

Allergy to bumblebee venom

I. Occupational anaphylaxis to bumblebee venom: diagnosis and treatment

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We describe six patients with severe occasional anaphylaxis, caused by stings of bumblebees. Sensitization to bumblebee venom was confirmed by intracutaneous tests and RAST with purified bumblebee venom. Three patients changed their occupation and will probably not be stung by bumblebees in the future. The other patients started immunotherapy with newly purified bumblebee venom extract. After 1 year of treatment, no severe side-effects had occurred and clinical benefit in two patients could be demonstrated, as both skin sensitivity or serum IgE to bumblebee venom had decreased. Moreover, both patients were unresponsive to in-hospital sting challenge.

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The role of the bumblebee in Hymenoptera anaphylaxis is limited. Bumblebees are fewer and less aggressive than honeybees or yellow jackets. Therefore, stings by bumblebees have been rare. However, a newly developing Dutch bioindustry uses bumblebees in greenhouses for the pollination of vegetable flowers such as those of tomatoes. This can account for the increasing number of anaphylactic reactions to bumblebee stings reported in the literature (4, 7).

This paper describes six cases of severe anaphylaxis after bumblebee sting: five of these cases were related to occupational exposure.

Case history

The general characteristics of the six patients referred to the outpatient clinic of the department of allergology of Dijkzigt Hospital (Rotterdam, The Netherlands) are summarized in Table 1.

Patient Rij worked in a tomato greenhouse for 15 years and was stung approximately 25 times (in 4 years) by bumblebees with only a mild local reaction. After a sting in his toe, he immediately noticed generalized itching and facial urticaria. After 20 min, he developed abdominal pain and hypotension.

Patient Ko owned a tomato greenhouse and used bumblebees for pollinating the flowers for 3 years.

Table 1. General characteristics of six patients with bumblebee venom allergy

Patient	Rij	Ko	Mu	Hu	Kr	Ba
Age (years)	48	58	49	19	31	27
Sex	M	M	F	M	M	F
Phadiatop	+	-	+	n.d.	n.d.	+
RAST grass pollen	18.9 (4)	n.d. (2)	2.88 (2)	2.64 (2)	<0.35 (0)	0.58 (1)
RAST house-dust mite	<0.35 (0)	n.d. (3)	3.65 (3)	58.3 (5)	<0.35 (0)	<0.35 (0)
RAST cat dander	<0.35 (0)	n.d. (0)	<0.35 (0)	2.94 (2)	<0.35 (0)	<0.35 (0)
Total IgE	129	46	731	685	73	66

RAST and total IgE expressed in KU/l and classes in parentheses, as derived from Pharmacia CAP System.
n.d.: not done.

He was stung seven times without any systemic reaction. However, after a sting in his eyelid, he immediately experienced complaints of nausea, dizziness, and transpiration. Finally he collapsed and hypotension was measured.

Patient Mu worked frequently in her garden and was stung many times by honeybees without a reaction. The first bumblebee sting in a finger resulted in edema of the arm for 1 week. After a second bumblebee sting in a finger, she developed within 10

min a huge local reaction, generalized urticaria, dizziness, and collapse, due to severe hypotension.

Patient Hu worked for 2 years in a bumblebee farm. He was stung 15 times with only mild local reactions, until the last time, when he was stung in his ear and developed generalized urticaria, dizziness, and muscle weakness within a few minutes. He collapsed, and hypotension was confirmed.

Patient Kr worked for 1 year as a carpenter in a bumblebee farm. After four local reactions to a sting, he was stung in his forearm and developed within 10 min stridor, hoarseness, pain in the chest, generalized edema, and urticaria.

Patient Ba worked for 6 months in a bumblebee farm and was stung approximately 30 times with only mild local reactions. After a sting in the neck she immediately developed generalized exanthema, conjunctivitis, and dizziness. After 30 min, she had generalized urticaria and facial edema, and severe hypotension followed after another 30 min.

All patients were treated successfully with epinephrine and clemastine, and, in the case of dyspnea, with corticosteroids. They were monitored for 24 h.

Three patients (Hu, Kr, Ba) worked temporarily with bumblebees and will not come into contact with stinging insects in their future occupations.

Patients Rij, Ko, and Mu will, due to their occupation, remain in contact with bumblebees. An Epipen-autodevice was prescribed, and we decided to start immunotherapy with bumblebee venom.

