70)	29 (43)	NS	3.14 (0.7–13.2)
Presence of nasal or respiratory symptoms at hives	8 (80)	21 (31)	.0027	8.95 (1.7–45.8)
No. of beehives > 15	5 (50)	24 (35)	NS	1.83 (0.5–7.0)
No. of stings/year < 10	4 (40)	16 (24)	NS	2.17 (0.5–8.7)
Years of beekeeping < 7 yr	5 (50)	13 (19)	.0304	4.23 (1.1–16.8)

ables. Ninety-five percent confidence intervals (CI) were calculated and the statistical significance was evaluated using standard chi-square tests.

A multiple logistic regression analysis was done to evaluate the influence of potential risk factors upon systemic sting reactions. Multivariate analyses were conducted using a forward stepwise logistic regression method. Variables considered in the model included all those used in the univariate analyses. The ages of the beekeepers were used as a continuous variable while all other variables were binary as shown in Table 1. Only those variables considered significant were retained in the final model. In the multiple logistic regression analyses the following selection criteria were used: $P < .10$ to enter, $P > .15$ to remove, and the asymptotic covariance estimate (ACE) method. Analyses were performed with the BMDP (BMDP Statistical Software, Inc., Los Angeles, CA) statistical software packages.

RESULTS

Eleven (14%) of the 78 subjects had experienced systemic symptoms after

bee stings in 1994. The reaction in one beekeeper was considered toxic because symptoms appeared after at least 50 simultaneous stings. He experienced a headache and nausea the day following the stings. This toxic reaction was excluded from the group of systemic reactions. Nine (90%) of ten systemic reactors and 24 (35%) of the nonreactive subjects had pre-season serum bee venom-specific IgE which exceeded 1.0 kU/L (Table 1). With the chi-square test, this difference was significant ($P = .0011$). Bee venom-specific IgE was positive in 58% and 50% of the subjects, respectively.

Systemic sting reactions prior to 1994 had occurred in eight (80%) of those experiencing reactions in 1994 and in 15 (22%) of the remaining subjects ($P = .0002$). The occurrence of nasal and respiratory symptoms while working at hives was significantly higher in systemic reactors than in those with no systemic sting reaction in 1994 (Table 1). Positive bee venom prick skin tests and histories of atopy and large local sting reactions were observed more frequently in beekeepers with a systemic sting reaction in

1994 than among others. These differences were not statistically significant. Systemic reactors had more beehives and fewer stings annually than the remaining subjects (Table 2). They were also younger and had been beekeepers for a shorter period than those having no systemic sting reaction in 1994, although these differences were not statistically significant.

In the multiple logistic regression analysis, four variables proved significant (Table 3). The presence of a history of former systemic sting reactions increased the risk of another reaction 8-fold. The occurrence of nasal or respiratory symptoms while working at beehives was associated with a 10-fold risk; and the presence of serum bee venom-specific IgE (>1.0 kU/L), a 12-fold risk of a systemic reaction. When the years spent in beekeeping were fewer than 8, the risk was 9-fold.

The following formula calculates the probability of a systemic sting reaction $P(SSR)$ for a given beekeeper:

$$P(SSR) = 1/(1 + \exp(-l))$$

where $l = -6.94 + 2.50C + 2.29N + 2.22Y + 2.09S$

C = bee venom CAP > 1.0 kU/L (1 = yes, 0 = no)

N = nasal or respiratory symptoms at hives (1 = yes, 0 = no)

Y = years of beekeeping seven years or less (1 = yes, 0 = no)

S = systemic bee sting reaction in history (1 = yes, 0 = no)

Table 2. Relationships Between Systemic Sting Reactions and Potential Risk Factors

	Systemic sting reaction in 1994		<i>P</i>
	Yes (n = 10) Mean (SEM)	No (n = 68) Mean (SEM)	
No. of beehives	47.6 (28.5)	25.1 (4.2)	NS
Stings/yr	35.3 (11.9)	60.3 (15.8)	NS
Years of beekeeping	11.6 (2.7)	17.4 (1.6)	NS
Age, yr	48.0 (4.0)	51.8 (1.3)	NS

Table 3. Adjusted Odds Ratios (OR) with 95% Confidence Intervals (95% CI) for Systemic Sting Reactions by All Significant Variables Found in Logistic Regression Analysis

Independent Variables	Values	OR	95% CI
Systemic sting reaction in history	no	1	
	yes	8.1	1.03–63.3
Years of beekeeping	≤7yr	9.25	1.05–81.7
	>8yr	1	
Nasal or respiratory symptoms at beehives	no	1	
	yes	9.82	0.901–107
Bee venom CAP > 1.0 kU/L	no	1	
	yes	12.1	1.02–144

DISCUSSION

The present data indicate that the risk of systemic sting reactions increases 12-fold when the concentration of bee venom-specific IgE in serum (CAP) exceeds 1.0 kU/L and 10-fold when nasal or respiratory symptoms occur while working at hives. A history of systemic sting reactions and a relatively short duration of beekeeping also significantly increase the risk of systemic sting reactions in beekeepers. These findings add further weight to our hypothesis that the use of detailed personal histories in combination with laboratory tests may improve the assessment of risk.

