

Bee venom allergy in beekeepers and their family members

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Purpose of review

To analyze prevalence of allergic sting reactions, including the clinical and diagnostic features as well as management options in a population heavily exposed to honeybee stings such as beekeepers and their family members.

Recent findings

The higher sting frequency is associated with an increased prevalence of allergic sting reactions. Major risk factors for allergic sting reactions in beekeepers are: fewer than 10 annual stings, an atopic constitution and symptoms of upper respiratory allergy during work in the beehive. Bee venom allergic beekeepers have higher levels of bee venom-specific IgG but lower skin sensitivity and bee venom-specific IgE than normally exposed bee venom allergic patients. Safety of bee venom immunotherapy is higher in beekeepers than in allergic controls, while efficacy of this treatment is similar in both groups.

Summary

Beekeepers and their family members are at an increased risk of severe sting anaphylaxis and therefore need especially careful instruction with regard to avoidance of re-exposure, emergency treatment and specific immunotherapy with bee venom.

Keywords

bee venom allergy, beekeepers, venom immunotherapy

Introduction

Hymenoptera venom allergy is one of the major reasons for anaphylaxis. Between 1961 and 2000, it caused 120 fatalities in Switzerland – an average of three every year [1•]. Extrapolated to Western Europe, this corresponds to more than 150 fatal Hymenoptera sting reactions every year in this region. Stings by honeybees and vespids are most often responsible for such reactions. Beekeepers and their family members are heavily exposed to honeybee stings and are thus at an especially high risk of becoming allergic, and therefore are an interesting population for the study of epidemiology and immunopathogenesis of venom allergy and the mechanism of its most effective treatment – venom immunotherapy. Finally, owing to the high degree of exposure of this population, indication and protocols for venom immunotherapy may differ from those for normally exposed patients.

Epidemiology

Systemic allergic reactions to Hymenoptera stings have been reported in 1–4% of the whole population in various large surveys in European countries and the USA [2–5]. In the highly exposed population of beekeepers (Table 1), up to 31% report large local and 14–32% report systemic allergic reactions following bee stings [6–12]. In 30 to 60% of beekeepers, positive skin tests with bee venom and venom-specific IgE-antibodies can be detected, respectively [8–16] (Table 2). The frequency of both positive diagnostic tests and sting reactions is highest during the first years of beekeeping [13,15]. In spite of continuation of beekeeping, systemic allergic reactions then disappear in the majority of beekeepers. Infrequently stung beekeepers are at the highest risk of developing systemic reactions [9]: systemic allergic reactions were observed in 45% of beekeepers with fewer than 15 stings annually but in none of those with more than 200 annual stings. In beginning and longstanding beekeepers, sting reactions occur most frequently following the first stings of the year. Analysis of 459 bee venom allergic patients examined over 5 years at our referring center for venom allergy in Bern, Switzerland showed that beekeepers made up 14% of the referred patients and their family members another 10% [17]. While beekeeping is very popular in Switzerland and most often practiced as a hobby, the share of beekeepers and their family members may be different in other countries with mostly professional beekeeping [6–8,11,12].

An atopic constitution is found with similar frequency in Hymenoptera venom allergic patients and in the general

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Abbreviation

VIT venom immunotherapy

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Table 1. Frequency of allergic reactions to bee stings in beekeepers

Author, year	n studied	n with large local reactions (%)	n with systemic reactions (%)
Light 1975 [6]	34	3 (9)	6 (18)
BK only			
Yunginger 1978 [7]	132	ND	27 (21)
BK and FM			
Miyachi 1979 [8]	137	39 (29)	44 (32)
BK and FM			
Bousquet 1984 [9]	200	24 (12)	28 (14)
BK only			
Böhny 1986 [10]	595	ND	99 (16.6)
BK only			
Annala 1995 [11]	102	29 (28)	31 (30)
BK only			
Torre Morin 1995 [12]	246	75 (31)	53 (21)
BK only			

ND, not done; BK, beekeepers; FM, family member of beekeepers.

