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RESEARCH PAPER

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Hymenoptera venom allergy in outdoor workers: Occupational exposure, clinical features and effects of allergen immunotherapy

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ABSTRACT

Objectives. To describe (i) the clinical characteristics of workers, exposed to hymenoptera stings, with an ascertained diagnosis of Hymenoptera Venom Allergy (HVA), (ii) the specific role of occupational exposure, (iii) the effect of Venom Immunotherapy (VIT) in reducing the severity of allergic episodes in workers exposed to repeated stings of hymenoptera, and (iv) the management of the occupational consequences caused by allergic reactions due to hymenoptera stings.

Methods. Between 2000 and 2013 an observational study, including patients referred to the regional reference hospital of Liguria, Italy, with an ascertained diagnosis of HVA and treated with VIT, was performed. A structured questionnaire was administered to all patients to investigate the occupational features of allergic reactions. These were graded according to standard systems in patients at the first episode, and after re-stings, during VIT.

Results. One-hundred and 8four out of the 202 patients referred had a complete data set. In 32 (17.4%) patients, the allergic reaction occurred during work activities performed outdoor. Of these, 31.2% previously stung by hymenoptera at work, and receiving VIT, were re-stung during occupational activity. The grades of reaction developed under VIT treatment resulted clinically less severe than of those occurred at the first sting (p-value = 0.031).

Conclusion. Our findings confirmed the clinical relevance of HVA, and described its occupational features in outdoor workers with sensitization, stressing the importance of an early identification and proper management of the professional categories recognized at high risk of hymenoptera stings. The Occupational Physician should be supported by other specialists to recommend appropriate diagnostic procedures and the prescription of VIT, which resulted an effective treatment for the prevention of episodes of severe reactions in workers with a proven HVA.

KEYWORDS

Hymenoptera-Venom Allergy (HVA); Venom Immunotherapy (VIT); Allergen Immunotherapy; anaphylaxis; occupational allergy; prevention; outdoor workers

Introduction

Venom immunotherapy (VIT) is an extremely effective form of treatment for individuals at risk of insect sting systemic reactions, i.e. flying hymenoptera, an order of insects comprising honeybees, yellow jackets, hornets, and wasps. VIT reduces the risk of a subsequent systemic sting reaction to as low as 5% compared with the risk of such reactions in untreated patients, for whom the risk might be as high as 60%.[1]

The prevalence of hymenoptera stings in the general population ranges from 56.6% to 94.5%, and can vary according to the location and the climatic conditions,[2] whereas the estimated prevalence of Hymenoptera-Venom Allergy (HVA) is around 5%.[3] IgE-mediated allergic reactions triggered by hymenoptera stings range from Large Local Reactions (LLR), to systemic reactions (urticaria, angioedema, asthma) with immediate symptoms, until anaphylaxis, which is often life-threatening.[4] Non-allergic reactions to hymenoptera stings include the well-known local irritative phenomena and, more rarely, toxic systemic reactions.[5,6]

LLR are usually defined by acute wheal and flare, with a diameter >10 cm, and a duration of >24 hours.[7] Anaphylactic systemic reactions are serious hypersensitivity events, with signs and symptoms that occur within 2 hours, but usually in a few minutes, after the insect sting. The clinical presentation is characterized by urticaria/angioedema, gastrointestinal symptoms, asthma and/or cardiovascular involvement, variously associated, until shock and loss of consciousness.[8]

In Europe, the prevalence of LLR due to hymenoptera stings is estimated to range between 2.4% and 26.4%, whereas that of systemic reactions vary between 0.3% and 8.9%.[9-11] Despite the available epidemiological data showing in the highly exposed population of beekeepers up to 26% of systemic allergic reactions,[3] few studies investigated HVA from an occupational

