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Title page

Title

Hymenoptera venom allergy: work disability and occupational impact of venom immunotherapy

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allergy, disability, hymenoptera, immunotherapy, venom.

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ABSTRACT

Objectives: Little is known about the Hymenoptera venom allergy impact on work ability and the effect of venom immunotherapy (VIT) on work. The objective of this study was to evaluate the prevalence and predictors of work disability in patients treated with VIT and the effects of VIT on occupational functioning.

Methods: 181 patients, aged 18–71, treated with VIT while working, were investigated by questionnaire. Subjects were classified into employed and self-employed and, based on work exposure to Hymenoptera, into three risk categories, high risk, occasionally high risk, and low risk. Work disability was defined as having to have changed jobs/tasks and/or suffered financial loss because of Hymenoptera venom allergy. Predictors of work disability were assessed in logistic regression models.

Results: 31 (17%) patients reported work disability. Being self employed and having the severe reaction at work were associated with work disability ($p<0.01$). Having a high-risk job for exposure to Hymenoptera was a significant predictor of work disability (OR 2.66, 95% CI 1.04-6.75). 24% of patients referred a positive effect of VIT on work. Determinants of the positive effect of VIT on work were having a high risk job for exposure to hymenoptera (OR 3.60, 95% CI 1.52 - 8.51) and having already concluded VIT (OR 2.82, 95% CI 1.30- 6.14).

Conclusions: Hymenoptera venom allergy could determine work disability. Patients with Hymenoptera venom allergy having a high risk job for exposure to Hymenoptera seem to have higher risk of work disability and refer more frequently a positive effect of VIT on work.

WHAT THIS PAPER ADDS

► Hymenoptera venom sting is recognized as a risk factor for relevant, often life-threatening, allergic reactions but little it is known about the socio-economical effects of hymenoptera venom allergy. In the present study, for the first time, work disability and occupational effects of venom immunotherapy were studied in a group of patients in working age.

► The results suggest that Hymenoptera venom allergy has an impact on work through causing work disability. Self-employed workers and workers at high risk of sting seem to be at higher risk of work disability related to Hymenoptera venom allergy. Type of job was also a predictor of a positive effect of VIT on work.

► To reduce the occupational burden of Hymenoptera venom allergy, interventions towards improving compliance to the treatment are urgently needed.

LIMITATIONS

► The small number of subjects could be considered a shortcoming of this survey

► The questionnaire has never been used in other studies

INTRODUCTION

Hymenoptera venom allergy affects approximately 5% of the general population and can provoke severe systemic or life-threatening reactions.[1] Epidemiological studies indicate a prevalence of self-reported systemic anaphylactic sting reactions between 0.3% and 7.5%, [2] and mortality due to insect sting ranging from 0.03 to 0.48 fatalities per 1,000,000 population per year.[3]

Since the late 1970s venom immunotherapy (VIT) has provided allergic subjects with protection from fatal anaphylaxis and prevented about 90% of all reactions to stings.[4] Patient compliance for long term continuation of VIT often decreases, making VIT an effective but challenging therapy.[5] Besides, even with VIT, for most patients as well as for their families, an anaphylactic reaction after a Hymenoptera sting is a very traumatic event, and the fear of a subsequent life-threatening episode may affect the emotional, social and occupational behaviour of the affected individual.[6] Recently a disease-specific questionnaire, the Vespid Allergy Quality of Life Questionnaire, was designed and validated for assessing health-related quality of life in patients with anaphylactic responses following yellow jacket stings. The survey showed that patients experienced quality of life impairment especially because of the emotional distress associated with having to be constantly on the alert while leading their everyday “normal” lives.[7]

One important part of the everyday “normal” life is work. Any factor that would affect occupational functioning could lead to work disability. Many definitions of work disability have been applied over the last decades. Recently, changing jobs or tasks, or having suffered loss in working days or in finance because of illness have often been used to define work disability in subjects with respiratory diseases.[8,9] Prevalence, incidence, determinants and VIT effects of allergic sting reactions have been largely investigated in selected occupational groups such as gardeners and beekeepers.[6] However, little is known about Hymenoptera venom allergy impact on work ability.

The main objective of this study is to evaluate the and predictors of work disability in a group of patients with Hymenoptera venom allergy treated with VIT and to investigate whether the impact of VIT is always positive or could negatively affect occupational functioning and work ability.

METHODS

Population and questionnaire

The clinical charts of 364 patients treated with VIT from 1997 to 2011 at the Perugia University Hospital, Italy, were reviewed. Prior to starting VIT, all the patients enrolled in this study underwent the diagnostic protocol according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines. The time required to reach the generally adequate maintenance venom dose of 100 µg with our protocol is several weeks and

immunotherapy is recommended for at least 5 years.[7] Of the 364 patients undergoing VIT, 183 were excluded from the study because they were retired, housewives or students. A total of 181 patients, aged 18–71, and treated with VIT while working, were eligible for the study. A questionnaire administered by a physician was used to collect data on demographic characteristics (age, gender, address), the offending insect and severity of symptoms after Hymenoptera stings, graded according to the Mueller classification. Circumstances regarding the Hymenoptera sting leading to the anaphylactic reaction and time from severe reaction were also reported. Subjects were classified as employed or self-employed and, as in according to a classification based on work exposure to Hymenoptera used in a previous study,[1] into three categories: high risk (individuals usually working outdoors or where Hymenoptera live: farmers, gardeners, fire fighters, truck drivers, masons, beekeepers, garbage collectors); occasionally at high risk (sometimes working outdoors e.g. plumbers); and at low risk (working indoors, e.g. clerks).

Work disability was defined as an affirmative response to at least one of these questions:

1) Did you change work because of Hymenoptera sting reaction?
2) Did you change your job tasks because of Hymenoptera sting reaction?
3) Did you suffer financial loss because of Hymenoptera sting reaction?

To assess the effect of VIT, specific questions were asked about a possible positive, negative or indifferent effect of the treatment on work. This included questions about possible indicators of a treatment-related positive effect, such as not having changed jobs or tasks and feeling safer at work, or indicators of a negative effect, such as financial loss, changes of job or task and changes in working time. Subject with negative or indifferent effect of VIT on work were classified as not having a positive effect on work.

The study protocol was approved by the Ethical Committee of Umbria Region (CEAS). All the patients gave their informed and written consent to participate in this study.

Statistical analysis

Differences between patients with and without work disability were evaluated by Chi-square test or Fisher's exact test, as appropriate, for categorical variables, and using Mann-Whitney U-test or *t*-test for continuous variables. Predictors of work disability and positive or negative VIT effects on work were assessed in logistic regression models, adjusted for gender and age, choosing as independent variables those showing a different distribution across the groups in the univariate analysis. The goodness of fit of the logistic regression models was confirmed by the Hosmer-Lemeshow test.[10] All the analyses were performed using SPSS statistical software, version 20.0 (SPSS, IBM Corporation, New York, NY, USA).

RESULTS

All 181 patients treated with VIT while working answered the questionnaire. Among them 68% were still undergoing VIT and 32% had concluded the therapy. The mean age was 49 years, 19% were female and more than half of the subjects lived in the countryside. Thirty-one patients (17%) reported work disability. No patient reported a complete work change because of Hymenoptera venom allergy, ten (5%) reported having had to change job tasks, and 25 (14%) reported financial loss because of Hymenoptera venom allergy, four (2%) reported both conditions. The characteristics of the study population, classified according to work disability due to Hymenoptera venom allergy, are shown in table 1. No differences were found in distribution of gender, residence, mean age, stinging insect, and severity of the allergic reaction between the two groups. In subjects with work disability, Vespula was responsible for 45% of the reactions, and 45% experienced a systemic allergic reaction grade 4, according to Mueller's classification.

Fourteen patients (45%) with work disability and 26 (17%) without work disability experienced a sting reaction to Hymenoptera during shift ($p<0.01$). Subjects with work disability were mostly workers at high risk of work exposure to Hymenoptera while subjects without work disability were mostly at low risk (68% *vs.* 41%, $p<0.001$) (table1).

Table 1 Characteristics of the patients with Hymenoptera venom allergy treated with venom immunotherapy (VIT), with or without work disability

	Subjects with work disability n=31	Subjects without work disability n=150	*p* value
Female, n (%)	6 (19.4)	37 (24.7)	NS
Age, mean ± SD	49.4±9.9	47.1±10.9	NS
Living in the countryside, n (%)	20 (64.5)	98 (65.3)	NS
VIT, n (%)			
Ongoing	21 (67.7)	101 (67.3)	NS
Concluded	10 (32.2)	49 (67.3)	
Treated with VIT for, n (%)			
Apis mellifera	11 (35.5)	48 (32)	NS
Vespula sp.	14 (45.2)	52 (34.7)	NS
Polistes sp.	3 (9.7)	38 (25.3)	NS
Vespa crabro	3 (9.7)	12 (8)	NS
Mueller reaction grade, n (%)			
I	6 (19.4)	27 (18)	NS
II	4 (12.9)	30 (20)	
III	7 (22.6)	30 (20)	
IV	14 (45.2)	63 (42)	
Ever stung before the reaction, n (%)	26 (83.9)	110 (73.3)	NS
Other severe hymenoptera reactions, n (%)	1 (3.2)	12 (8)	NS
Years after the first severe reaction, mean ± SD	9±6.7	7.1±5.7	NS
Having the severe reaction, n (%)			
at work	14 (45.2)	26(17.3)	<0.01
during sport	1 (3.2)	4 (2.7)	NS
during hobby activity	9 (29)	52 (34.7)	NS
at home	6 (19.4)	44 (29.3)	NS
in car/motorcycle	3 (9.7)	24 (16)	NS
Work-related risk of exposure to Hymenoptera, n (%)			
High	21 (67.7)	53 (35.3)	<0.01
Occasionally high	5 (16.1)	35 (23.3)	
Low	5 (16.1)	62 (41.3)	
Self-employed worker, n (%)	16 (51.6)	42 (28)	<0.01

NS = not significant; SD = standard deviation.

Forty-four subjects (24%) reported a positive effect of VIT on work, 93 no impact (51%) and 44 negative (24%) (table 2).

Table 2. **Effect of venom immunotherapy (VIT) on work**

Effect of venom immunotherapy (VIT) on work, n=183	
Positive effect of VIT on work, n (%)	**44 (24)**
-not having changed jobs or tasks, n (%)	*13 (7)*
-feeling safer at work, n (%)	*44 (24)*
Negative effect of VIT on work, n (%)	**44 (24)**
- having changed jobs or tasks, n (%)	*0 (0)*
-financial loss, n (%)	*29 (16)*
-changes in working time, n (%)	*41 (22)*
No effect of VIT on work, n (%)	**93 (51)**

VIT= venom immunotherapy

The characteristics of the population, classified by the presence or absence of the positive impact of VIT on work, are displayed in table 3.