The deliberate insect sting challenge for venom-allergic patients is considered risky.^{15,16} Furthermore, sting challenges are expensive since they must be performed under intensive care unit conditions. Franken et al¹⁷ suggested that a single negative challenge sting may not provide sufficient proof of lack of reactivity to future stings; however, in selected patients deliberate insect stings are a useful diagnostic tool.¹⁸ By monitoring the effects of unintentional field stings, these problems were avoided. Most of the beekeepers were stung by honeybees several times during the study period. Systemic sting reactions are easily remembered and the severity of reactions can still be graded several years afterwards. The number of years spent in beekeeping and the presence of nasal or eye symptoms while working at beehives are other risk factors that can be reliably evaluated by questioning.

Systemic reactions following a honeybee sting are known to be associated with venom-specific IgE. Among beekeepers with systemic sting reactions in their histories, serum venom-specific IgE has been found in 64% to 88% of subjects.^{1,2,4} Sensitization is also common in nonsymptomatic beekeepers. In previous studies, the prevalence of serum venom-specific IgE in nonsensitive beekeepers ranged from 27% to 73%.^{1,2,4} Beyond laboratory parameters, serum venom-specific IgE has been the best predictor of reactivity in beekeepers.^{10,19} Day et al¹⁰ found that the combination of serum venom-specific IgE and venom-specific skin testing is the best indicator of allergic reactivity. It has been suggested that low levels of venom-specific IgG increase the risk of allergic reaction.^{2,3} The suggestion is supported by studies in which serum venom-specific IgG has been significantly higher in nonallergic than in allergic beekeepers.^{2,3,21} Furthermore, it has been shown that specific IgG and IgG4 become prominent upon chronic bee venom stimulation.^{20–22} These variables, however, were not associated in later studies with protection from systemic reactivity and do not improve risk assessment in determining systemic reactivity.^{10,11,23–25}

It has been suggested that bee sting allergy is self-limiting for some individuals.^{26–28} This is supported by our result indicating that only 35% of those subjects with a history of previous systemic sting reactions reacted in 1994. This is also in accordance with studies

of patients having histories of allergic systemic reactions. In these studies, the rate of systemic reaction to a bee sting challenge was 36% to 52%.^{10,15,23} In some reports, no systemic reaction was found in the sting challenges of bee venom-allergic patients.^{18,29} The presence of nasal and ocular symptoms while working at beehives was associated with a significant risk of systemic sting reactions. Numerous observations of beekeepers with inhalant allergy to bee body components have been described.^{30–33} Our results indicate that this inhalant allergy is associated with bee venom allergy. Our finding that the years spent in beekeeping are inversely associated with the risk of systemic sting reactions is probably caused by the self-selection of beekeepers.

The study population consisted of registered beekeepers in a geographically defined area of Finland. Some allergic and nonallergic beekeepers were excluded from the study since in 1994 they had received stings only through clothing. Age and sex distribution matched the original study population of 191 beekeepers, as did the prevalence of sting reactions. There is no reason to believe that the study population differs markedly from the respective population as a whole. The use of unintentional field stings may cause a bias since nonreactive beekeepers are stung more often than allergic ones.^{2,3,13} Venom-sensitive individuals in another study, however, were stung significantly more often than nonsensitive individuals.³⁴ Due to the limited size of the sample, the clinical use of any formula should be considered suggestive.

Atopic beekeepers seem to become more readily allergic to honeybee venom than non-atopics, and atopy has been shown to predispose to more severe reactions.^{1,26,35–37} The prevalence of atopy varies from 20% to 47% in different studies.^{1,12,26,35,37,38} Although not statistically significant in our study, atopy seems more common among those with systemic sting reactions than others. Systemic reactors seem to have more large local sting

reactions in their histories than non-reactors. They also have more hives and fewer stings, respectively; however, these potential risk factors proved not to be significant.

All the risk factors found significant in our study can easily be evaluated by physicians. An awareness of possible life-threatening sting reactions causes anxiety among beekeepers. Furthermore, hypersensitivity to insect stings may be effectively treated with immunotherapy. Even rapid immunotherapy has proven to be safe.³⁹ Our formula, though not yet tested prospectively, makes it possible to estimate the risk of future sting reactions for current beekeepers. It may also be helpful in considering the initiation of venom immunotherapy. Risk assessment through laboratory tests alone has been unsatisfactory.^{10,11}

Our study indicates that the risk of systemic sting reactions increases 12-fold when bee venom CAP exceeds 1.0 kU/L and 10-fold when nasal or respiratory symptoms are present while working at hives. The risk of future systemic reactions increases 8-fold when a history of systemic sting reactions is positive and 9-fold when the years spent in beekeeping are seven or fewer. We conclude that, by combining the data of personal history with measurements of serum venom-specific IgE, it might be possible to improve risk assessments in determining the systemic reactivity of beekeepers to honeybee stings.

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