Table 2. Skin tests and serum-specific IgE-antibodies to honeybee venom in beekeepers

Author, year	Number tested	Skin test positive (%)	Specific IgE positive (%)
Müller 1977 [13]	57	ND	23 (40) RAST
Miyachi 1979 [8]	137	ND	41 (30) RAST
Bousquet 1984 [9]	200	59/176 (34)	84 (42) RAST
Annala 1995 [11]	102	55 (54)	61 (60) CAP
Torre-Morin 1995 [12]	246	84 (38)	126 (51) CAP

population [18–20]. In contrast to this, a history of atopic disease is more often reported in beekeepers with than those without bee venom allergy (Table 3) [8,11,14]. Beekeepers who suffer from symptoms of allergic rhinoconjunctivitis or asthma when working in the beehive are most often sensitized to bee whole-body extract, sometimes also to bee venom [10], and are at a significantly increased risk of developing systemic allergic sting reactions [15]. It has been suggested [8] that during their work in the beehive, atopic beekeepers get more easily sensitized than non-atopic beekeepers, most likely through inhalation of bee dust or multiple stings.

Immunopathogenesis of bee venom allergy and mechanisms of venom immunotherapy

Systemic allergic reactions to honeybee stings are considered to be due to IgE-mediated allergy. The most promi-

nent allergic symptoms during sting reactions – urticaria, angioedema, bronchial asthma and anaphylactic shock – are consistent with IgE-mediated type I allergy. Immediate type skin tests with bee venom are positive in more than 95% of patients and specific IgE-antibodies to bee venom allergens can be detected in more than 90% of them during the first year after an allergic sting reaction [21].

High levels of bee venom-specific IgG-antibodies have been found in heavily exposed beekeepers [22,23] as well as in patients on immunotherapy with bee venom [21]. While during early exposure, bee venom-specific IgG1-, IgG2- and IgG4-antibodies can be detected [24,25], venom-specific IgG4-antibodies dominate during long-standing immunotherapy or in heavily exposed beekeepers [22]. Passive immunotherapy with beekeeper gammaglobulin was shown to protect bee venom allergic patients effectively in several studies [26–28]. On the other hand, it has so far not been possible to reliably predict protection induced by venom immunotherapy on the basis of venom-specific IgG-, IgG4- or the quotient of IgG4- to IgE-antibodies in the serum taken immediately before a sting provocation test [29–31]. Several explanations have been offered for this discrepancy: (1) If IgE- and IgG/IgG4-antibodies to total bee venom are estimated, lacking IgG/IgG4-antibody formation to an individual allergen to which IgE-antibodies are present may be responsible for absent protection in spite of high total IgG/IgG4-antibodies. A recent blinded multicenter study analyzing individual venom-specific antibodies by immunoblot before a sting challenge during venom immunotherapy in 362 patients [30], however, did not result in a reliable predictive value either. (2) Anti-idiotypic antibodies against bee venom-specific IgE- or IgG-antibodies have been detected in the serum of beekeepers and of patients on venom immunotherapy but usually not in allergic patients before immunotherapy [32,33]. It was speculated that such anti-idiotypic antibodies directed against the allergen-specific variable domain of venom-specific IgE-antibodies could induce

Table 3. Atopy and bee venom allergy in beekeepers

Author, year		Allergic BK (%)		Non-allergic BK (%)
atopy from	n		n	
Miyachi 1979 [8]				
History	34	16 (47)	47	6 (13)
RAST	34	15 (44)	47	5 (11)
Bousquet 1982 [14]				
History	100	41 (41)	150	24 (16)
Annala 1995 [11]				
History	31	13 (42)	42	9 (21)
Phadiatop	31	6 (19)	42	7 (17)

BK, beekeepers.

protection by interfering with the interaction of IgE-antibodies with the allergen. In another study, however, such anti-idiotypic antibodies were more often observed in patients on immunotherapy who reacted to a subsequent sting challenge than those who tolerated it [34].