Table 3 Characteristics of the patients with regard to the impact of venom immunotherapy (VIT) on work

	Impact of VIT on work		
	Positive n=44	Negative or indifferent n=137	p value
Female, n (%)	12 (27.3)	31 (22.6)	NS
Age, mean ± SD	49.7±11.7	46.8±10.3	NS
VIT, n (%)			
Ongoing	22 (50)	100 (73)	<0.01
Concluded	22 (50)	37 (27)	
Treated with VIT for, n (%)			
Apis mellifera	11 (25)	48 (35)	NS
Vespula sp.	17 (38.6)	49 (35.8)	NS
Polistes sp.	13 (22.7)	31 (22.6)	NS
Vespa crabro	6 (13.6)	9 (6.6)	NS
Mueller reaction grade, n (%)			
I	7 (15.9)	26 (19)	NS
II	6 (13.6)	28 (20.4)	
III	12 (27.3)	25 (18.2)	
IV	19 (43.2)	58 (42.3)	
Ever stung before the reaction, n (%)	38 (86.4)	102 (74.5)	NS
Other severe Hymenoptera reactions, n (%)	2 (4.5)	11 (8)	NS
Years after the first severe reaction, mean ± SD	7.7±5.4	7.3±6.1	NS
Having the severe reaction at work, n (%)	17 (38.6)	23 (16.8)	<0.005
Work-related risk of exposure to Hymenoptera, n (%)			
High	28 (63.6)	46 (33.6)	<0.01
Occasionally high	5 (11.4)	35 (25.5)	
Low	11 (25)	56 (40.9)	
Self-employed worker, n (%)	20 (45.5)	38 (27.7)	<0.05

. F = female; NS = not significant; SD = standard deviation

Subjects reporting a positive effect of VIT on work were more frequently at higher risk of work exposure to hymenoptera, self employed workers and have experienced the allergic reaction at work (table 3). Evaluating the same characteristics presented in table 3, there were no significant differences between those with a negative impact of VIT and the other participants (those with a positive o indifferent impact on work).

In the logistic regression analysis adjusted for gender and age, significant predictor of work disability was having a high-risk job for exposure to Hymenoptera (OR 2.66, 95% CI 1.04-6.75) (table 4).

Table 4. Predictors of work disability (WD) among patients undergoing Hymenoptera venom immunotherapy (VIT), adjusted for gender and age

	WD OR	95% CI	
Having the severe reaction at work	2.306	0.909	5.852
Workers at high risk of exposure to Hymenoptera	2.655	1.044	6.754
Self-employed workers	2.079	0.883	4.892

CI = confidence interval; OR = odds ratio

Working in a high-risk job for exposure to Hymenoptera was a determinant of the positive effect of VIT on work (OR 3.60, 95% CI 1.522 - 8.508) as well having already concluded VIT (OR 2.82, 95% CI 1.30- 6.14) (table 5).

Table 5. Predictors of the effect of venom immunotherapy (VIT) on work, adjusted for gender and age

Positive VIT effect	**OR**	**95% CI**	
VIT concluded	2.822	1.296	6.144
Having the severe reaction at work	1.777	0.721	4.384
Workers at high risk of exposure to Hymenoptera	3.599	1.522	8.508
Self-employed workers	1.323	0.601	2.912

CI = confidence interval; OR = odds ratio

DISCUSSION

Hymenoptera venom allergy and work disability

In this study a not negligible percentage of patients with severe Hymenoptera venom allergy requiring VIT reported work disability. Our main finding is the association between occupational characteristics (jobs at a high risk of exposure to Hymenoptera) and work disability related to Hymenoptera venom allergy.

To our knowledge, this is the first study where risk predictors of work disability related to Hymenoptera venom allergy and predictors of VIT impact on work were assessed in the same population. Our results suggest that presence of systemic Hymenoptera allergy can lead to occupational problems, especially when the severe reaction took place during work. This was consistent with the data in the literature.[6]

In our study the percentage of workers at high risk of sting (beekeepers, farmers, truck drivers) was slightly higher (41%) compared with workers occasionally at risk (22%) or those with low risk of sting (37%). Working in these high-risk jobs for sting was a significant risk factor for work disability. These findings support the hypothesis that Hymenoptera venom allergy could be considered an occupational disease.[1]

Work disability and decreased work productivity usually occur also in other similar diseases such as asthma and allergic rhinitis, [9,11] especially if ocular symptoms are present.[12] In studies on respiratory work disability the exposure to the risk factors, such as irritants, is the most important predictor of work disability.[13] This was the finding also in this study, where workers most likely to be exposed to Hymenoptera were at higher risk of work disability. In other studies blue-collar workers have been reported to be at higher risk of occupational consequences of Hymenoptera venom allergy than white-collar workers;[6] similar in our study the category of workers at high risk of exposure to Hymenoptera referred more work disability (change work/task and/or economic loss) than the other two groups (occasionally at high risk, and at low risk). In this study the risk of work disability for self employed workers was not statistically significant as expected because some authors reported that employees were usually at higher risk of health-related job loss than self-employed workers.[14]

The non-significant risk increase related to “having the reaction at work” could be explained by the obvious correlation between high-risk jobs for sting and the occurrence of reaction in a population characterized by severe allergic reaction to Hymenoptera venom.

Venom immunotherapy impact on work

VIT is globally accepted as the treatment of choice in venom allergy.[15] Epidemiological studies report that although VIT does not eliminate the risk of a systemic reaction during and after treatment, it is the only specific therapy that can prevent morbidity and mortality, as well as improve quality of life by removing fear of recurrence.[1]

Although 44 patients in the present study declared a negative effect of VIT on work, caused by changing working time and financial loss due to VIT, most of our subjects declared an indifferent effect of VIT on work. Subjects at high risk of sting reported a positive VIT impact on work. This will support the accepted medical approach that occupation may influence the decision to initiate VIT, also for non-life-threatening reactions.[5]

Another predictor of a perceived positive effect from VIT was completion of treatment. Subjects who have already completed VIT are probably more aware of the long-term beneficial effects of treatment. They are less likely to report any drawbacks of VIT, such as the time spent in therapy, which can affect work and social life. A relevant number of participants reported a negative impact of VIT on work and even if we could not find any peculiar characteristic of this group, this finding deserves attention. To prevent this side effect of VIT related to the amount of time spent in therapy, it is important to underline that we have room for improvement, developing new forms and routes of VIT (e.g. sublingual VIT),[16] or more convenient regimens such as rush up-dosing, which may lead to improved patient compliance. Unfortunately some studies have concluded that the accelerated VIT protocols are associated with a significant increase in the incidence of systemic reactions compared with conventional protocols.[17] Moreover, such accelerated protocols may necessitate new allocations of medical services and further timetabling in relation to employment.[6] Venom immunotherapy could be considered a workplace intervention to reduce work disability, even if, as a result of the few available studies on work intervention to prevent work disability, no convincing conclusions can be drawn about the effectiveness of these interventions.[18]

Validity issues

The small number of subjects could be considered a shortcoming of this study, anyway the subject is novel, the disease is rare and in the literature previous reports on work disability with similar numbers were already been published.[8,19] Since the existing questionnaire about quality of life in patients with Hymenoptera venom allergy does not take into account work disability,[20] we had to design our questionnaire, defining work disability as job/task change or financial loss due to the disease (in our case, Hymenoptera venom allergy).[8,19,21] We were aware of a possible recall bias, as reported in other questionnaire-based surveys. To minimize recall bias we also considered the entity of the allergic reaction according to the Mueller grading scale, as well as the presence of other severe reactions and the time from the severe reaction that push the subject to consult an allergologist. None of these variables had a significant effect on work disability. Furthermore, we preferred to use prompted questions, which are less prone to recall bias, especially for occupational exposures.[22]

CONCLUSIONS

This cross-sectional study suggests that Hymenoptera venom allergy has an impact on work through causing work disability. Having a high-risk job for sting appears to be a significant risk factor for work disability as well a predictor of a perceived positive impact of VIT on work. Therefore, to reduce the occupational burden of Hymenoptera venom allergy, interventions towards improving compliance to the treatment are urgently needed, especially in workers with an high risk of Hymenoptera exposure.

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Competing Interests None.

References

1 Bonadonna P, Schiappoli M, Dama A, et al. Is hymenoptera venom allergy an occupational disease? Occup Environ Med 2008;65(3):217–8.

2 Gregorian Ch, Galatas ID, Klamouris Ch, et al. Insect venom allergy in Greek adults. *Allergy* 1997;52:51–7.

3 Müller UR. Insect Sting Allergy. Stuttgart, Germany: Gustav Fischer, 1990.

4. Incorvaia C, Mauro M, Pravettoni V, et al. Hypersensitivity to hymenoptera venom: advances in diagnosis and implications for treatment. *Recent Pat Inflamm Allergy Drug Discov* 2011;5 (2):128–35.

5 Bonifazi F, Jutel M, Bilò MB, et al. Prevention and treatment of hymenoptera venom allergy. *Allergy* 2005;60:1459–70.

6 Kahan E, Ben-Moshe R, Derazne E, et al. The impact of Hymenoptera venom allergy on occupational activities. *Occup Med.*1997;47(5):273–6.

7 Bilo BM, Rueff F, Mosbech H, et al. Diagnosis of Hymenoptera venom allergy. *Allergy* 2005;60:1339–49.

8 Eisner MD, Yelin EH, Katz PP, et al. Risk factors for work disability in severe adult asthma. *Am J Med.* 2006;119(10):884–91.

9 Torén K, Zock JP, Kogevinas M, et al. An international prospective general population-based study of respiratory work disability. *Thorax* 2009;64:339–344.

10 Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol.* 1982;115(1):92–106.

11 De la HozCaballer B, Rodriguez M, Fraj J, et al. Allergic rhinitis and its impact on work productivity in primary care practice and a comparison with other common diseases: the cross-sectional study to evaluate work productivity in allergic rhinitis compared with other common diseases (CAPRI) study. *Am J Rhinol Allergy* 2012;26(5):390–4.

12 Virchow JC, Kay S, Demoly P, et al. Impact of ocular symptoms on quality of life (QoL), work productivity and resource utilisation in allergic rhinitis patients – an observational, cross sectional study in four countries in Europe. *J Med Econ.* 2011;14(3):305–14.

13 Murgia N, Torén K, Kim JL, Andersson E. Risk factors for respiratory work disability in a cohort of pulp mill workers exposed to irritant gases. *BMC Public Health.*2011;11:689.

14 Solomon C, Poole J, Palmer KT, et al. Health-related job loss: findings from a community-based survey. *Occup Environ Med.* 2007;64(3):144–9.

15 Ozdemir C., Kucuksezer UC, Akdis M, et al. Mechanism of immunotherapy to wasp and bee venom. *Clin Exp Allergy*. 2011;41:1226–34.

16 Bilò MB. Anaphylaxis caused by Hymenoptera stings: from epidemiology to treatment. *Allergy* 2011; 66(95):35–7.

17 Krishna MT, Ewan PW, Diwakar L, et al. Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and Clinical Immunology (BSACI) guidelines. *Clinical ε t experimental Allergy*. 2011;41(9):1201–20.

18 Van Oostrom SH, Driessen MT, de Vet HC et al. Workplace interventions for preventing work disability. *Cochrane database Syst Rev.* 2009 Apr 15;(2):CD006955.

19 Blanc PD, Ellbjar S, Janson C, et al. Asthma-related work disability in Sweden. The impact of workplace exposures. *Am J Respir Crit Care Med* 1999; 160(6): 2028–33.

20 Oude Elberink JN, de Monchy JG, Golden DB, et al. Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. *J Allergy Clin Immunol.*2002;109(1):162–70.

21 Omachi TA, Claman DM, Blanc PD, et al. Obstructive sleep apnea: a risk factor for work disability. *Sleep.* 2009;32(6):791–8.

22 Teschke K, Smith JC, Olshan AF. Evidence of recall bias in volunteered vs. prompted responses about occupational exposures. *Am J Ind Med.* 2000;38(4):385–8

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Conclusions: Hymenoptera venom allergy could determine work disability. Patients with Hymenoptera venom allergy having a high risk job for exposure to Hymenoptera seem to have higher risk of work disability and refer more frequently a positive effect of VIT on work.

WHAT THIS PAPER ADDS

► Hymenoptera venom sting is recognized as a risk factor for relevant, often life-threatening, allergic reactions but little it is known about the socio-economical effects of hymenoptera venom allergy. In the present study, for the first time, work disability and occupational effects of venom immunotherapy were studied in a group of patients in working age.

► The results suggest that Hymenoptera venom allergy has an impact on work through causing work disability.

► Self-employed workers and workers at high risk of sting seem to be at higher risk of work disability related to Hymenoptera venom allergy. Type of job was also a predictor of a positive effect of VIT on work.