Material and methods

Skin test

Skin tests were performed intracutaneously with 0.02 ml of 10-fold dilutions of Hymenoptera venoms (yellow jacket venom, honeybee venom, and bumblebee venom (*Bombus terrestris*). After 20 min, wheal-and-flare reactions were measured with the grading system of standardized plus signs devised by Norman (6). The negative control wheal with dilution buffer only was considered valid if the wheal disappeared or was less than 2 mm. The positive control test was histamine diphosphate (0.1 mg/ml). All skin tests were performed by the same skilled nurses. Venom extracts were obtained from Diephuis Groningen, ALK Benelux, Groningen, The Netherlands. Bumblebee venom used for skin tests and immunotherapy was obtained by electric stimulation.

RAST

For routine RAST with honeybee venom, yellow jacket venom, and common inhalant allergens, the Pharmacia Cap method was used according to the manufacturer's instructions. For detection of IgE antibodies to bumblebee venom, isolated bumblebee

venom sacs were extracted and proteins were insolubilized by coupling to CNBr-activated Sepharose (1).

In-hospital sting challenge

Patients underwent sting challenge under intensive care conditions. Intravenous access and cardiac monitoring were established. Blood pressure, pulse rate, and expiratory peak flow were recorded every 5 min for 1 h after a sting. Patients spent another hour in our outpatient clinic under close observation.

Fresh bumblebees were obtained on the morning of the challenge. One bumblebee was applied to the upper leg of each patient, until the insect died after 2–4 stings.

Results

Diagnosis of bumblebee venom anaphylaxis was confirmed with skin test and RAST for the six patients described above. The results of the skin tests and determination of venom-specific IgE against bumblebee venom, honeybee venom, and yellow jacket venom, respectively, are summarized in Tables 2 and 3. All patients showed a strong positive skin reaction to bumblebee venom and high levels of bumblebee-specific IgE antibodies. To evaluate the specificity of the positive skin reactions, three control subjects were tested intracutaneously with 100 µg of bumblebee venom extract. No positive reactions were found. In most patients, increased levels of IgE against honeybee venom were found, and to a lesser extent against yellow jacket venom.

RAST inhibition experiments with patient Rij showed a low (less than 50%) percentage of cross-reactivity between bumblebee venom and honeybee venom (preliminary data). Moreover, patient Ko showed no evidence of cross-reactivity between bumblebee venom and honeybee venom, as allergy

Table 2. Results of intracutaneous tests with Hymenoptera venoms of six patients with bumblebee venom anaphylaxis

Patient:	Rij	Ko	Mu	Hu	Kr	Ba
Venom						
Bumblebee	0.1 (0.1)	10 (100)	0.0001	0.0001	0.00001	0.0001
Yellow jacket	–	–	10	–	–	–
Honeybee	100	–	1	100	–	10

Intracutaneous test data expressed as end-point titration in ng/ml venom injected with positive reaction (erythema of 11–20 mm and wheal of 5–10 mm each), according to grading system of Norman (6).

– represents erythema and wheal of <5 mm each, up to concentration of bumblebee venom of 100 ng injected. For patients Rij and Ko, data after 1 year of immunotherapy with bumblebee venom are shown in parentheses.

Table 3. Results of RAST with Hymenoptera venoms of six patients with bumblebee venom allergy

Patient:	Rij	Ko	Mu	Hu	Kr	Ba
Venom						
Bumblebee	4+ (3+)	3+ (3+)	4+	4+	5+	4+
Yellow jacket	36.0 (4)	<0.35 (0)	2.53 (2)	0.46 (1)	0.49 (1)	<0.35 (0)
Honeybee	61.2 (5)	<0.35 (0)	49.7 (4)	1.59 (2)	1.59 (2)	3.17 (2)

RAST expressed in KU/l and classes in parentheses, as derived from Pharmacia CAP System, for yellow jacket venom and honeybee venom. For bumblebee venom, RAST classes are shown derived from percent binding of ^{125}I -radiolabeled anti-IgE to bumblebee Sepharose. 10–20% bound means class 3+, 20–40% class 4+, and >40% bound anti-IgE class 5+. Percent binding of ^{125}I -labeled anti-IgE to bumblebee venom Sepharose produced by normal control sera was always less than 2%.

