

Bee sting allergy in beekeepers

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Summary

Background Beekeepers are strongly exposed to honey bee stings and therefore at an increased risk to develop IgE-mediated allergy to bee venom.

Objective We wondered whether bee venom-allergic beekeepers were different from normally exposed bee venom-allergic patients with regard to clinical and immunological parameters as well as their response to venom immunotherapy.

Method Among the 459 bee venom-allergic patients seen over the 5 year period 1987–91, 62 (14%) were beekeepers and 44 (10%) family members of beekeepers. These two groups were compared with 101 normally exposed bee venom-allergic patients matched with the allergic beekeepers for age and sex, regarding clinical parameters, skin sensitivity, specific IgE and IgG antibodies to bee venom as well as safety and efficacy of venom immunotherapy.

Results As expected, allergic beekeepers had been stung most frequently before the first allergic reaction. The three groups showed a similar severity of allergic symptoms following bee stings and had an equal incidence of atopic diseases. Allergic beekeepers showed higher levels of bee venom-specific serum IgG, lower skin sensitivity and lower levels of bee venom specific serum IgE than bee venom-allergic control patients. A negative correlation between number of stings and skin sensitivity as well as specific IgE was found in allergic beekeepers and their family members, while the number of stings was positively correlated with specific IgG in these two groups. Venom immunotherapy was equally effective in the three groups, but better tolerated by allergic beekeepers than the two other groups. The majority of allergic beekeepers continued bee-keeping successfully under the protection of venom immunotherapy.

Conclusion The lower level of sensitivity in diagnostic tests and the better tolerance of immunotherapy in allergic beekeepers is most likely related to the high level of specific IgG in this group.

Keywords: bee venom allergy, beekeepers, venom immunotherapy, skin tests, specific IgE, specific IgG

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Introduction

The risk of bee sting allergy increases with the degree of exposure [1]. Therefore, beekeepers are at high risk for bee sting allergy. In a number of studies it was shown [2–7], that between 14 and 35% of beekeepers give a history of at least one episode of systemic allergic reaction after bee stings. According to Bousquet [8], however, those who are least frequently stung within a population of beekeepers, most

often develop an allergic reaction: none of those beekeepers receiving more than 200 stings each year reported a systemic reaction, whereas 45% of those receiving only up to 25 stings did.

High levels of bee venom-specific IgE antibodies (sIgE) are mainly found in allergic patients [3,7,9,10], whereas sera of non-allergic beekeepers usually contain high levels of bee venom (BV) specific IgG antibodies (sIgG) [3,5,11–16], mainly of the IgG4 subclass [13,16]. This observation and the positive results of passive immunotherapy trials with beekeepers gammaglobulin [17–19] indicate a protective role for sIgG in bee venom allergy.

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In this paper we analyse, whether BV allergic beekeepers differ from normally exposed BV allergic patients with regard to clinical and diagnostic parameters or to the response to venom immunotherapy (VIT).

Methods

Patients

Between 1987 and 1991, 459 bee sting-allergic patients with a history of grade I–IV allergic reaction according to the classification of Mueller [20] were seen at our hospital. Among these, 62 (14%) were beekeepers (aBK) and 44 (10%) family members of beekeepers (aFM). These two groups were compared with a control group of 101 of the remaining BV allergic patients (aC), who were matched for age and sex to the aBK. All aBK and most aFM and aC had a history of recent sting reactions within the last year. The three groups were analysed for clinical parameters such as exposure to bee stings, atopic background and grade of severity of the allergic reaction, immunological parameters (i.e. skin tests, sIgE, sIgG) and the response to VIT. The aBK were questioned again in 1994 about the long-term results of VIT and their habits as beekeepers before and after the manifestation of BV allergy. This questionnaire was answered by 53 of the 62 aBK.

Atopy

An atopic background was assumed either in the presence of a history of seasonal allergic rhinitis, allergic bronchial asthma or atopic dermatitis, or at least one 3+ positive skin prick test reaction to nine common inhalants (pollen of mixed grass, birch, mugwort; dander of cat and dog; *D. pteronyssinus*, *D. farinae*, *Cladosporium herbarum* and *Alternaria alternata*, ALK, Horsholm, Denmark).