Distinct alterations of the cellular immune response during bee venom immunotherapy have also been observed [35–37]. During this treatment, a decrease of T-cell proliferation following allergen stimulation in lymphocyte cultures, as well as a diminished secretion of Th2-cytokines IL4, IL5 and IL13, was described, indicating a suppression of the Th2-dominated immune response typical for IgE-mediated allergy. The results were less consistent with regard to Th1 cells. Some authors observed increased secretion of Th1-cytokines, especially IFN γ , following allergen stimulation, indicating a switch from a Th2 to a Th1-dominated immune response [35,36]; others did not [37]. More recently, it was observed that the secretion of IL-10 increases rapidly during venom immunotherapy (VIT), more or less in parallel with the suppression of both Th1 and Th2 response [38]. In the beekeeper model, T-cell proliferation and cytokine secretion in allergen stimulated T-cell cultures increase during the sting-free winter season, while specific serum IgG4-antibodies decrease. Following heavy re-exposure in spring, the situation is rapidly reversed: specific serum IgG4-antibodies increase while in-vitro T-cell proliferation and both Th2- and

Th1-cytokine secretion following allergen stimulation decrease rapidly. These changes are in parallel to a strong increase in IL-10 secretion and can be inhibited by addition of anti-IL-10 receptor antibodies to the culture medium [39[•]]. Moreover, IL-10 induces a change in the isotype of venom-specific antibodies from IgE to IgG4 and by suppression of Th2-cytokine secretion interferes with priming, survival and activity of effector cells such as mast cells, basophils and eosinophils [40^{••}]. These observations lead to the concept that high dose allergen exposure as during venom immunotherapy or beekeeping induces CD4+ CD25+ T-regulatory cells which, over IL-10 secretion, balance the deviated immune response and thus induce allergen-specific immune tolerance [39[•],40^{••}].

Characterization of bee venom allergic beekeepers and their family members

The comparison of 62 bee venom allergic beekeepers and 44 family members of beekeepers with 101 normally exposed bee venom allergic patients [17] revealed highly significant differences between the three groups, as shown in Table 4. As expected, the number of stings before the first allergic reaction was very much higher in beekeepers than in their family members and non-beekeepers. Consequently, the level of specific IgG-antibodies to bee venom was significantly higher in beekeepers than in the two other groups. On the other hand, type I sensitivity according to i.c. skin test threshold to bee venom and serum bee venom-specific IgE-antibodies

Table 4. Comparison of patients with bee venom allergy among beekeepers, their family members and normally exposed patients (after [17])

	BK (n = 62)	FM (n = 44)	Controls (n = 101)	p value**	
				BK vs FM	BK vs C
Number of stings so far-% with				<0.001	<0.001
<10	8	60	75		
10–50	44	28	22		
>50	48	12	3		
Grade of allergic reaction*-% with				ns	ns
I	10	7	5		
II	23	27	24		
III	44	36	40		
IV	23	30	31		
i.c. skin test with BV-% with EPC				<0.05	<0.05
$\leq 10^{-8}$ g/l	20	42	42		
$\leq 10^{-6}$ g/l	36	37	32		
$\leq 10^{-4}$ g/l	44	21	26		
BV-specific IgE (RAST)-% with kU/l				ns	<0.05
≥ 17.5	8	9	20		
3.5–17.4	28	44	38		
0.35–3.4	57	40	39		
<0.35	7	7	3		
BV-specific IgG (ELISA)-% with mg/l				<0.05	<0.05
≥ 5	63	54	45		
0.31–5	37	31	42		
<0.31	0	15	13		

BK, allergic beekeepers; BV, bee venom; C, allergic controls; EPC, endpoint concentration: lowest venom concentration resulting in a wheal of 5 mm in diameter with erythema; FM, allergic family members.

*grade of reaction after HL Mueller [41];

**contingency table chi-square test. ns, not significant; i.c., intracutaneous.

were significantly lower in beekeepers than in the two other groups. While all allergic beekeepers had positive i.c. skin test with bee venom, no venom-specific serum IgE could be detected in 7% of them. In allergic – as in non-allergic beekeepers [9,17] – the bee venom-specific IgG-antibodies are positively correlated with the number of stings, while skin sensitivity and bee venom-specific IgE-antibodies are negatively correlated with this parameter. The significantly reduced sensitivity according to skin tests and serum bee venom-specific IgE-antibodies in beekeepers as compared with normally exposed bee venom allergic individuals suggests that specific IgG-antibodies might interfere directly with allergen IgE-antibody interaction during skin testing or in the RAST assay. Suppression of IgE-antibody formation in B-cells and increased specific IgG4-antibody formation owing to the stimulation of T-regulatory cells by the high number of stings may be an alternative explanation [39,40]. Interestingly, no difference in the severity of allergic sting reactions was observed.