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point of view, in other workers exposed to the specific professional risk. Hayashi et al., in a Japanese study, reported a 21% and 14% prevalence of systemic reactions in forest rangers and electrical systems technicians, respectively,[12] whereas Kochuyt et al. reported a rate of 10% in workers performing pollination with bumblebees in greenhouses.[13] Some cases of hymenoptera-venom anaphylactic reactions, in gardeners, masons and truck drivers have been reported as an occupational risk.[14]

VIT is currently considered the only disease-modifying treatment, that can protect against severe reactions at re-sting more than 90% of subjects, when correctly prescribed.[9] The IRCCS AOU San Martino – IST teaching Hospital of Genoa in Liguria, Italy, is a regional reference center, and for many years has dealt with the preventive, diagnostic, clinical, and therapeutic aspects related to HVA, also involving the occupational field. In this context, we performed an observational study in patients with an ascertained diagnosis of HVA, and prescribed with VIT, with the purpose to describe (i) the clinical characteristics of workers, exposed to hymenoptera stings, with an ascertained diagnosis of HVA, (ii) the specific role of occupational exposure, (iii) the effect of VIT in reducing the severity of allergic episodes in workers exposed to repeated stings of hymenoptera, and (iv) the management of the occupational consequences caused by allergic reactions due to hymenoptera stings.

In addition, indications for proper risk-management in the workplace for subjects at high risk of exposure to hymenoptera stings have been proposed.

Results

We conducted an observational study on patients seen in the period 2000–2013 at the Allergy Unit and the Clinic of Respiratory Diseases and Allergy, within the IRCCS AOU San Martino – IST teaching Hospital of Genoa, Italy. During the study period, 202 patients (65.8% men; mean age = 56 years; Standard Deviation (SD) = 16.2; range 9–90 years) had a confirmed diagnosis of HVA and consequently received a VIT prescription. To better identify and dissect the characteristics of hymenoptera stings during current or previous occupational activities, and to identify the exposure related to work environment, we administered a structured questionnaire. Detailed information concerning the structured questionnaire used in the survey is available in Appendix 1 (Supplementary File). The questionnaire was administered to all patients: 184 subjects were eligible for the analysis, since 18 were lost upon follow-up or provided incomplete responses. Out of the 184 patients included in the survey, 145 (78.0%) had been admitted to Emergency Department (ED) and the remaining were referred by their General Practitioner. The characteristics of the study population, also according to their occupational activity and to the occurrence of re-sting, are detailed in Figure 1.

The clinical features of the allergic reactions at first referral, classified according to the grade of severity,[15] are shown in Table 1, while the types of occupational activity of the patients stung by hymenoptera at work are summarized in Table 2. The insect involved, when recognized, were the Yellow-jacket (n = 30, 16.3%), Polistes (n = 7, 3.8%), European Hornet (n = 57, 31.0%), Honeybee (n = 27, 14.7%); in 63 (34.2%) cases the insect was unknown. 114 (62.0%) out of the 184 patients were regularly employed, whereas 70 (38.0%) were not (i.e., retired, housewives, students). The latter group reported to have been stung by hymenoptera by one or more times, during recreational activities performed outdoor (i.e., gardening or sport activities). Out of the regularly employed patients, 69 (60.5%) and 45 (39.5%) worked outdoor and indoor, respectively: none of the individuals working indoor reported previous hymenoptera stings. Thirty-two (28.0%) currently employed subjects developed an allergic reaction during work activity. If we consider only the outdoor population of workers as the denominator, this figure goes up to 46.4%.