Skin tests

Intracutaneous skin test end point titration was performed as described previously [21]. The endpoint concentration (EPC) is the lowest concentration resulting in a weal of at least 5 mm in diameter with erythema. An EPC of 10^{-4} g/L or less is considered as definitely positive, an EPC of 10^{-3} g/L as doubtful and an EPC of $>10^{-3}$ g/L as negative (due to non-specific skin irritation).

sIgE

These were estimated by the commercially available Phadezym® RAST (Pharmacia Diagnostics AB, Uppsala, Sweden) according to the prescriptions of the supplier. Results are given in RAST classes from 0 to 4. Classes II–

IV are considered as a definitely positive, class I as a doubtful and class 0 as a negative result.

sIgG

sIgG were determined by a protein A-based ELISA technique as described previously [21]. The results are given in $\mu\text{g/mL}$ as estimated by comparison with a dilution series of a beekeeper serum pool with a known content of BV specific IgG.

Values of $<0.31 \mu\text{g/mL}$ are usually observed in non-exposed controls, while levels $>5 \mu\text{g/mL}$ are seen in beekeepers and patients on VIT.

Venom immunotherapy

VIT conformed to the recommendations of the EAACI subcommittee on insect venom allergy [22]. Both rush and conventional protocols were used [22,23]. The usual maintenance dose was $100 \mu\text{g}$ for aFM and aC and $200 \mu\text{g}$ for aBK. Efficacy of VIT was judged from the result of re-exposure to a bee sting either by field sting or by sting provocation test. Only the presence of objective systemic allergic symptoms was considered as indicating treatment failure. Safety was judged from the rate of occurrence of objective or subjective systemic allergic symptoms following VIT injections.

Statistical evaluation

Safety and efficacy of VIT between aBK and aC were compared by chi-square-test. Differences between groups regarding number of stings, grade of allergic reaction, skin sensitivity, sIgE and sIgG were analysed by contingency table chi-square test.

For correlations between number of stings and diagnostic parameters Spearman rank was used.

Results

Clinical parameters

Table 1 shows that aBK and aC are similar in age and sex distribution, while aFM are significantly younger, many of them being children, and more often female, most beekeepers being male. The distribution of the grade of severity of the last allergic reaction is similar in the three groups and so is the frequency of an atopic background. As seen in Fig. 1, aBK were stung significantly more frequently than the two other groups, aFM taking an intermediate position between aBK and aC. The subgroup of adult aFM (>20 years) was stung significantly more frequently than aC ($P < 0.05$). Surprisingly, 48% of aBK developed their first

Table 1. Clinical data in allergic beekeepers (aBK), allergic family members of beekeepers (aFM) and in a control group of normally exposed patients with BV allergy (aC)

	aBK	aFM	aC
Number of patients (%)	62 (13)	44 (10)	101 (22)
Sex: m/f (%)	46/16 (74/26)	19/25 (43/57)	72/29 (64/36)
Mean age (range)	42.8 (16–84)	34.4 (8–84)	42.4 (15–75)
Atopy (%)			
History	21 (34)	13 (30)	26 (26)
Skin prick test	7/49 (14)	5/38 (13)	21/84 (25)
Grade of SR (%)			
I	6 (10)	3 (7)	5 (5)
II	14 (22.5)	12 (27)	24 (24)
III	28 (45)	16 (36)	41 (40)
IV	14 (22.5)	13 (30)	31 (31)

SR, last systemic allergic reaction.

allergic reaction only after 50 or more bee stings. In 51% of aBK the first sting reaction occurred within 2 years of starting their hobby, but in 15% only after more than 10 years of bee-keeping.

Diagnostic parameters

As shown in Fig. 2 aBK had significantly lower skin

sensitivity to BV, as indicated by EPC, than the two other groups. sIgE were also lower in aBK than in aFM and aC, but this difference was only significant between aBK and aC (Fig. 3). On the contrary, sIgG were significantly higher in aBK than in aFM and in aC (Fig. 4). For all three diagnostic parameters the values of aFM lie between the two other groups but closer to the aC.