LIMITATIONS

► The small number of subjects could be considered a shortcoming of this survey

INTRODUCTION

Hymenoptera venom allergy affects approximately 5% of the general population and can provoke severe systemic or life-threatening reactions.[1] Epidemiological studies indicate a prevalence of self-reported systemic anaphylactic sting reactions between 0.3% and 7.5%, [2] and mortality due to insect sting ranging from 0.03 to 0.48 fatalities per 1,000,000 population per year.[3]

Since the late 1970s venom immunotherapy (VIT) has provided allergic subjects with protection from fatal anaphylaxis and prevented about 90% of all reactions to stings.[4] Patient compliance for long term continuation of VIT often decreases, making VIT an effective but challenging therapy.[5] Besides, even with VIT, for most patients as well as for their families, an anaphylactic reaction after a Hymenoptera sting is a very traumatic event, and the fear of a subsequent life-threatening episode may affect the emotional, social and occupational behaviour of the affected individual.[6] Recently a disease-specific questionnaire, the Vespid Allergy Quality of Life Questionnaire, was designed and validated for assessing health-related quality of life in patients with anaphylactic responses following yellow jacket stings. The survey showed that patients experienced quality of life impairment especially because of the emotional distress associated with having to be constantly on the alert while leading their everyday “normal” lives.[7]

One important part of the everyday “normal” life is work. Any factor that would affect occupational functioning could lead to work disability. Many definitions of work disability have been applied over the last decades. Recently, changing jobs or tasks, or having suffered loss in working days or in finance because of illness have often been used to define work disability in subjects with respiratory diseases.[8,9] Prevalence, incidence, determinants and VIT effects of allergic sting reactions have been largely investigated in selected occupational groups such as gardeners and beekeepers.[6] However, little is known about Hymenoptera venom allergy impact on work ability.

The primary aim of this study is to evaluate the prevalence and the predictors of work-disability due to hymenoptera venom allergy in a group of patient treated with Venom Immunotherapy (VIT). The secondary outcome was to assess the effects of VIT on occupational functioning..

METHODS

Population and questionnaire

The clinical charts of 364 patients treated with VIT from 1997 to 2011 at the Perugia University Hospital, Italy, were reviewed. In these subjects VIT was prescribed because they reported a history of systemic reaction and a documented sensitization to the respective insect with either skin tests and/or specific serum IgE tests. Prior to starting VIT, all the patients enrolled in this study underwent the diagnostic protocol according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines[7]. Serum IgE for hymenoptera venom were assessed by Phadia 100 (Phadia AB, Uppsala, Sweden); skin tests were performed with venom extract of *Apis mellifera Vespula sp., Polistes sp. Vespa crabro* from Stallergenes (Antony, France).

Selection of venom to be used in immunotherapy was based on the identification of the species of Hymenoptera involved. The extract used for VIT were from Stallergenes (Antony, France), Alk-Abello (Hørsholm, Denmark) and Anallergo (Firenze, Italy). 127 subjects were treated with aqueous extract, 54 with depot.

For al the subjects was used a slow protocol of desensitization. The time required to reach the generally adequate maintenance venom dose of 100 μg with was 10-15 weeks and immunotherapy was recommended for at least 5 years.[7]

Of the 364 patients undergoing VIT, 183 were excluded from the study because they were retired, housewives or students. A total of 181 patients, aged 18–71, and treated with VIT while working, were eligible for the study. A questionnaire administered by a physician was used to collect data on demographic characteristics (age, gender, address), the offending insect and severity of symptoms after Hymenoptera stings, graded according to the Mueller classification. Circumstances regarding the Hymenoptera sting leading to the anaphylactic reaction and time from severe reaction were also reported. Subjects were classified as employed or self-employed and, as in according to a classification based on work exposure to Hymenoptera used in a previous study,[1] into three

categories: high risk (individuals usually working outdoors or where Hymenoptera live: farmers, gardeners, fire fighters, truck drivers, masons, beekeepers, garbage collectors); occasionally at high risk (sometimes working outdoors e.g. plumbers); and at low risk (working indoors, e.g. clerks).

Work disability was defined as an affirmative response to at least one of these key questions:

1) Did you change work because of Hymenoptera sting reaction?
2) Did you change your job tasks because of Hymenoptera sting reaction?
3) Did you suffer economic loss because of Hymenoptera sting reaction?

The definition of work disability was formulated on the basis of previous surveys about work disability, widely available in the literature [8,9]. To assess the effect of VIT, specific questions were asked about a possible positive, negative or indifferent effect of the treatment on work. Since there were not other questionnaire about this topic, a panel of allergologists and occupational physicians reviewed and proposed the questions used in this study. The indicators of a treatment-related positive effect were not having changed jobs or tasks and feeling safer at work, indicators of a negative effect were economic loss, changes of job or task and changes in working time due to VIT. Subject with negative or indifferent effect of VIT on work were classified as not having a positive effect on work.

The study protocol was approved by the Ethical Committee of Umbria Region (CEAS Umbria). All the patients gave their informed and written consent to participate in this study.

Statistical analysis

Differences between patients with and without work disability were evaluated by Chi-square test or Fisher's exact test, as appropriate, for categorical variables, and using Mann-Whitney U-test or *t*-test for continuous variables. Predictors of work disability and positive or negative VIT effects on work were assessed in logistic regression models, adjusted for gender and age, choosing as independent variables those showing a different distribution across the groups in the univariate analysis. The goodness of fit of the logistic regression models was confirmed by the Hosmer-

Lemeshow test.[10] All the analyses were performed using SPSS statistical software, version 20.0 (SPSS, IBM Corporation, New York, NY, USA).

RESULTS

All 181 patients treated with VIT while working answered the questionnaire. Among them 68% were still undergoing VIT and 32% had concluded the therapy. The mean age was 49 years, 19% were female and more than half of the subjects lived in the countryside. Thirty-one patients (17%) reported work disability. No patient reported a complete work change because of Hymenoptera venom allergy, ten (5%) reported having had to change job tasks, and 25 (14%) reported economic loss because of Hymenoptera venom allergy, four (2%) reported both conditions. The characteristics of the study population, classified according to work disability due to Hymenoptera venom allergy, are shown in table 1. No differences were found in distribution of gender, residence, mean age, stinging insect, and severity of the allergic reaction between the two groups. In subjects with work disability, Vespula was responsible for 45% of the reactions, and 45% experienced a systemic allergic reaction grade 4, according to Mueller's classification.

Fourteen patients (45%) with work disability and 26 (17%) without work disability experienced a sting reaction to Hymenoptera during shift ($p<0.01$). Subjects with work disability were mostly workers at high risk of work exposure to Hymenoptera while subjects without work disability were mostly at low risk (68% *vs.* 41%, $p<0.001$) (table1).

Table 1 Characteristics of the patients with Hymenoptera venom allergy treated with venom immunotherapy (VIT), with or without work disability

	Subjects with work disability n=31	**Subjects without work disability n=150**	***p* value**
Women, n (%)	6 (19.4)	37 (24.7)	NS
Age, mean ± SD	49.4±9.9	47.1±10.9	NS
Living in the countryside, n (%)	20 (64.5)	98 (65.3)	NS
VIT, n (%)			
On-going	21 (67.7)	101 (67.3)	NS

Concluded	10 (32.2)	49 (67.3)	
Treated with VIT for, n (%)			
Apis mellifera	11 (35.5)	48 (32)	NS
Vespula sp.	14 (45.2)	52 (34.7)	NS
Polistes sp.	3 (9.7)	38 (25.3)	NS
Vespa crabro	3 (9.7)	12 (8)	NS
Type of VIT extract			
Aqueous	23 (74.2)	104 (69.3)	NS
Depot	8 (25.8)	46 (30.7)	
Mueller reaction grade, n (%)			
I	6 (19.4)	27 (18)	NS
II	4 (12.9)	30 (20)	
III	7 (22.6)	30 (20)	
IV	14 (45.2)	63 (42)	
Ever stung before the reaction, n (%)	26 (83.9)	110 (73.3)	NS
Other severe hymenoptera reactions, n (%)	1 (3.2)	12 (8)	NS
Years after the first severe reaction, mean ± SD	9±6.7	7.1±5.7	NS
Having the severe reaction, n (%)			
at work	14 (45.2)	26(17.3)	<0.01
during sport	1 (3.2)	4 (2.7)	NS
during hobby activity	9 (29)	52 (34.7)	NS
at home	6 (19.4)	44 (29.3)	NS
in car/motorcycle	3 (9.7)	24 (16)	NS
Work-related risk of exposure to Hymenoptera, n (%)			
High	21 (67.7)	53 (35.3)	<0.01
Occasionally high	5 (16.1)	35 (23.3)	
Low	5 (16.1)	62 (41.3)	
Self-employed worker, n (%)	16 (51.6)	42 (28)	<0.01

	Impact of VIT on work		
	Positive	Negative or	p value

NS = not significant; SD = standard deviation.

Forty-four subjects (24%) reported a positive effect of VIT on work, 93 no impact (51%) and 44 negative (24%). The characteristics of the population, classified by the presence or absence of the positive impact of VIT on work, are displayed in table

Table 2 Characteristics of the patients with regard to the impact of venom immunotherapy (VIT) on work

	n=44	indifferent n=137	
Women, n (%)	12 (27.3)	31 (22.6)	NS
Age, mean ± SD	49.7±11.7	46.8±10.3	NS
VIT, n (%)			
On-going	22 (50)	100 (73)	<0.01
Concluded	22 (50)	37 (27)	
Treated with VIT for, n (%)			
Apis mellifera	11 (25)	48 (35)	NS
Vespula sp.	17 (38.6)	49 (35.8)	NS
Polistes sp.	13 (22.7)	31 (22.6)	NS
Vespa crabro	6 (13.6)	9 (6.6)	NS
Mueller reaction grade, n (%)			
I	7 (15.9)	26 (19)	NS
II	6 (13.6)	28 (20.4)	
III	12 (27.3)	25 (18.2)	
IV	19 (43.2)	58 (42.3)	
Ever stung before the reaction, n (%)	38 (86.4)	102 (74.5)	NS
Other severe Hymenoptera reactions, n (%)	2 (4.5)	11 (8)	NS
Years after the first severe reaction, mean ± SD	7.7±5.4	7.3±6.1	NS
Having the severe reaction at work, n (%)	17 (38.6)	23 (16.8)	<0.005
Work-related risk of exposure to Hymenoptera, n (%)			
High	28 (63.6)	46 (33.6)	<0.01
Occasionally high	5 (11.4)	35 (25.5)	
Low	11 (25)	56 (40.9)	
Self-employed worker, n (%)	20 (45.5)	38 (27.7)	<0.05

F = female; NS = not significant; SD = standard deviation

Subjects reporting a positive effect of VIT on work were more frequently at higher risk of work exposure to hymenoptera, self employed workers and have experienced the allergic reaction at work

(table 2). Evaluating the same characteristics presented in table 2, there were no significant differences between those with a negative impact of VIT and the other participants (those with a positive o indifferent impact on work).

In the logistic regression analysis, adjusted for gender and age, significant predictor of work disability was having a high-risk job for exposure to Hymenoptera (OR 2.66, 95% CI 1.04-6.75)(table 3).

Table 3. Predictors of work disability among patients undergoing Hymenoptera venom immunotherapy (VIT), adjusted for gender and age

CI = confidence interval; OR = odds ratio

Working in a high-risk job for exposure to Hymenoptera was a determinant of the positive effect of VIT on work (OR 3.60, 95% CI 1.522 - 8.508) as well having already concluded VIT (OR 2.82, 95% CI 1.30- 6.14) (table 4).