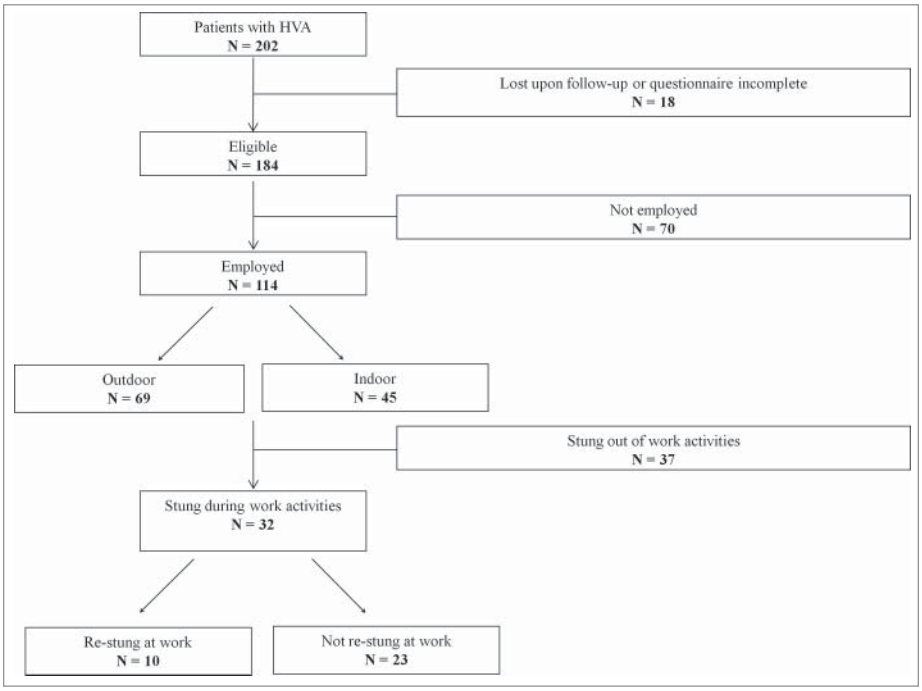

Figure 1. Disposition of the population according to characteristics of the occupational activity, occurrence of re-sting and Venom Immunotherapy (VIT).

Table 1. Clinical characteristics of the allergic reactions occurred at the first sting including those occurred in patients with access to the Emergency Department and referred by the General Practitioner.

Severity grade	N	%
Large Local Reaction	5	2.7
Systemic reaction Grade I	22	12.0
Systemic reaction Grade II	38	20.7
Systemic reaction Grade III	45	24.4
Systemic reaction Grade IV	56	30.4
Undefined reaction	18	9.8
Total	**184**	**100.0**

Table 3. Severity grade and need of access to the Emergency Department (ED) in patients stung during outdoor work activities.

	Access to ED N (%)	No access to ED N (%)	Total N (%)
Large local reaction	1 (5.0)	2 (16.7)	3 (9.4)
Grade I systemic reaction	1 (5.0)	4 (33.4)	5 (15.6)
Grade II systemic reaction	2 (10.0)	3 (25.0)	5 (15.6)
Grade III systemic reaction	6 (30.0)	1 (8.3)	7 (21.9)
Grade IV Systemic reaction	7 (35.0)	1 (8.3)	8 (25.0)
Unidentified reaction	3 (15.0)	1 (8.3)	4 (12.5)
Total	**20 (100.0)**	**12 (100.0)**	**32 (100.0)**

The severity of the reaction grade and the access to the ED of the 32 subjects stung during outdoor work activities are shown in Table 3: a high frequency of grade IV severity was reported. Out of 20 (62.5%) patients who accessed the ED, 13 (65.0%) reported systemic reactions classified as grade III or IV.

Fifteen (75.0%) of these 20 workers were employed workers. Nine out of these 20 workers (45.0%) claimed for occupational injury to the Italian National Institute for Injuries at Work and Professional Diseases (INAIL), being the occupational injury recognized in 2 cases (grade III systemic reaction). Globally, 23 (71.8%) workers maintained their activity after the allergic reactions: 9 workers had either to change their occupation (3 subjects) or to retire (6 subjects).

Only beekeepers declared to use Personal Protective Equipment (PPE) during work activity, although not regularly, and emergency pharmacological kits resulted not to be always available, even in categories usually considered to be at high risk of occupational exposure to hymenoptera stings.[14]

Ten (31.2%) workers, all under VIT treatment, were re-stung on more than one occasion during occupational activity: none of these individuals had an ED admission and no grade II-IV systemic allergic reactions occurred. The clinical characteristics of the HVA reactions at the first sting and at re-sting during VIT are reported in Table 4: a significant difference (p-value = 0.031) emerged from the inter-group comparison.