In aBK a positive correlation was found between the

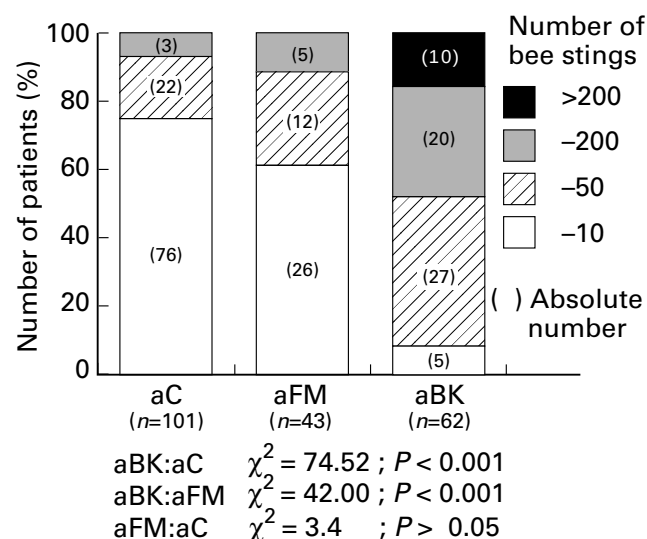


Fig. 1. Number of bee stings before the first allergic reaction in BV-allergic beekeepers (aBK), family members of beekeepers (aFM) and normally exposed patients (aC). The figures in the bars give absolute numbers of patients. The sting frequency is significantly higher in aBK than in aFM and aC.

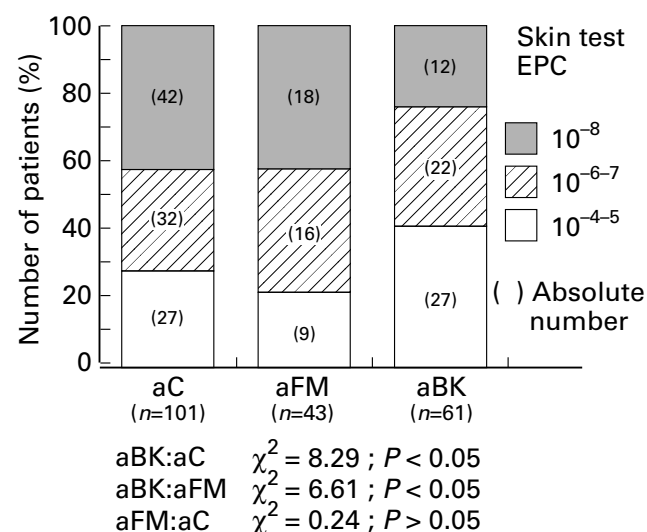


Fig. 2. Skin sensitivity to BV in BV-allergic beekeepers (aBK), family members of beekeepers (aFM) and in normally exposed patients (aC). The skin sensitivity, as indicated by the negative log of the EPC, is significantly lower in aBK than in the two other groups.

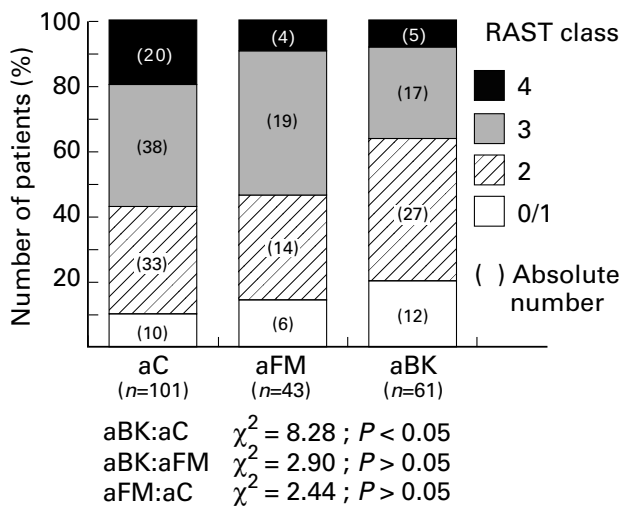


Fig. 3. BV-specific IgE (sIgE) in BV-allergic beekeepers (aBK), family members of beekeepers (aFM) and normally exposed patients (aC). sIgE are significantly lower in aBK than in aC.

number of stings per year and sIgG ($r = 0.49$, $P < 0.005$) and a negative correlation between number of stings and skin sensitivity ($r = 0.44$, $P < 0.007$) as well as sIgE ($r = 0.404$, $P < 0.002$). No correlation between number of stings and any of the parameters was observed in aC, while in aFM a negative correlation was also observed between number of stings and skin sensitivity ($r = 0.354$, $P < 0.02$) and sIgE ($r = 0.498$, $P < 0.001$). sIgG were positively correlated to the number of stings only in the subgroup of adult aFM ($r = 0.555$, $P < 0.01$), who were stung more frequently.