Table 4. Predictors of a positive effect of venom immunotherapy (VIT) on work, adjusted for gender and age

	OR	95% CI	
VIT concluded	2.822	1.296	6.144

	OR	95% CI	
Having the severe reaction at work	2.306	0.909	5.852
Workers at high risk of exposure to Hymenoptera	2.655	1.044	6.754
Self-employed workers	2.079	0.883	4.892

Having the severe reaction at work	1.777	0.721	4.384
Workers at high risk of exposure to Hymenoptera	3.599	1.522	8.508
Self-employed workers	1.323	0.601	2.912

CI = confidence interval; OR = odds ratio

DISCUSSION

Hymenoptera venom allergy and work disability

In this study a not negligible percentage of patients with severe Hymenoptera venom allergy requiring VIT reported work disability. Our main finding is the association between occupational characteristics (jobs at a high risk of exposure to Hymenoptera) and work disability related to Hymenoptera venom allergy.

In our study the percentage of workers at high risk of sting (beekeepers, farmers, truck drivers) was slightly higher (41%) compared with workers occasionally at risk (22%) or those with low risk of sting (37%). Working in these high-risk jobs for sting was a significant risk factor for work disability. These findings support the hypothesis that Hymenoptera venom allergy could be considered an occupational disease.[1]

Work disability and decreased work productivity usually occur also in other similar diseases such as asthma and allergic rhinitis, [9,11] especially if ocular symptoms are present.[12] In studies on respiratory work disability the exposure to the risk factors, such as irritants, is the most important predictor of work disability.[13] This was the finding also in this study, where workers most likely to be exposed to Hymenoptera were at higher risk of work disability. In other studies blue-collar workers have been reported to be at higher risk of occupational consequences of Hymenoptera venom allergy than white-collar workers;[6] In this study the risk of work disability for self employed workers was higher than employed workers, even if not statistically significant. In other studies employed workers showed an higher risk of work disability defined as health-related job loss [14]; one reason of our finding could be that we have not considered just this indicator of work disability but also the indicator “suffering of economic loss”. The non-significant risk increase

related to “having the reaction at work” could be explained by the obvious correlation between high-risk jobs for sting and the occurrence of reaction in a population characterized by severe allergic reaction to Hymenoptera venom.

Venom immunotherapy impact on work

VIT is globally accepted as the treatment of choice in venom allergy.[15]

Although 44 patients in the present study declared a negative effect of VIT on work, caused by changing working time and economic loss due to VIT, most of our subjects declared an indifferent effect of VIT on work. Subjects at high risk of sting reported a positive VIT impact on work. This will support the accepted medical approach that occupation may influence the decision to initiate VIT, also for non-life-threatening reactions.[16]

Another predictor of a perceived positive effect of VIT was completion of treatment. Subjects who have already completed VIT are probably more aware of the long-term beneficial effects of treatment. They are less likely to report any drawbacks of VIT, such as the time spent in therapy, which can affect work and social life. A relevant number of participants reported a negative impact of VIT on work and even if we could not find any peculiar characteristic of this group, this finding deserves attention. To prevent this side effect of VIT related to the amount of time spent in therapy, it is important to underline that we have room for improvement, developing new forms and routes of VIT (e.g. sublingual VIT),[17] or more convenient regimens such as rush up-dosing, which may lead to improved patient compliance. Unfortunately some studies have concluded that the accelerated VIT protocols are associated with a significant increase in the incidence of systemic reactions compared with conventional protocols.[18] Moreover, such accelerated protocols may necessitate new allocations of medical services and further timetabling in relation to employment.[6] Venom immunotherapy could be considered a workplace intervention to reduce work disability, even if, as a result of the few available studies on work intervention to prevent work disability, no convincing conclusions can be drawn about the effectiveness of these interventions.[19]

Validity issues

The small number of subjects could be considered a shortcoming of this study, anyway the subject is novel, the disease is rare and in the literature previous reports on work disability with similar numbers were already been published.[8,20] Since the existing questionnaire about quality of life in patients with Hymenoptera venom allergy does not take into account work disability,[21] we had to design our questionnaire, defining work disability as job/task change or economic loss due to the disease (in our case, Hymenoptera venom allergy).[8,20,22] We were aware of a possible recall bias, as reported in other questionnaire-based surveys. To minimize recall bias we also considered the entity of the allergic reaction according to the Mueller grading scale, as well as the presence of other severe reactions and the time from the severe reaction that push the subject to consult an allergologist. None of these variables had a significant effect on work disability. Furthermore, we preferred to use prompted questions, which are less prone to recall bias, especially for occupational exposures.[23]

Conclusions

This cross-sectional study suggests that Hymenoptera venom allergy has an impact on work through causing work disability. Having a high-risk job for sting appears to be a significant risk factor for work disability as well a predictor of a perceived positive impact of VIT on work.

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Contributorship Statement Giulia Paolocci and Nicola Murgia designed the study; Giulia Paolocci, Ilenia Folletti, Nicola Murgia were responsible for data collection. Nicola Murgia, Kjell Torèn, Giacomo Muzi managed and analysed the data. All authors participated in the interpretation and final drafting of the manuscript.

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Competing Interests None.

Data Sharing Statement No additional data available

References

1 Bonadonna P, Schiappoli M, Dama A, et al. Is hymenoptera venom allergy an occupational disease? Occup Environ Med 2008;65(3):217–8.

2 Gregorian Ch, Galatas ID, Klamouris Ch, et al. Insect venom allergy in Greek adults. *Allergy* 1997;52:51–7.

3 Müller UR. Insect Sting Allergy. Stuttgart, Germany: Gustav Fischer, 1990.

4. Incorvaia C, Mauro M, Pravettoni V, et al. Hypersensitivity to hymenoptera venom: advances in diagnosis and implications for treatment. *Recent Pat Inflamm Allergy Drug Discov* 2011;5 (2):128–35.

5 Confino-Cohen R, Melamed S, Goldberg A. Debilitating beliefs, emotional distress and quality of life in patients given immunotherapy for insect sting allergy. Clin Exp Allergy 1999; 29:1626-1631.

6 Kahan E, Ben-Moshe R, Derazne E, et al. The impact of Hymenoptera venom allergy on occupational activities. *Occup Med.*1997;47(5):273–6.

7 Bilo BM, Rueff F, Mosbech H, et al. Diagnosis of Hymenoptera venom allergy. *Allergy* 2005;60:1339–49.

8 Eisner MD, Yelin EH, Katz PP, et al. Risk factors for work disability in severe adult asthma. *Am J Med.* 2006;119(10):884–91.

9 Torén K, Zock JP, Kogevinas M, et al. An international prospective general population-based study of respiratory work disability. *Thorax* 2009;64:339–344.

10 Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol.* 1982;115(1):92–106.

11 De la HozCaballer B, Rodriguez M, Fraj J, et al. Allergic rhinitis and its impact on work productivity in primary care practice and a comparison with other common diseases: the cross-sectional study to evaluate work productivity in allergic rhinitis compared with other common diseases (CAPRI) study. *Am J Rhinol Allergy* 2012;26(5):390–4.

12 Virchow JC, Kay S, Demoly P, et al. Impact of ocular symptoms on quality of life (QoL), work productivity and resource utilisation in allergic rhinitis patients – an observational, cross sectional study in four countries in Europe. *J Med Econ.* 2011;14(3):305–14.

13 Murgia N, Torén K, Kim JL, et al. Risk factors for respiratory work disability in a cohort of pulp mill workers exposed to irritant gases. *BMC Public Health.*2011;11:689.

14 Solomon C, Poole J, Palmer KT, et al. Health-related job loss: findings from a community-based survey. *Occup Environ Med.* 2007;64(3):144–9.

15 Ozdemir C., Kucuksezer UC, Akdis M, et al. Mechanism of immunotherapy to wasp and bee venom. *Clin Exp Allergy*. 2011;41:1226–34.

16 Bonifazi F, Jutel M, Bilò MB, et al. Prevention and treatment of hymenoptera venom allergy. *Allergy* 2005;60:1459–70.

17 Bilò MB. Anaphylaxis caused by Hymenoptera stings: from epidemiology to treatment. *Allergy* 2011; 66(95):35–7.

18 Krishna MT, Ewan PW, Diwakar L, et al. Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and Clinical Immunology (BSACI) guidelines. *Clinical εt experimental Allergy*. 2011;41(9):1201–20.

19 Van Oostrom SH, Driessen MT, de Vet HC et al. Workplace interventions for preventing work disability. *Cochrane database Syst Rev.* 2009 Apr 15;(2):CD006955.

20 Blanc PD, Ellbjar S, Janson C, et al. Asthma-related work disability in Sweden. The impact of workplace exposures. *Am J Respir Crit Care Med* 1999; 160(6): 2028–33.

21 Oude Elberink JN, de Monchy JG, Golden DB, et al. Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. *J Allergy Clin Immunol.*2002;109(1):162–70.

22 Omachi TA, Claman DM, Blanc PD, et al. Obstructive sleep apnea: a risk factor for work disability. *Sleep.* 2009;32(6):791–8.

23 Teschke K, Smith JC, Olshan AF. Evidence of recall bias in volunteered vs. prompted responses about occupational exposures. *Am J Ind Med.* 2000;38(4):385–8

Title page

Title

Hymenoptera venom allergy: work disability and occupational impact of venom immunotherapy

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Key words

allergy, disability, hymenoptera, immunotherapy, venom.

Word count: 2231

ABSTRACT

Objectives: Little is known about the Hymenoptera venom allergy impact on work ability and the effect of venom immunotherapy (VIT) on work. The objective of this study was to evaluate the prevalence and predictors of work disability in patients treated with VIT and the effects of VIT on occupational functioning.

Methods: 181 patients, aged 18–71, treated with VIT while working, were investigated by questionnaire. Subjects were classified into employed and self-employed and, based on work exposure to Hymenoptera, into three risk categories, high risk, occasionally high risk, and low risk. Work disability was defined as having to have changed jobs/tasks and/or suffered economic~~financial~~ loss because of Hymenoptera venom allergy. Predictors of work disability were assessed in logistic regression models.

Results: 31 (17%) patients reported work disability. Being self employed and having the severe reaction at work were associated with work disability ($p<0.01$). Having a high-risk job for exposure to Hymenoptera was a significant predictor of work disability (OR 2.66, 95% CI 1.04-6.75). 24% of patients referred a positive effect of VIT on work. Determinants of the positive effect of VIT on work were having a high risk job for exposure to hymenoptera (OR 3.60, 95% CI 1.52 - 8.51) and having already concluded VIT (OR 2.82, 95% CI 1.30- 6.14).

Conclusions: Hymenoptera venom allergy could determine work disability. Patients with Hymenoptera venom allergy having a high risk job for exposure to Hymenoptera seem to have higher risk of work disability and refer more frequently a positive effect of VIT on work.

WHAT THIS PAPER ADDS

► Hymenoptera venom sting is recognized as a risk factor for relevant, often life-threatening, allergic reactions but little it is known about the socio-economical effects of hymenoptera venom allergy. In the present study, for the first time, work disability and occupational effects of venom immunotherapy were studied in a group of patients in working age.

► The results suggest that Hymenoptera venom allergy has an impact on work through causing work disability.

► Self-employed workers and workers at high risk of sting seem to be at higher risk of work disability related to Hymenoptera venom allergy. Type of job was also a predictor of a positive effect of VIT on work.

~~► To reduce the occupational burden of Hymenoptera venom allergy, interventions towards improving compliance to the treatment are urgently needed.~~

LIMITATIONS

► The small number of subjects could be considered a shortcoming of this survey

~~► The questionnaire has never been used in other studies~~

INTRODUCTION

Hymenoptera venom allergy affects approximately 5% of the general population and can provoke severe systemic or life-threatening reactions.[1] Epidemiological studies indicate a prevalence of self-reported systemic anaphylactic sting reactions between 0.3% and 7.5%, [2] and mortality due to insect sting ranging from 0.03 to 0.48 fatalities per 1,000,000 population per year.[3]

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The primary aim of this study is to evaluate the prevalence and the predictors of work-disability due to hymenoptera venom allergy in a group of patient treated with Venom Immunotherapy (VIT). The secondary outcome was to assess the effects of VIT on occupational functioning. ~~The main objective of this study is to evaluate the and predictors of work disability in a group of patients with Hymenoptera venom allergy treated with VIT and to investigate whether the impact of VIT is always positive or could negatively affect occupational functioning and work ability~~.