Discussion

HVA represents a Public Health issue due to the estimated prevalence of about 5% in the general population, and the associated risk of serious reactions (i.e., anaphylaxis) reported at values up to 9% in Europe.[2,3] Any effort to improve the knowledge on the clinical burden and proper management of HVA is desirable and can be useful to improve its prevention, especially if HVA is considered as an occupational problem. In this observational study, performed in a large case series of patients with HVA, we focused on the role of occupational exposure, the effects of VIT, attempting to provide indications for proper risk-management in the work places for subjects at high risk of exposure to hymenoptera stings.

The clinical relevance of allergic reactions in patients stung by hymenoptera was confirmed in our survey, where 101 (55%) of the overall cases investigated reported systemic reactions classified as grade III–IV, with 145 (79%) of them requiring admission to the hospital ED.

More than 17% of the patients developed at least one allergic reaction at work, unlike indoor workers, among which no cases were reported. More than 46% of the study sample included outdoor workers. Workers who resulted to be mostly affected were beekeepers and masons (22%), followed by gardeners (12.5%), drivers and technicians (9.4%). All these subjects had an ascertained occupational risk for hymenoptera sting, although at a different grade according to the type of occupational activity. Similar experiences in various populations of workers have been performed in Italy: a 5% prevalence of systemic reactions was observed in forest rangers,[16] whereas prevalences of 1% and 27% of systemic reactions and LLR were found among firemen, respectively.[17] Interestingly, Bonadonna et al., by comparing patients with HVA belonging to various work-categories (farmers, masons, truck drivers, gardeners, beekeepers, and dustmen) with the general population, found a significant higher frequency (range p-values = 0.01–0.05) in the first 3 professional categories; therefore they hypothesized a specific risk of sensitization to hymenoptera venom in specific groups of workers, suggesting that HVA needs to be considered

Table 2. Types of occupational activity in patients stung during outdoor work activities.

Occupational activity	N	%
Beekeeper	7	21.9
Construction worker	7	21.9
Gardener	4	12.5
Driver	3	9.4
Technicians	3	9.4
Police Officer	2	6.0
Farmer	2	6.3
Professional cyclist	1	3.1
Fruit and vegetable saleswoman	1	3.1
Plumber	1	3.1
Postman	1	3.1
Total	**32**	**100.0**

Table 4. Allergic reactions due to hymenoptera stings in workers under Venom Immunotherapy (VIT) (n = 10) who were stung on more than one occasion during occupational activity (pre vs. post-treatment, p-value = 0.031).

Allergic reaction	N of patients with first sting before VIT treatment	N of patients with repeated stings after VIT treatment
Large local reaction	1	8
Grade I Systemic reaction	1	2
Grade II Systemic reaction	1	0
Grade III Systemic reaction	1	0
Grade IV Systemic reaction	5	0
Unidentified reaction	1	0
Total	**10**	**10**

an occupational threat among these individuals.[14] Other Italian authors studied this phenomenon, confirming this specific occupational risk in farmers and among emergency workers.[18,19]

To date, according to the Italian Law, hymenoptera stings during work activities are specifically recognized as an occupational risk only for beekeepers, while they are considered as an "increased generic risk" in other outdoor workers.[20] In our study, in addition to beekeepers, also other categories appeared to share the same or similar occupational risks (construction workers, gardeners, drivers, and technicians). Notwithstanding this, we found that, apart from beekeepers, none of other workers who had been stung by hymenoptera used PPE, and life-saving pharmacological kits were occasionally available only for beekeepers, while absent in any other workplace.