For patients Rij and Ko, data after 1 year of immunotherapy with bumblebee venom are shown in parentheses.

to honeybee venom could not be established in RAST and skin tests. We therefore decided to treat patients Ko, Rij, and Mu with purified bumblebee venom extract. The injection schedule for the first two patients is presented in Table 4. There were no systemic reactions so far.

After 1 year of immunotherapy, patients Ko and Rij were evaluated by RAST, skin test, and in-hospital sting challenge. Sensitivity to bumblebee venom was lower after 1 year of treatment in both patients, a finding which was in accordance with the decreased results for the bumblebee venom RAST and the intracutaneous skin tests (Tables 2 and 3). After in-hospital sting challenge, only large local reactions were seen, without systemic complaints, in both patients. Moreover, circulation parameters and lung function remained normal for more than 2 h after the bumblebee stings.

No additional field stings were experienced by any of the patients.

Table 4. Cluster venom immunotherapy regimen and maintenance venom immunotherapy with bumblebee venom in patients Rij and Ko

Cluster venom immunotherapy					
Week	Injection interval (h)	Doses (μg venom per ml injected)			
1	1	0.00001	0.00005		
2	1	0.0001	0.0005	0.001	0.005
3	1	0.01	0.05	0.1	0.3
4	1	0.5	0.8	1.0	2.0
5	1	4.0	6.0	8.0	10.0
6	1	10	20	40	
7	1	50	50		
8	1	100			
10		100			
12		100			

Maintenance venom immunotherapy: every 4 weeks 1 ml injected, containing 100 μg bumblebee venom.

Discussion

Field stings by bumblebees are uncommon because of the habitat and nonaggressiveness of bumblebees. More stings have been reported lately in The Netherlands because of the increasing use of bumblebees in industries such as tomato growing.

This article describes six patients with an anaphylactic reaction to bumblebee venom. Five patients developed a grade IV reaction and one patient a grade III reaction, according to the classification of anaphylaxis by Mueller (5). Sensitization to bumblebee venom was confirmed by intracutaneous skin tests and RAST with purified bumblebee venom extract.

Five patients were stung at work in the tomato greenhouse or bumblebee farm. Three of them were persuaded to change their job; therefore, their chance of being stung in the future is negligible. As the other patients could not avoid bumblebees, immunotherapy was started. Kochuyt et al. reported successful immunotherapy in seven bumblebee-allergic patients with honeybee venom, attributing the efficacy of treatment to the similarity of honeybee venom and bumblebee venom. Six patients were resting on 36 occasions. A large local reaction occurred in two subjects, but no systemic reactions were noted (4).

We used immunotherapy with bumblebee venom for three reasons. Firstly, purified bumblebee venom extract is readily available. Secondly, RAST inhibition in one of our patients suggested that the major part of the IgE response of this patient was directed to bumblebee-specific allergens (preliminary data). Thirdly, in another patient, only sensitization to bumblebee venom was found without evidence of sensitization to honeybee venom. Hoffman reported a high cross-reactivity rate between bumblebee venom and honeybee venom extract, with at least four similar *Apis* allergens (3). However, in our patients, primary sensitization occurred after stings with bumblebees, and not with honeybees. Probably, this resulted in less cross-reactive sera.

Immunotherapy with purified bumblebee venom extract was started very carefully in the first two patients. We used a cluster protocol, starting with very low doses of venom injected subcutaneously. No severe reactions occurred during this treatment, and we started to treat a third patient with a more rapid increase in the dose of venom injected.

After 1 year of immunotherapy, the first two patients could be evaluated. They have not been resting at work. Sensitization was lower, using intracutaneous skin tests and RAST, compared to pretreatment data. A challenge test with a live bumblebee was performed under strict monitoring conditions. No systemic anaphylactic reactions occurred in these patients; however, a single negative

response to an in-hospital sting challenge should be interpreted with caution due to the lack of reproducibility, as shown in the case of yellow jackets in in-hospital stings by Franken et al. (2).

The decrease of skin test sensitivity and specific IgE, in addition to the negative challenge outcome, suggests that there is clinical benefit from 1-year immunotherapy with bumblebee venom.

We will continue with immunotherapy with purified bumblebee venom extract in the three patients described and will soon administer this kind of treatment to more patients with occupational anaphylaxis to bumblebees.

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