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METHODS

Population and questionnaire

The clinical charts of 364 patients treated with VIT from 1997 to 2011 at the Perugia University Hospital, Italy, were reviewed. In these subjects VIT was prescribed because they reported a history of systemic reaction and a documented sensitization to the respective insect with either skin tests

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For al the subjects was used a slow protocol of desensitization. The time required to reach the generally adequate maintenance venom dose of 100 µg with ~~our protocol~~ was~~is~~ 10-15 ~~several~~ weeks and immunotherapy was~~is~~ recommended for at least 5 years.[7]

Of the 364 patients undergoing VIT, 183 were excluded from the study because they were retired, housewives or students. A total of 181 patients, aged 18–71, and treated with VIT while working, were eligible for the study. A questionnaire administered by a physician was used to collect data on demographic characteristics (age, gender, address), the offending insect and severity of symptoms after Hymenoptera stings, graded according to the Mueller classification. Circumstances regarding the Hymenoptera sting leading to the anaphylactic reaction and time from severe reaction were also reported. Subjects were classified as employed or self-employed and, as in according to a classification based on work exposure to Hymenoptera used in a previous study,[1] into three categories: high risk (individuals usually working outdoors or where Hymenoptera live: farmers, gardeners, fire fighters, truck drivers, masons, beekeepers, garbage collectors); occasionally at high risk (sometimes working outdoors e.g. plumbers); and at low risk (working indoors, e.g. clerks).

Work disability was defined as an affirmative response to at least one of these key questions:

1) Did you change work because of Hymenoptera sting reaction?

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2) Did you change your job tasks because of Hymenoptera sting reaction?

3) Did you suffer ~~financial~~ economic loss because of Hymenoptera sting reaction?

The definition of work disability was formulated on the basis of previous surveys about work disability, widely available in the literature [8,9]. To assess the effect of VIT, specific questions were asked about a possible positive, negative or indifferent effect of the treatment on work. Since there were not other questionnaire about this topic, a panel of allergologists and occupational physicians reviewed and proposed the questions~~This included questions~~ used in this study. The indicators~~about possible indicators~~ of a treatment-related positive effect~~, such as~~ were not having changed jobs or tasks and feeling safer at work, ~~or~~ indicators of a negative effect~~, such as~~were economic~~financial~~ loss, changes of job or task and changes in working time due to VIT. Subject with negative or indifferent effect of VIT on work were classified as not having a positive effect on work.

The study protocol was approved by the Ethical Committee of Umbria Region (CEAS Umbria). All the patients gave their informed and written consent to participate in this study.

Statistical analysis

Differences between patients with and without work disability were evaluated by Chi-square test or Fisher's exact test, as appropriate, for categorical variables, and using Mann-Whitney U-test or *t*-test for continuous variables. Predictors of work disability and positive or negative VIT effects on work were assessed in logistic regression models, adjusted for gender and age, choosing as independent variables those showing a different distribution across the groups in the univariate analysis. The goodness of fit of the logistic regression models was confirmed by the Hosmer-Lemeshow test.[10] All the analyses were performed using SPSS statistical software, version 20.0 (SPSS, IBM Corporation, New York, NY, USA).

RESULTS

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All 181 patients treated with VIT while working answered the questionnaire. Among them 68% were still undergoing VIT and 32% had concluded the therapy. The mean age was 49 years, 19% were female and more than half of the subjects lived in the countryside. Thirty-one patients (17%) reported work disability. No patient reported a complete work change because of Hymenoptera venom allergy, ten (5%) reported having had to change job tasks, and 25 (14%) reported economic~~financial~~ loss because of Hymenoptera venom allergy, four (2%) reported both conditions. The characteristics of the study population, classified according to work disability due to Hymenoptera venom allergy, are shown in table 1. No differences were found in distribution of gender, residence, mean age, stinging insect, and severity of the allergic reaction between the two groups. In subjects with work disability, Vespula was responsible for 45% of the reactions, and 45% experienced a systemic allergic reaction grade 4, according to Mueller's classification.

Fourteen patients (45%) with work disability and 26 (17%) without work disability experienced a sting reaction to Hymenoptera during shift ($p<0.01$). Subjects with work disability were mostly workers at high risk of work exposure to Hymenoptera while subjects without work disability were mostly at low risk (68% *vs.* 41%, $p<0.001$) (table1).

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Table 1 Characteristics of the patients with Hymenoptera venom allergy treated with venom immunotherapy (VIT), with or without work disability

	Subjects with work disability n=31	Subjects without work disability n=150	*p* value
Women, n (%)	6 (19.4)	37 (24.7)	NS
Age, mean ± SD	49.4±9.9	47.1±10.9	NS
Living in the countryside, n (%)	20 (64.5)	98 (65.3)	NS
VIT, n (%)			
Ongoing	21 (67.7)	101 (67.3)	NS
Concluded	10 (32.2)	49 (67.3)	
Treated with VIT for, n (%)			
Apis mellifera	11 (35.5)	48 (32)	NS
Vespula sp.	14 (45.2)	52 (34.7)	NS
Polistes sp.	3 (9.7)	38 (25.3)	NS
Vespa crabro	3 (9.7)	12 (8)	NS
Type of VIT extract			
Aqueous	23 (74.2)	104 (69.3)	NS

Depot	8 (25.8)	46 (30.7)	
Mueller reaction grade, n (%)			
I	6 (19.4)	27 (18)	NS
II	4 (12.9)	30 (20)	
III	7 (22.6)	30 (20)	
IV	14 (45.2)	63 (42)	
Ever stung before the reaction, n (%)	26 (83.9)	110 (73.3)	NS
Other severe hymenoptera reactions, n (%)	1 (3.2)	12 (8)	NS
Years after the first severe reaction, mean ± SD	9±6.7	7.1±5.7	NS
Having the severe reaction, n (%)			
at work	14 (45.2)	26(17.3)	<0.01
during sport	1 (3.2)	4 (2.7)	NS
during hobby activity	9 (29)	52 (34.7)	NS
at home	6 (19.4)	44 (29.3)	NS
in car/motorcycle	3 (9.7)	24 (16)	NS
Work-related risk of exposure to Hymenoptera, n (%)			
High	21 (67.7)	53 (35.3)	<0.01
Occasionally high	5 (16.1)	35 (23.3)	
Low	5 (16.1)	62 (41.3)	
Self-employed worker, n (%)	16 (51.6)	42 (28)	<0.01

NS = not significant; SD = standard deviation.

	~~Subjects with work disability n=31~~	~~Subjects without work disability n=150~~	~~*p* value~~
~~Female, n (%)~~	~~6 (19.4)~~	~~37 (24.7)~~	~~NS~~
~~Age, mean ± SD~~	~~49.4±9.9~~	~~47.1±10.9~~	~~NS~~
~~Living in the countryside, n (%)~~	~~20 (64.5)~~	~~98 (65.3)~~	~~NS~~
~~VIT, n (%)~~			
~~Ongoing~~	~~21 (67.7)~~	~~101 (67.3)~~	~~NS~~
~~Concluded~~	~~10 (32.2)~~	~~49 (67.3)~~	
~~Treated with VIT for, n (%)~~			
~~*Apis mellifera*~~	~~11 (35.5)~~	~~48 (32)~~	~~NS~~
~~*Vespula sp.*~~	~~14 (45.2)~~	~~52 (34.7)~~	~~NS~~
~~*Polistes sp.*~~	~~3 (9.7)~~	~~38 (25.3)~~	~~NS~~
~~*Vespa crabro*~~	~~3 (9.7)~~	~~12 (8)~~	~~NS~~
~~Type of VIT extract~~			
~~Aqueous~~	~~23 (74.2)~~	~~104 (69.3)~~	
~~Depot~~	~~8 (25.8)~~	~~46 (30.7)~~	
~~Mueller reaction grade, n (%)~~			

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	6 (19.4)		
I		27 (18)	NS
II	4 (12.9)	30 (20)	
III	7 (22.6)	30 (20)	
IV	14 (45.2)	63 (42)	
Ever stung before the reaction, n (%)	26 (83.9)	110 (73.3)	NS
Other severe hymenoptera reactions, n (%)	1 (3.2)	12 (8)	NS
Years after the first severe reaction, mean ± SD	9±6.7	7.1±5.7	NS
Having the severe reaction, n (%)			
at work	14 (45.2)	26(17.3)	<0.01
during sport	1 (3.2)	4 (2.7)	NS
during hobby activity	9 (29)	52 (34.7)	NS
at home	6 (19.4)	44 (29.3)	NS
in car/motorcycle	3 (9.7)	24 (16)	NS
Work-related risk of exposure to Hymenoptera, n (%)			
High	21 (67.7)	53 (35.3)	<0.01
Occasionally high	5 (16.1)	35 (23.3)	
Low	5 (16.1)	62 (41.3)	
Self-employed worker, n (%)	16 (51.6)	42 (28)	<0.01

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FForty-four subjects (24%) reported a positive effect of VIT on work, 93 no impact (51%) and 44 negative (24%) (table 2). The characteristics of the population, classified by the presence or absence of the positive impact of VIT on work, are displayed in table 2.

Table 2 Characteristics of the patients with regard to the impact of venom immunotherapy (VIT) on work

Table 3 Characteristics of the patients with regard to the impact of venom immunotherapy (VIT) on work

Table 2. Effect of venom immunotherapy (VIT) on work

Effect of venom immunotherapy (VIT) on work, n=183	
Positive effect of VIT on work, n (%)	**44 (24)**
not having changed jobs or tasks, n (%)	*13 (7)*
feeling safer at work, n (%)	*44 (24)*
Negative effect of VIT on work, n (%)	**44 (24)**
having changed jobs or tasks, n (%)	*0 (0)*
financial loss, n (%)	*29 (16)*
changes in working time, n (%)	*41 (22)*
No effect of VIT on work, n (%)	**93 (51)**

VIT= venom immunotherapy

The characteristics of the population, classified by the presence or absence of the positive impact of VIT on work, are displayed in table 3.

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	Impact of VIT on work		
	Positive n=44	Negative or indifferent n=137	p value
Women, n (%)	12 (27.3)	31 (22.6)	NS
Age, mean ± SD	49.7±11.7	46.8±10.3	NS
VIT, n (%)			
Ongoing	22 (50)	100 (73)	<0.01
Concluded	22 (50)	37 (27)	
Treated with VIT for, n (%)			
Apis mellifera	11 (25)	48 (35)	NS
Vespula sp.	17 (38.6)	49 (35.8)	NS
Polistes sp.	13 (22.7)	31 (22.6)	NS
Vespa crabro	6 (13.6)	9 (6.6)	NS
Mueller reaction grade, n (%)			
I	7 (15.9)	26 (19)	NS
II	6 (13.6)	28 (20.4)	
III	12 (27.3)	25 (18.2)	
IV	19 (43.2)	58 (42.3)	
Ever stung before the reaction, n (%)	38 (86.4)	102 (74.5)	NS
Other severe Hymenoptera reactions, n (%)	2 (4.5)	11 (8)	NS
Years after the first severe reaction, mean ± SD	7.7±5.4	7.3±6.1	NS
Having the severe reaction at work, n (%)	17 (38.6)	23 (16.8)	<0.005
Work-related risk of exposure to Hymenoptera, n (%)			
High	28 (63.6)	46 (33.6)	<0.01
Occasionally high	5 (11.4)	35 (25.5)	
Low	11 (25)	56 (40.9)	
Self-employed worker, n (%)	20 (45.5)	38 (27.7)	<0.05

. F = female; NS = not significant; SD = standard deviation

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Subjects reporting a positive effect of VIT on work were more frequently at higher risk of work exposure to hymenoptera, self employed workers and have experienced the allergic reaction at work (table 23). Evaluating the same characteristics presented in table 23, there were no significant differences between those with a negative impact of VIT and the other participants (those with a positive o indifferent impact on work).