In literature, risk factors that increase the frequency of sensitization to hymenoptera venom have been investigated: major exposure to risk in the living and working environments, number of stings, short intervals of time between stings. The role of individual atopy is controversial in literature. Moreover, previous severe reactions, together with specific individual conditions, such as systemic mastocytosis, cardiovascular diseases, β-blocking or ACE inhibitor treatments, or both, and high basal serum tryptase levels, can be considered as risk factors that increase the severity of subsequent reactions.[21] Bilò et al. reported that repeated exposure to stings was one of the leading risk factors for the onset of sensitization and allergic reactions, where a merely local reaction escalates to a serious systemic reaction, up to an anaphylaxis: this factor has been extensively proven in beekeepers and their family members.[22] Annila estimated a 26% prevalence of systemic reactions precisely in beekeepers,[3] whereas other authors have reported a prevalence that varied between 14 and 42%.[23]

The goals of VIT are to prevent systemic reactions and alleviate patient's anxiety related to insect stings.[1] Our survey showed the effectiveness of VIT in preventing episodes of severe reactions in workers with a proven HVA, exposed to the risk of being repeatedly stung by hymenoptera: a significant reduction in the frequency of serious reactions pre- vs. post-treatment was demonstrated. To our knowledge, this is the first time that the positive effect of this preventive practice is reported in the occupational field, and this supports its specific recommendation at least in workers with a high occupational risk. Some studies from the literature have shown how previous reactions to hymenoptera venom can lead to occupational problems, especially when severe reactions occur during work.[24] In our survey, workers greatly benefited from VIT, with more than 70% of them continuing their occupational activity, whereas only less than 30% had to change or cease it. Our data are plausible and in line with the highly effective VIT treatment results (90%) in reducing systemic reactions, both in the occupational and in the non-occupational settings.[24-26] Therefore, VIT as well as protecting health in some allergic individuals, could represent a valid tool to recommend in specific categories of outdoor workers recognized at high risk for HVA.[27] Recently, also Moscato at al. showed how immunotherapy, together with other biological treatments, such as omalizumab, can help people to continue their work in the event exposure is unavoidable.[28]

This study has some limits: the small number of participants, together with a lack of demographic and clinical epidemiological information concerning the patients who did not take part in the survey. Moreover, a structured, but not validated, questionnaire was used.

Our data suggest that, during routine healthcare surveillance, it could be useful for the Occupational Physician to conduct an accurate anamnesis in order to identify individuals at risk of developing HVA reactions. These workers should be referred to a specialist in allergy for diagnostic exams and, eventually, start VIT as a targeted preventive measure.

Finally, it would be crucial to improve worker's ability to properly manage acute allergic reactions directly at the workplace: this entails the capability to recognize clinical signs and symptoms early, and to administer specific treatments that need to be immediately available (i.e., an emergency pharmacological kit, including an antihistaminic and oral steroid, and self-injectable adrenalin for the most serious cases).[27] The provision of specific information and education, also with training courses for workers selected to conduct emergency procedures at the company level, could greatly improve the successful management of acute cases, both LLR and systemic reactions: this is of particular meaning especially in companies where there are workers known to be allergic, and who carry out jobs recognized to be at high risk.

Material & methods

The Allergy Unit and the Clinic of Respiratory Diseases and Allergy, within the IRCCS AOU San Martino – IST teaching Hospital of Genoa, Italy, receive on average 5.500 patients per year, and approximately 1.5% are referred for suspect allergy to insect stings. We conducted an observational study on patients seen in the period 2000–2013, selected according to the following criteria: (i) ascertained diagnosis of allergic reaction to hymenoptera sting, and (ii) prescribed treatment with VIT, according to international guidelines.[29-31] We collected demographic data (race, age, gender), information on the type of stinging insect, as well as a detailed clinical information about the type and severity of the reaction through medical charts. The severity was classified according to Mueller, as usually done in clinical trials.[15] Concerning anaphylaxis, several clinical criteria are proposed: for occupational anaphylaxis we adhered to the criteria available in literature.[32,33]

The structured questionnaire, administered to all patients, included: occupational history (outdoor high-risk environment/indoor low-risk environment, type of exposure), access to an ED, frequency, type and outcome of episodes due to hymenoptera re-stings, type of work (employee/independent), accidents during work, acknowledgment of the accident by the INAIL, variations in fitness to work by the Occupational Physician and/or maintaining the occupation, availability and use of PPE, availability and ability to use a pharmacological emergency kit.