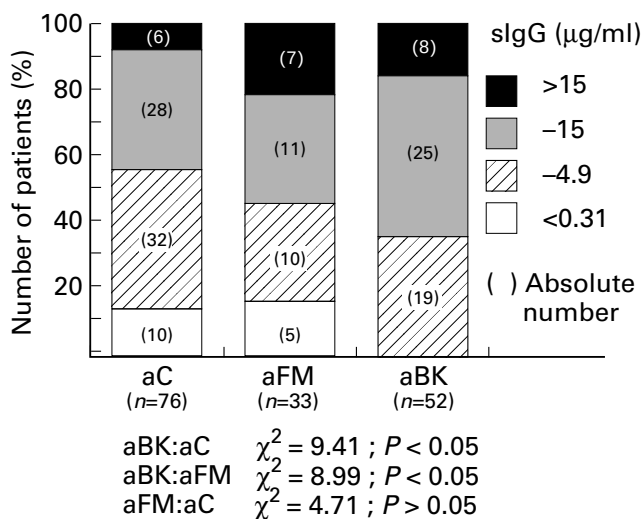


Fig. 4. BV specific IgG (sIgG) in BV-allergic beekeepers (aBK), family members of beekeepers (aFM) and normally exposed patients (aC). sIgG are significantly higher in aBK than in the two other groups.

Immunotherapy

As shown in Table 2, 43 (69%) of aBK, 24 of aFM (56%) and 61 of aC (60%) underwent VIT. Although aBK usually received a maintenance dose of 200 μ g, while aC and aFM got only a maintenance dose of 100 μ g, allergic side-effects were observed significantly less frequently in aBK than in the two other groups. Both in aBK and aC side-effects occurred more frequently in patients with a severe (grade III–IV) pre-treatment reaction than in those with only grade I–II reactions. In aBK allergic side-effects were observed in 11% [1/9] of those with mild and 34% [11/32] of those with severe pre-treatment reactions, in aC, the respective data were 0% [0/5] and 53% (30/56). The groups with only mild pre-treatment reactions were however, so small, that statistical analysis did not seem appropriate. No difference in the frequency of side-effects in either group was observed in relation to the pre-treatment RAST score.

As expected the highest resting rate was observed in aBK. The rate of objective systemic allergic reactions did not differ significantly between groups. The severity of the pre-treatment reaction did not influence the result of a re-sting during VIT: 22% [2/9] aBK with mild and 16% [5/32] with severe reactions developed systemic allergic symptoms when re-stung ($P \geq 0.1$). No re-stings during VIT were recorded in the 5 aC with mild pre-treatment reactions, while 21% [7/33] of aC with severe pre-treatment reactions developed systemic allergic symptoms following the re-sting. The pre-treatment RAST score had no influence on the result of a re-exposure during VIT.

Special aspects in allergic beekeepers

The following recommendations were given to all aBK: (1) give up bee-keeping, (2) start immunotherapy with BV, (3) return to bee-keeping only after a well-tolerated sting

Table 2. Side-effects and efficacy of VIT as indicated by a sting provocation test

	aBK	aFM	aC
SIT (%)	43 (69)	24 (56)	61 (60)
Allergic side-effects (%)*	12 (28)	12 (50)	30 (49)
<i>Efficacy</i>			
Re-exposed patients (%)	41 (95)	11 (45)	33 (45)
Systemic reaction after re-exposure (%)**	7 (17)	1 (6)	7 (21)

* aBK:aC $\chi^2 = 6.83$; $P < 0.01$. aBK:aFM $\chi^2 = 4.46$; $P < 0.05$. aFM:aC $\chi^2 = 0.01$; $P > 0.1$. ** aBK:aC $\chi^2 = 1.29$; $P > 0.05$. aBK:aFM $\chi^2 = 0.82$; $P > 0.05$. aFM:aC $\chi^2 = 1.96$; $P > 0.05$.

provocation test, and (4) when bee-keeping, always wear protective clothing, have an emergency kit available and inform family members before going to attend to the bees. Table 3 shows the compliance of aBK with these recommendations. Significantly more female aBK stopped bee-keeping, while somewhat more male aBK underwent VIT. Precautions while working in the beehive were followed slightly better by female aBK. Of 31 aBK who continued bee-keeping, 22 received VIT. None of these developed a systemic allergic reaction when restung, while four of the nine who rejected VIT did.

In seven aBK, after successful VIT of at least 3 years duration, we agreed to a special protocol to maintain tolerance by self-application of bee stings. These patients, in addition to the recommendations given above, were instructed to avoid more than two stings at the time by strictly wearing protective clothing, to apply one or two weekly stings during the warm season and during winter to apply at least one sting per month or to restart monthly maintenance injections with 200 µg of BV at the family doctor. Table 4 shows data on these seven patients: only one developed a mild systemic allergic reaction (grade I) each spring, when restarting the work with bees, during the first 3 years after stopping VIT.