In the logistic regression analysis, adjusted for gender and age, significant predictor of work disability was having a high-risk job for exposure to Hymenoptera (OR 2.66, 95% CI 1.04-6.75) (table 34).

Table 34. Predictors of work disability ~~(WD)~~ among patients undergoing Hymenoptera venom immunotherapy (VIT), adjusted for gender and age

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	~~WD OR~~	~~95% CI~~	
~~Having the severe reaction at work~~	~~2.306~~	~~0.909~~	~~5.852~~
~~Workers at high risk of exposure to Hymenoptera~~	~~2.655~~	~~1.044~~	~~6.754~~
~~Self-employed workers~~	~~2.079~~	~~0.883~~	~~4.892~~

	~~OR~~	~~95% CI~~	
Having the severe reaction at work	2.306	0.909	5.852
Workers at high risk of exposure to Hymenoptera	2.655	1.044	6.754
Self-employed workers	2.079	0.883	4.892

~~CI = confidence interval; OR = odds ratio~~

CI = confidence interval; OR = odds ratio

Working in a high-risk job for exposure to Hymenoptera was a determinant of the positive effect of VIT on work (OR 3.60, 95% CI 1.522 - 8.508) as well having already concluded VIT (OR 2.82, 95% CI 1.30- 6.14) (table 4~~5~~).

Table 4~~5~~. Predictors of a positive ~~the~~ effect of venom immunotherapy (VIT) on work, adjusted for gender and age

~~*Positive VIT effect*~~	OR	95% CI	
VIT concluded	2.822	1.296	6.144
Having the severe reaction at work	1.777	0.721	4.384
Workers at high risk of exposure to Hymenoptera	3.599	1.522	8.508
Self-employed workers	1.323	0.601	2.912

CI = confidence interval; OR = odds ratio

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DISCUSSION

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Hymenoptera venom allergy and work disability

In this study a not negligible percentage of patients with severe Hymenoptera venom allergy requiring VIT reported work disability. Our main finding is the association between occupational characteristics (jobs at a high risk of exposure to Hymenoptera) and work disability related to Hymenoptera venom allergy.

~~To our knowledge, this is the first study where risk predictors of work disability related to Hymenoptera venom allergy and predictors of VIT impact on work were assessed in the same population. Our results suggest that presence of systemic Hymenoptera allergy can lead to occupational problems, especially when the severe reaction took place during work. This was consistent with the data in the literature.[6]~~

In our study the percentage of workers at high risk of sting (beekeepers, farmers, truck drivers) was slightly higher (41%) compared with workers occasionally at risk (22%) or those with low risk of sting (37%). Working in these high-risk jobs for sting was a significant risk factor for work disability. These findings support the hypothesis that Hymenoptera venom allergy could be considered an occupational disease.[1]

Work disability and decreased work productivity usually occur also in other similar diseases such as asthma and allergic rhinitis, [9,11] especially if ocular symptoms are present.[12] In studies on respiratory work disability the exposure to the risk factors, such as irritants, is the most important predictor of work disability.[13] This was the finding also in this study, where workers most likely to be exposed to Hymenoptera were at higher risk of work disability. In other studies blue-collar workers have been reported to be at higher risk of occupational consequences of Hymenoptera venom allergy than white-collar workers;[6] ~~similar in our study the category of workers at high risk of exposure to Hymenoptera referred more work disability (change work/task and/or economic loss) than the other two groups (occasionally at high risk, and at low risk).~~ In this study the risk of work disability for self employed workers was higher than employed workers, even if -not

statistically significant. In other studies employed workers showed an higher risk of work disability defined as health-related job loss [14]; one reason of our finding could be that -we have not considered just this indicator of work disability but also the indicator "suffering of economic loss". ~~as expected because some authors reported that employees were usually at higher risk of health-related job loss than self-employed workers.[14] Th~~The non-significant risk increase related to "having the reaction at work" could be explained by the obvious correlation between high-risk jobs for sting and the occurrence of reaction in a population characterized by severe allergic reaction to Hymenoptera venom.

Venom immunotherapy impact on work

VIT is globally accepted as the treatment of choice in venom allergy.[15] ~~Epidemiological studies report that although VIT does not eliminate the risk of a systemic reaction during and after treatment, it is the only specific therapy that can prevent morbidity and mortality, as well as improve quality of life by removing fear of recurrence.[1]~~

Although 44 patients in the present study declared a negative effect of VIT on work, caused by changing working time and economic~~financial~~ loss due to VIT, most of our subjects declared an indifferent effect of VIT on work. Subjects at high risk of sting reported a positive VIT impact on work. This will support the accepted medical approach that occupation may influence the decision to initiate VIT, also for non-life-threatening reactions.[~~5~~16]

Another predictor of a perceived positive effect of~~from~~ VIT was completion of treatment. Subjects who have already completed VIT are probably more aware of the long-term beneficial effects of treatment. They are less likely to report any drawbacks of VIT, such as the time spent in therapy, which can affect work and social life. A relevant number of participants reported a negative impact of VIT on work and even if we could not find any peculiar characteristic of this group, this finding deserves attention. To prevent this side effect of VIT related to the amount of time spent in therapy, it is important to underline that we have room for improvement, developing new forms and routes of VIT (e.g. sublingual VIT),[17~~6~~] or more convenient regimens such as rush up-dosing, which may

lead to improved patient compliance. Unfortunately some studies have concluded that the accelerated VIT protocols are associated with a significant increase in the incidence of systemic reactions compared with conventional protocols.[187] Moreover, such accelerated protocols may necessitate new allocations of medical services and further timetabling in relation to employment.[6] Venom immunotherapy could be considered a workplace intervention to reduce work disability, even if, as a result of the few available studies on work intervention to prevent work disability, no convincing conclusions can be drawn about the effectiveness of these interventions.[198]

Validity issues

The small number of subjects could be considered a shortcoming of this study, anyway the subject is novel, the disease is rare and in the literature previous reports on work disability with similar numbers were already been published.[8,2019] Since the existing questionnaire about quality of life in patients with Hymenoptera venom allergy does not take into account work disability,[210] we had to design our questionnaire, defining work disability as job/task change or economic~~financial~~ loss due to the disease (in our case, Hymenoptera venom allergy).[8,2019,221] We were aware of a possible recall bias, as reported in other questionnaire-based surveys. To minimize recall bias we also considered the entity of the allergic reaction according to the Mueller grading scale, as well as the presence of other severe reactions and the time from the severe reaction that push the subject to consult an allergologist. None of these variables had a significant effect on work disability. Furthermore, we preferred to use prompted questions, which are less prone to recall bias, especially for occupational exposures.[232]

CONCLUSIONS

This cross-sectional study suggests that Hymenoptera venom allergy has an impact on work through causing work disability. Having a high-risk job for sting appears to be a significant risk factor for work disability as well a predictor of a perceived positive impact of VIT on work. ~~Therefore, to reduce the occupational burden of Hymenoptera venom allergy, interventions towards improving compliance to the treatment are urgently needed, especially in workers with an high risk of Hymenoptera exposure.~~

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Competing Interests None.

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References

1 Bonadonna P, Schiappoli M, Dama A, et al. Is hymenoptera venom allergy an occupational disease? Occup Environ Med 2008;65(3):217–8.

2 Gregorian Ch, Galatas ID, Klamouris Ch, et al. Insect venom allergy in Greek adults. *Allergy* 1997;52:51–7.

3 Möller UR. Insect Sting Allergy. Stuttgart, Germany: Gustav Fischer, 1990.

4. Incorvaia C, Mauro M, Pravettoni V, et al. Hypersensitivity to hymenoptera venom: advances in diagnosis and implications for treatment. *Recent Pat Inflamm Allergy Drug Discov* 2011;5 (2):128–35.

5 Confino-Cohen R, Melamed S, Goldberg A. Debilitating beliefs, emotional distress and quality of life in patients given immunotherapy for insect sting allergy. Clin Exp Allergy 1999; 29:1626-1631. ~~Bonifazi F, Jutel M, Bilò MB, et al. Prevention and treatment of hymenoptera venom allergy. *Allergy* 2005;60:1459–70.~~

6 Kahan E, Ben-Moshe R, Derazne E, et al. The impact of Hymenoptera venom allergy on occupational activities. *Occup Med.*1997;47(5):273–6.

7 Bilo BM, Rueff F, Mosbech H, et al. Diagnosis of Hymenoptera venom allergy. *Allergy* 2005;60:1339–49.

8 Eisner MD, Yelin EH, Katz PP, et al. Risk factors for work disability in severe adult asthma. *Am J Med.* 2006;119(10):884–91.

9 Torén K, Zock JP, Kogevinas M, et al. An international prospective general population-based study of respiratory work disability. *Thorax* 2009;64:339–344.

10 Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol.* 1982;115(1):92–106.

11 De la HozCaballer B, Rodriguez M, Fraj J, et al. Allergic rhinitis and its impact on work productivity in primary care practice and a comparison with other common diseases: the cross-

sectional study to evaluate work productivity in allergic rhinitis compared with other common diseases (CAPRI) study. *Am J Rhinol Allergy* 2012;26(5):390–4.

12 Virchow JC, Kay S, Demoly P, et al. Impact of ocular symptoms on quality of life (QoL), work productivity and resource utilisation in allergic rhinitis patients – an observational, cross sectional study in four countries in Europe. *J Med Econ.* 2011;14(3):305–14.

13 Murgia N, Torén K, Kim JL, Andersson E. Risk factors for respiratory work disability in a cohort of pulp mill workers exposed to irritant gases. *BMC Public Health.*2011;11:689.

14 Solomon C, Poole J, Palmer KT, et al. Health-related job loss: findings from a community-based survey. *Occup Environ Med.* 2007;64(3):144–9.

15 Ozdemir C., Kucuksezer UC, Akdis M, et al. Mechanism of immunotherapy to wasp and bee venom. *Clin Exp Allergy*. 2011;41:1226–34.

16 Bonifazi F, Jutel M, Bilò MB, et al. Prevention and treatment of hymenoptera venom allergy. *Allergy* 2005;60:1459–70.

-17 Bilò MB. Anaphylaxis caused by Hymenoptera stings: from epidemiology to treatment. *Allergy* 2011; 66(95):35–7.

187 Krishna MT, Ewan PW, Diwakar L, et al. Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and Clinical Immunology (BSACI) guidelines. *Clinical et experimental Allergy*. 2011;41(9):1201–20.

198 Van Oostrom SH, Driessen MT, de Vet HC et al. Workplace interventions for preventing work disability. *Cochrane database Syst Rev.* 2009 Apr 15;(2):CD006955.

2019 Blanc PD, Ellbjar S, Janson C, et al. Asthma-related work disability in Sweden. The impact of workplace exposures. *Am J Respir Crit Care Med* 1999; 160(6): 2028–33.

210 Oude Elberink JN, de Monchy JG, Golden DB, et al. Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. *J Allergy Clin Immunol.*2002;109(1):162–70.

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221 Omachi TA, Claman DM, Blanc PD, et al. Obstructive sleep apnea: a risk factor for work disability. *Sleep.* 2009;32(6):791–8.