Management of bee venom allergy in beekeepers and their family members

Management of patients with bee venom allergy comprises: (1) instruction for reduction of exposure to bee stings, including the procedure in case of re-exposure especially; (2) self-medication for emergency treatment; and, in most cases, (3) allergen immunotherapy with honeybee venom.

Reduction of exposure

The most obvious measure in beekeepers is to recommend reducing exposure [21,42] by stopping beekeeping and, in family members of beekeepers, by removing the hives from the vicinity of the home of the family. Many beekeepers, however, reject such recommendations because they are very fond of their bees. Allergic family members should certainly not assist in beekeeping activities and allergic beekeepers who continue beekeeping must always wear protective clothes and veils in the hive in order to avoid multiple simultaneous stings [17].

Self-medication for emergency treatment

Several sets of emergency medication, especially adrenaline for autoinjection (Epipen®) must be available in the beehive and in the home of the beekeeper. Thorough and repeated instruction in the use of the autoinjector by means of training devices is mandatory [43].

Indication and protocols for venom immunotherapy

In allergic beekeepers who agree to stop beekeeping and in allergic family members of a beekeeper who abandons beekeeping, the indications are the same as in other bee venom allergic patients [42]: VIT is strongly recommended in patients with positive diagnostic tests and a history of moderate to severe systemic allergic reactions,

Table 5. Tolerance and efficacy of bee venom immunotherapy in allergic beekeepers (BK) as compared with allergic family members (FM) and normally exposed bee venom allergic patients (C) (after [17])

	Allergic BK	Allergic FM	Allergic C
Number on VIT	43	24	61
<i>Tolerance</i>			
Allergic side effects (%)	12 (28)	12 (50)	30 (49)
<i>Efficacy</i>			
Number challenged	41	11	33
Systemic reaction to challenge (%)	7 (17)	1 (6)	7 (21)
Side effects:	allergic BK versus allergic C allergic BK versus allergic FM		$p < 0.01$ $p < 0.05$
Efficacy:	allergic BK versus allergic C		not significant

notably with respiratory or cardiovascular symptoms. In patients with only cutaneous reactions, VIT is indicated if the patient remains highly exposed or such reactions occurred repeatedly. Allergic beekeepers who continue beekeeping should be started on VIT. In order to achieve rapid protection, an ultra-rush protocol is usually chosen [42]. We recommend a maintenance dose of 200 µg [17], as such patients may be stung by more than one insect at the time, even when wearing protective clothes and veils [21]. A sting provocation test under clinical conditions should be performed and tolerated before the patient goes back to beekeeping. In our experience [17], the rate of allergic side effects of venom immunotherapy is lower in beekeepers than in normally exposed bee venom allergic patients, while the efficacy according to a sting challenge is similar (Table 5).

We recommend continuing VIT with monthly injections of 200 µg as long as the patient continues beekeeping. Once maintenance injections and field stings have been well tolerated for 3 years, regular re-exposure with one to two weekly stings at the hive may replace treatment injections during the flying season, but treatment injections should go on during winter.

Conclusion

Beekeepers and, to a lesser degree, their family members are especially at risk of developing allergic bee sting reactions. Definite risk factors in beekeepers are:

- (1) the first years of beekeeping; the first stings in spring [10,13,15];
- (2) fewer than 10 annual bee stings [9,17];
- (3) high skin sensitivity and serum-specific IgE to bee venom and low serum venom-specific IgG [15,17];
- (4) a history of atopic disease [8,9]; and
- (5) symptoms of upper respiratory tract allergy during work in beehives [15].

Venom immunotherapy is better tolerated in beekeepers than in normally exposed bee venom allergic patients,

but efficacy is similar. Careful instruction of this highly exposed population with regard to avoidance of re-exposure, emergency treatment and specific immunotherapy with bee venom is mandatory.

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