Discussion

In our study population aBK and aFM represent only 1/4 of all BV-allergic patients, whereas in most other countries [3,7,8] the majority of BV-allergic patients are beekeepers or their family members. The reason for this difference most likely lies in the higher degree of exposure of the whole population in Switzerland, where bee-keeping is extremely popular as a hobby and often also practised in suburban areas. As in other studies [25,26,27], an atopic background was found with similar frequency in aBK, aFM and aC, and not significantly more often than in the general population. Interestingly, Miyachi *et al.* [9] observed a significantly higher frequency of atopic background in allergic than in non-allergic beekeepers. They suggested that during their

Table 4. Maintenance of tolerance by self-application of bee stings in seven aBK

Number of stings/year	20–100
Number of aBK with systemic reaction 1 (three reactions in 3 years)	
<i>Therapy during wintertime</i>	
BV-Injections	2
Self-application	5
Mean follow-up in years	2.64

work, either through inhalation or multiple stings, atopic beekeepers are more easily sensitized than non-atopic beekeepers. This finding is in no contradiction with our results, since we did not investigate a group of non-allergic beekeepers and the rate of atopy, at least from history, was rather high in our aBK. Surprisingly, almost half of the aBK developed their first allergic reaction after more than 50 bee stings. The majority of aBK first reacted shortly after starting bee-keeping, at a time when stings occurred more frequently than in their previous life. Many of the remaining indicated that the first reaction occurred after the winter break, thus following a period of several months without stings during which protection may have waned.

As expected, aBK had significantly higher levels of sIgG than aFM and aC and these antibodies were positively correlated to the number of stings in aBK. This confirms results from unselected populations of beekeepers [5,7,10,12,28]. In addition we observed a lower skin sensitivity and lower sIgE in aBK, which were negatively correlated to the number of stings. These findings suggest that sIgG either interfere directly with the allergen–IgE interaction during skin testing or in the RAST assay, or else may suppress IgE-antibody formation by B cells. Moreover, it is likely that the superior tolerance of VIT in aBK in spite of the double maintenance dose is related to the increased level of sIgG. On the other hand it comes as a surprise that, despite the much higher sIgG levels in aBK, no difference was observed between the three groups regarding the severity of allergic sting reactions, and that the rate of protection during re-exposure was similar in aBK and aC. One reason for the second finding could be that the re-sting rate was much higher (near to 100%) in aBK, and that most aBK were re-exposed during the first months of VIT, while aC were re-stung most often only after several years of VIT. It must, however, be considered that besides sIgG other protective mechanisms may be induced by VIT such as alterations in releasability of effector cells [29] or changes in T-cell reactivity [30,31]. While the predictive value of sIgG with regard to protection from stings seems reasonable during early VIT, it is very limited before starting this

Table 3. Compliance of allergic beekeepers with our recommendations

	Total	Male (%)	Female (%)	P-value
Number	53	38 (72)	15 (28)	
Stop bee-keeping	22	12 (32)	10 (67)	<0.025
VIT	36	28 (74)	8 (53)	NS
<i>Precautions</i>				
Emergency kit in bee hive	41	28 (74)	13 (87)	NS

treatment, during protracted VIT and after stopping it [22]. Not surprisingly, aBK who continued bee-keeping were fully protected when on VIT, whereas those who declined to start VIT, frequently developed systemic allergic reactions again.

Most aBK on VIT sooner or later ask whether they could not maintain protection by self application of bee stings. Our preliminary results in 7 aBK show that this is feasible. It is, however, extremely important that adequate precautions are prescribed. It is mandatory, that these aBK continue to wear protective clothing in order to avoid multiple stings at a time. The protection induced by VIT most likely is not an all or nothing phenomenon, but it must be expected that allergic reactions may re-occur in such patients when exposed to very high BV doses, as applied by multiple bee stings, since most aBK continue to have positive skin tests and sIgE even after many years of VIT. The protection must be maintained during winter time either by self-application of stings or by maintenance injections at the doctor.

Finally, emergency medication must be available in the bee house of every aBK. In conclusion, our study shows that allergic beekeepers differ from normally exposed BV allergic patients with regard to diagnostic but not clinical parameters. Tolerance of VIT is superior in aBK and this treatment allows most beekeepers to continue their work with honey bees safely.

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