232 Teschke K, Smith JC, Olshan AF. Evidence of recall bias in volunteered vs. prompted responses about occupational exposures. *Am J Ind Med.* 2000;38(4):385–8

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Title page

Title

Hymenoptera venom allergy: work disability and occupational impact of venom immunotherapy

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ABSTRACT

Objectives: Little is known about the Hymenoptera venom allergy impact on work ability and the effect of venom immunotherapy (VIT) on work. The objective of this study was to evaluate the prevalence and predictors of work disability in patients treated with VIT and the effects of VIT on occupational functioning.

Methods: 181 patients, aged 18–71, treated with VIT while working, were investigated by questionnaire. Subjects were classified into employed and self-employed and, based on work exposure to Hymenoptera, into three risk categories, high risk, occasionally high risk, and low risk. Work disability was defined as having to have changed jobs/tasks and/or suffered economic loss because of Hymenoptera venom allergy. Predictors of work disability were assessed in logistic regression models.

Results: 31 (17%) patients reported work disability. Being self employed and having the severe reaction at work were associated with work disability ($p<0.01$). Having a high-risk job for exposure to Hymenoptera was a significant predictor of work disability (OR 2.66, 95% CI 1.04-6.75). 24% of patients referred a positive effect of VIT on work. Determinants of the positive effect of VIT on work were having a high risk job for exposure to hymenoptera (OR 3.60, 95% CI 1.52 - 8.51) and having already concluded VIT (OR 2.82, 95% CI 1.30- 6.14).

Conclusions: Hymenoptera venom allergy could determine work disability. Patients with Hymenoptera venom allergy having a high risk job for exposure to Hymenoptera seem to have higher risk of work disability and refer more frequently a positive effect of VIT on work.

LIMITATIONS

► The small number of subjects could be considered a shortcoming of this survey

► The questionnaire has never been used in other studies

WHAT THIS PAPER ADDS

► Hymenoptera venom sting is recognized as a risk factor for relevant, often life-threatening, allergic reactions but little it is known about the socio-economical effects of hymenoptera venom allergy. In the present study, for the first time, work disability and occupational effects of venom immunotherapy were studied in a group of patients in working age.

► The results suggest that Hymenoptera venom allergy has an impact on work through causing work disability.

► Self-employed workers and workers at high risk of sting seem to be at higher risk of work disability related to Hymenoptera venom allergy. Type of job was also a predictor of a positive effect of VIT on work.

INTRODUCTION

Hymenoptera venom allergy affects approximately 5% of the general population and can provoke severe systemic or life-threatening reactions.[1] Epidemiological studies indicate a prevalence of self-reported systemic anaphylactic sting reactions between 0.3% and 7.5%, [2] and mortality due to insect sting ranging from 0.03 to 0.48 fatalities per 1,000,000 population per year.[3]

Since the late 1970s venom immunotherapy (VIT) has provided allergic subjects with protection from fatal anaphylaxis and prevented about 90% of all reactions to stings.[4] Patient compliance for long term continuation of VIT often decreases, making VIT an effective but challenging therapy.[5] Besides, even with VIT, for most patients as well as for their families, an anaphylactic reaction after a Hymenoptera sting is a very traumatic event, and the fear of a subsequent life-threatening episode may affect the emotional, social and occupational behaviour of the affected individual.[6] Recently a disease-specific questionnaire, the Vespid Allergy Quality of Life Questionnaire, was designed and validated for assessing health-related quality of life in patients with anaphylactic responses following yellow jacket stings. The survey showed that patients experienced quality of life impairment especially because of the emotional distress associated with having to be constantly on the alert while leading their everyday “normal” lives.[7]

One important part of the everyday “normal” life is work. Any factor that would affect occupational functioning could lead to work disability. Many definitions of work disability have been applied over the last decades. Recently, changing jobs or tasks, or having suffered loss in working days or in finance because of illness have often been used to define work disability in subjects with respiratory diseases.[8,9] Prevalence, incidence, determinants and VIT effects of allergic sting reactions have been largely investigated in selected occupational groups such as gardeners and beekeepers.[6] However, little is known about Hymenoptera venom allergy impact on work ability.

The primary aim of this study is to evaluate the prevalence and predictors of work-disability in a group of patient treated with Venom Immunotherapy (VIT). The secondary outcome was to assess the effects of VIT on occupational functioning..

METHODS

Population and questionnaire

The clinical charts of 364 patients treated with VIT from 1997 to 2011 at the Perugia University Hospital, Italy, were reviewed. In this subjects VIT was prescribed because they reported a hystory of systemic severe reaction and a documented sensitization to the respective insect with either skin tests and/or specific serum IgE tests. Prior to starting VIT, all the patients enrolled in this study underwent the diagnostic protocol according to European Academy of Allergy and Clinical Immunology (EAACI) guidelines[7]. Serum IgE for hymenoptera venom were assessed by Phadia 100 (Phadia AB, Uppsala, Sweden); skin tests were performed with venom extract of *Apis mellifera Vespula sp., Polistes sp. Vespa crabro* from Stallergenes (Antony, France).

Selection of venom to be used in immunotherapy was based on the identification of the species of Hymenoptera involved and on cross-reactivity between venoms, where the exact identification of the responsible insect was not possible. The extract used for VIT were from Stallergenes (Antony, France), Alk-Abello (Hørsholm, Denmark) and Anallergo (Firenze, Italy). 127 subjects were treated with aqueous extract, 54 with depot.

For al the subjects was used a slow protocol of desensitization. The time required to reach the generally adequate maintenance venom dose of 100 μg with was 10-15 weeks and immunotherapy was recommended for at least 5 years.[7]

Of the 364 patients undergoing VIT, 183 were excluded from the study because they were retired, housewives or students. A total of 181 patients, aged 18–71, and treated with VIT while working, were eligible for the study. A questionnaire administered by a physician was used to collect data on demographic characteristics (age, gender, address), the offending insect and severity of symptoms after Hymenoptera stings, graded according to the Mueller classification. Circumstances regarding the Hymenoptera sting leading to the anaphylactic reaction and time from severe reaction were also reported. Subjects were classified as employed or self-employed and, as in according to a

classification based on work exposure to Hymenoptera used in a previous study,[1] into three categories: high risk (individuals usually working outdoors or where Hymenoptera live: farmers, gardeners, fire fighters, truck drivers, masons, beekeepers, garbage collectors); occasionally at high risk (sometimes working outdoors e.g. plumbers); and at low risk (working indoors, e.g. clerks).

Work disability was defined as an affirmative response to at least one of these key questions:

1) Did you change work because of Hymenoptera sting reaction?
2) Did you change your job tasks because of Hymenoptera sting reaction?
3) Did you suffer economic loss because of Hymenoptera sting reaction?

The definition of work disability was formulated on the basis of previous surveys about work disability, widely available in the literature [8,9]. To assess the effect of VIT, specific questions were asked about a possible positive, negative or indifferent effect of the treatment on work. Since there were not other questionnaire about this topic, a panel of allergologists and occupational physicians reviewed and proposed the questions used in this study about possible indicators of a treatment-related positive effect, such as not having changed jobs or tasks and feeling safer at work, or indicators of a negative effect, such as economic loss, changes of job or task and changes in working time. Subject with negative or indifferent effect of VIT on work were classified as not having a positive effect on work.

The study protocol was approved by the Ethical Committee of Umbria Region (CEAS). All the patients gave their informed and written consent to participate in this study.

Statistical analysis

Differences between patients with and without work disability were evaluated by Chi-square test or Fisher's exact test, as appropriate, for categorical variables, and using Mann-Whitney U-test or *t*-test for continuous variables. Predictors of work disability and positive or negative VIT effects on work were assessed in logistic regression models, adjusted for gender and age, choosing as independent variables those showing a different distribution across the groups in the univariate

analysis. The goodness of fit of the logistic regression models was confirmed by the Hosmer-Lemeshow test.[10] All the analyses were performed using SPSS statistical software, version 20.0 (SPSS, IBM Corporation, New York, NY, USA).

RESULTS

All 181 patients treated with VIT while working answered the questionnaire. Among them 68% were still undergoing VIT and 32% had concluded the therapy. The mean age was 49 years, 19% were female and more than half of the subjects lived in the countryside. Thirty-one patients (17%) reported work disability. No patient reported a complete work change because of Hymenoptera venom allergy, ten (5%) reported having had to change job tasks, and 25 (14%) reported economic loss because of Hymenoptera venom allergy, four (2%) reported both conditions. The characteristics of the study population, classified according to work disability due to Hymenoptera venom allergy, are shown in table 1. No differences were found in distribution of gender, residence, mean age, stinging insect, and severity of the allergic reaction between the two groups. In subjects with work disability, Vespula was responsible for 45% of the reactions, and 45% experienced a systemic allergic reaction grade 4, according to Mueller's classification.

Fourteen patients (45%) with work disability and 26 (17%) without work disability experienced a sting reaction to Hymenoptera during shift ($p<0.01$). Subjects with work disability were mostly workers at high risk of work exposure to Hymenoptera while subjects without work disability were mostly at low risk (68% *vs.* 41%, $p<0.001$) (table1).

Table 1 Characteristics of the patients with Hymenoptera venom allergy treated with venom immunotherapy (VIT), with or without work disability

		Subjects with work disability n=31	Subjects without work disability n=150	*p* value
Female, n (%)		6 (19.4)	37 (24.7)	NS
Age, mean ± SD		49.4±9.9	47.1±10.9	NS
Living in the countryside, n (%)		20 (64.5)	98 (65.3)	NS
VIT, n (%)				
	Ongoing	21 (67.7)	101 (67.3)	NS
	Concluded	10 (32.2)	49 (67.3)	
Treated with VIT for, n (%)				
	Apis mellifera	11 (35.5)	48 (32)	NS
	Vespula sp.	14 (45.2)	52 (34.7)	NS
	Polistes sp.	3 (9.7)	38 (25.3)	NS
	Vespa crabro	3 (9.7)	12 (8)	NS
Type of VIT extract				
	Aqueous	23 (74.2)	104 (69.3)	NS
	Depot	8 (25.8)	46 (30.7)	
Mueller reaction grade, n (%)				
	I	6 (19.4)	27 (18)	NS
	II	4 (12.9)	30 (20)	
	III	7 (22.6)	30 (20)	
	IV	14 (45.2)	63 (42)	
Ever stung before the reaction, n (%)		26 (83.9)	110 (73.3)	NS
Other severe hymenoptera reactions, n (%)		1 (3.2)	12 (8)	NS
Years after the first severe reaction, mean ± SD		9±6.7	7.1±5.7	NS
Having the severe reaction, n (%)				
	at work	14 (45.2)	26(17.3)	<0.01
	during sport	1 (3.2)	4 (2.7)	NS
	during hobby activity	9 (29)	52 (34.7)	NS
	at home	6 (19.4)	44 (29.3)	NS
	in car/motorcycle	3 (9.7)	24 (16)	NS
Work-related risk of exposure to Hymenoptera, n (%)				
	High	21 (67.7)	53 (35.3)	<0.01
	Occasionally high	5 (16.1)	35 (23.3)	
	Low	5 (16.1)	62 (41.3)	
Self-employed worker, n (%)		16 (51.6)	42 (28)	<0.01

NS = not significant; SD = standard deviation.

Forty-four subjects (24%) reported a positive effect of VIT on work, 93 no impact (51%) and 44 negative (24%). The characteristics of the population, classified by the presence or absence of the positive impact of VIT on work, are displayed in table 2.