The study involved only standard procedures, therefore, according to Italian rules, the Regional Ethics Committee was simply notified.[34,35] Personal information was protected according to Italian law.[36]

Mean, SD and ranges were considered for continuous variables, whereas absolute frequencies and percentages were considered for all the other measurements. McNemar's test was used to compare pre-post frequencies of the grade of allergic reaction in patients with an ascertained re-sting during occupational activity. For the application of the test, the category including the systemic reactions of any grade was considered as a whole, and compared versus the category of the LLR. SPSS (v.20; IBM) software was used for the analysis.

Abbreviations

ED	Emergency Department
HVA	Hymenoptera Venom Allergy
INAIL	Italian National Institute for Injuries at Work and Professional Diseases
LLR	Large Local Reactions
PPE	Personal Protective Equipment
SD	Standard Deviation
VIT	Venom Immunotherapy

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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Appendix

Appendix 1. The structured questionnaire used in the survey; the questionnaire was administered to all patients in Italian language.

Appendix 1

IRCCS Azienda Ospedaliera Universitaria San Martino – IST
Istituto Nazionale per la Ricerca sul Cancro
Largo Rosanna Benzi, 10 - 16132 Genova

QUESTIONNAIRE

Title of the study
"An observational study in patients with hymenoptera allergy: role of occupational exposure, allergen immunotherapy, and indications for prevention"
ID N ° |___|___|___| **Date of birth** |___|___| / |___|___| / |___|___|___|___| **Name initials** |___|___|
Gender: ☐ **M** ☐ **F**
Current and former work activities (i.e., regular, occasional, other):
_____
_____

1. Have you ever been stung by hymenoptera during your work?	YES		NO
IF "YES:"			
2. Please describe your job:			
3. The environment where you work was:	OUTDOOR OR MAINLY OUTDOOR		INDOOR OR MAINLY INDOOR
4. Type of employment:	EMPLOYEE		SELF EMPLOYEE / INDEPENDENT WORKER
5. Have you ever taken medications (i.e., antihistamines, cortisone, epinephrine) to manage a reaction?	YES		NO
6. Did you need to go to the Emergency Department?	YES		NO
7. Did you claim for occupational injury at work in the Emergency Department?	YES		NO
8. **If YES**, was the claim recognized by the Italian National Institute for Injuries at Work and Professional Diseases (INAIL)?	YES		NO
9. Since your first administration of hymenoptera venom "vaccination," have you been stung by hymenoptera again at work?	YES		NO
10. **If YES**, how was the reaction compare with the first one?	MORE SERIOUS	LESS SERIOUS	SIMILAR TO PREVIOUS
Please, describe signs and symptoms:			
11. How do you rate your job in terms of risk of being stung by hymenoptera?	LOW RISK	MEDIUM RISK	HIGH RISK
12. Do you currently practice or did you practice hobbies, outdoor sports, other recreational activities, and specific work activities with exposure to the risk of hymenoptera stings?	YES		NO
If YES, describe which:			
13. Did you need to change or stop your recreational or work activities after being stung by hymenoptera?	YES		NO
14. During work, have you ever used personal protective equipment to protect yourself against insect bites?	YES		NO
If YES, describe which:			
15. Is your Occupational Physician aware of your allergy?	YES		NO
16. Has your hymenoptera venom allergy ever caused any specific problem with respect to your professional activity? (i.e., critical issues with the Employer, variations in fitness to work, etc.)	YES		NO
If YES, provide further details:			
17. Notes by the Occupational Physician:			