Table 2 Characteristics of the patients with regard to the impact of venom immunotherapy (VIT) on work

		Impact of VIT on work		
		Positive n=44	Negative or indifferent n=137	p value
Female, n (%)		12 (27.3)	31 (22.6)	NS
Age, mean ± SD		49.7±11.7	46.8±10.3	NS
VIT, n (%)				
	Ongoing	22 (50)	100 (73)	<0.01
	Concluded	22 (50)	37 (27)	
Treated with VIT for, n (%)				
	Apis mellifera	11 (25)	48 (35)	NS
	Vespula sp.	17 (38.6)	49 (35.8)	NS
	Polistes sp.	13 (22.7)	31 (22.6)	NS
	Vespa crabro	6 (13.6)	9 (6.6)	NS
Mueller reaction grade, n (%)				
	I	7 (15.9)	26 (19)	NS
	II	6 (13.6)	28 (20.4)	
	III	12 (27.3)	25 (18.2)	
	IV	19 (43.2)	58 (42.3)	
Ever stung before the reaction, n (%)		38 (86.4)	102 (74.5)	NS
Other severe Hymenoptera reactions, n (%)		2 (4.5)	11 (8)	NS
Years after the first severe reaction, mean ± SD		7.7±5.4	7.3±6.1	NS
Having the severe reaction at work, n (%)		17 (38.6)	23 (16.8)	<0.005

Work-related risk of exposure to Hymenoptera, n (%)				
	High	28 (63.6)	46 (33.6)	<0.01
	Occasionally high	5 (11.4)	35 (25.5)	
	Low	11 (25)	56 (40.9)	
Self-employed worker, n (%)		20 (45.5)	38 (27.7)	<0.05

F = female; NS = not significant; SD = standard deviation

Subjects reporting a positive effect of VIT on work were more frequently at higher risk of work exposure to hymenoptera, self employed workers and have experienced the allergic reaction at work (table 2). Evaluating the same characteristics presented in table 2, there were no significant differences between those with a negative impact of VIT and the other participants (those with a positive o indifferent impact on work).

In the logistic regression analysis, adjusted for gender and age, significant predictor of work disability was having a high-risk job for exposure to Hymenoptera (OR 2.66, 95% CI 1.04-6.75)(table 3).

Table 3. Predictors of work disability among patients undergoing Hymenoptera venom immunotherapy (VIT), adjusted for gender and age

	OR	**95% CI**	
Having the severe reaction at work	2.306	0.909	5.852
Workers at high risk of exposure to Hymenoptera	2.655	1.044	6.754
Self-employed workers	2.079	0.883	4.892

CI = confidence interval; OR = odds ratio

Working in a high-risk job for exposure to Hymenoptera was a determinant of the positive effect of VIT on work (OR 3.60, 95% CI 1.522 - 8.508) as well having already concluded VIT (OR 2.82, 95% CI 1.30- 6.14) (table 4).

Table 4. Predictors of the effect of venom immunotherapy (VIT) on work, adjusted for gender and age

Positive VIT effect	**OR**	**95% CI**	
VIT concluded	2.822	1.296	6.144
Having the severe reaction at work	1.777	0.721	4.384
Workers at high risk of exposure to Hymenoptera	3.599	1.522	8.508
Self-employed workers	1.323	0.601	2.912

CI = confidence interval; OR = odds ratio

DISCUSSION

Hymenoptera venom allergy and work disability

In this study a not negligible percentage of patients with severe Hymenoptera venom allergy requiring VIT reported work disability. Our main finding is the association between occupational characteristics (jobs at a high risk of exposure to Hymenoptera) and work disability related to Hymenoptera venom allergy.

Our results suggest that presence of systemic Hymenoptera allergy can lead to occupational problems, especially when the severe reaction took place during work. This was consistent with the data in the literature.[6]

In our study the percentage of workers at high risk of sting (beekeepers, farmers, truck drivers) was slightly higher (41%) compared with workers occasionally at risk (22%) or those with low risk of sting (37%). Working in these high-risk jobs for sting was a significant risk factor for work

disability. These findings support the hypothesis that Hymenoptera venom allergy could be considered an occupational disease.[1]

Work disability and decreased work productivity usually occur also in other similar diseases such as asthma and allergic rhinitis, [9,11] especially if ocular symptoms are present.[12] In studies on respiratory work disability the exposure to the risk factors, such as irritants, is the most important predictor of work disability.[13] This was the finding also in this study, where workers most likely to be exposed to Hymenoptera were at higher risk of work disability. In other studies blue-collar workers have been reported to be at higher risk of occupational consequences of Hymenoptera venom allergy than white-collar workers;[6] similar in our study the category of workers at high risk of exposure to Hymenoptera referred more work disability (change work/task and/or economic loss) than the other two groups (occasionally at high risk, and at low risk). In this study the risk of work disability for self employed workers was not statistically significant as expected because some authors reported that employees were usually at higher risk of health-related job loss than self-employed workers.[14] The non-significant risk increase related to "having the reaction at work" could be explained by the obvious correlation between high-risk jobs for sting and the occurrence of reaction in a population characterized by severe allergic reaction to Hymenoptera venom.

Venom immunotherapy impact on work

VIT is globally accepted as the treatment of choice in venom allergy.[15]

Although 44 patients in the present study declared a negative effect of VIT on work, caused by changing working time and economic loss due to VIT, most of our subjects declared an indifferent effect of VIT on work. Subjects at high risk of sting reported a positive VIT impact on work. This will support the accepted medical approach that occupation may influence the decision to initiate VIT, also for non-life-threatening reactions.[5]

Another predictor of a perceived positive effect from VIT was completion of treatment. Subjects who have already completed VIT are probably more aware of the long-term beneficial effects of

treatment. They are less likely to report any drawbacks of VIT, such as the time spent in therapy, which can affect work and social life. A relevant number of participants reported a negative impact of VIT on work and even if we could not find any peculiar characteristic of this group, this finding deserves attention. To prevent this side effect of VIT related to the amount of time spent in therapy, it is important to underline that we have room for improvement, developing new forms and routes of VIT (e.g. sublingual VIT),[16] or more convenient regimens such as rush up-dosing, which may lead to improved patient compliance. Unfortunately some studies have concluded that the accelerated VIT protocols are associated with a significant increase in the incidence of systemic reactions compared with conventional protocols.[17] Moreover, such accelerated protocols may necessitate new allocations of medical services and further timetabling in relation to employment.[6] Another way to reduce the reported negative effect of VIT could be to improve information about the risks related to a new reaction to hymenoptera venom among patients selected for VIT, who are those at higher risk of severe reactions. During this study we had the impression that information about venom related life- threatening reaction is not homogenous in our group of patient. Stressing the efficacy of VIT for the prevention of life-threatening reaction could be a good strategy to improve the acceptance of this treatment. Venom immunotherapy could be considered a workplace intervention to reduce work disability, even if, as a result of the few available studies on work intervention to prevent work disability, no convincing conclusions can be drawn about the effectiveness of these interventions.[18]

Validity issues

The small number of subjects could be considered a shortcoming of this study, anyway the subject is novel, the disease is rare and in the literature previous reports on work disability with similar numbers were already been published.[8,19] Since the existing questionnaire about quality of life in patients with Hymenoptera venom allergy does not take into account work disability,[20] we had to design our questionnaire, defining work disability as job/task change or economic loss due to the disease (in our case, Hymenoptera venom allergy).[8,19,21] We were aware of a possible recall

bias, as reported in other questionnaire-based surveys. To minimize recall bias we also considered the entity of the allergic reaction according to the Mueller grading scale, as well as the presence of other severe reactions and the time from the severe reaction that push the subject to consult an allergologist. None of these variables had a significant effect on work disability. Furthermore, we preferred to use prompted questions, which are less prone to recall bias, especially for occupational exposures.[22]

CONCLUSIONS

This cross-sectional study suggests that Hymenoptera venom allergy has an impact on work through causing work disability. Having a high-risk job for sting appears to be a significant risk factor for work disability as well a predictor of a perceived positive impact of VIT on work. Therefore, for the prevention and treatment of patients we have to consider also the occupational burden of Hymenoptera venom allergy.,

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Contributorship Statement Giulia Paolocci and Nicola Murgia designed the study; Giulia Paolocci, Ilenia Folletti, Nicola Murgia were responsible for data collection. Nicola Murgia, Kjell Torèn, Giacomo Muzi managed and analysed the data. All authors participated in the interpretation and final drafting of the manuscript.

Competing Interests None.

Data Sharing Statement: No additional data available

References

1 Bonadonna P, Schiappoli M, Dama A, et al. Is hymenoptera venom allergy an occupational disease? Occup Environ Med 2008;65(3):217–8.

2 Gregorian Ch, Galatas ID, Klamouris Ch, et al. Insect venom allergy in Greek adults. *Allergy* 1997;52:51–7.

3 Müller UR. Insect Sting Allergy. Stuttgart, Germany: Gustav Fischer, 1990.

4. Incorvaia C, Mauro M, Pravettoni V, et al. Hypersensitivity to hymenoptera venom: advances in diagnosis and implications for treatment. *Recent Pat Inflamm Allergy Drug Discov* 2011;5 (2):128–35.

5 Bonifazi F, Jutel M, Bilò MB, et al. Prevention and treatment of hymenoptera venom allergy. *Allergy* 2005;60:1459–70.

6 Kahan E, Ben-Moshe R, Derazne E, et al. The impact of Hymenoptera venom allergy on occupational activities. *Occup Med.*1997;47(5):273–6.

7 Bilo BM, Rueff F, Mosbech H, et al. Diagnosis of Hymenoptera venom allergy. *Allergy* 2005;60:1339–49.

8 Eisner MD, Yelin EH, Katz PP, et al. Risk factors for work disability in severe adult asthma. *Am J Med.* 2006;119(10):884–91.

9 Torén K, Zock JP, Kogevinas M, et al. An international prospective general population-based study of respiratory work disability. *Thorax* 2009;64:339–344.

10 Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol.* 1982;115(1):92–106.

11 De la HozCaballer B, Rodriguez M, Fraj J, et al. Allergic rhinitis and its impact on work productivity in primary care practice and a comparison with other common diseases: the cross-sectional study to evaluate work productivity in allergic rhinitis compared with other common diseases (CAPRI) study. *Am J Rhinol Allergy* 2012;26(5):390–4.

12 Virchow JC, Kay S, Demoly P, et al. Impact of ocular symptoms on quality of life (QoL), work productivity and resource utilisation in allergic rhinitis patients – an observational, cross sectional study in four countries in Europe. *J Med Econ.* 2011;14(3):305–14.

13 Murgia N, Torén K, Kim JL, et al. Risk factors for respiratory work disability in a cohort of pulp mill workers exposed to irritant gases. *BMC Public Health.*2011;11:689.

14 Solomon C, Poole J, Palmer KT, et al. Health-related job loss: findings from a community-based survey. *Occup Environ Med.* 2007;64(3):144–9.

15 Ozdemir C., Kucuksezer UC, Akdis M, et al. Mechanism of immunotherapy to wasp and bee venom. *Clin Exp Allergy*. 2011;41:1226–34.

16 Bilò MB. Anaphylaxis caused by Hymenoptera stings: from epidemiology to treatment. *Allergy* 2011; 66(95):35–7.

17 Krishna MT, Ewan PW, Diwakar L, et al. Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and Clinical Immunology (BSACI) guidelines. *Clinical et experimental Allergy*. 2011;41(9):1201–20.

18 Van Oostrom SH, Driessen MT, de Vet HC et al. Workplace interventions for preventing work disability. *Cochrane database Syst Rev.* 2009 Apr 15;(2):CD006955.

19 Blanc PD, Ellbjar S, Janson C, et al. Asthma-related work disability in Sweden. The impact of workplace exposures. *Am J Respir Crit Care Med* 1999; 160(6): 2028–33.

20 Oude Elberink JN, de Monchy JG, Golden DB, et al. Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. *J Allergy Clin Immunol.*2002;109(1):162–70.

21 Omachi TA, Claman DM, Blanc PD, et al. Obstructive sleep apnea: a risk factor for work disability. *Sleep.* 2009;32(6):791–8.

22 Teschke K, Smith JC, Olshan AF. Evidence of recall bias in volunteered vs. prompted responses about occupational exposures. *Am J Ind Med.* 2000;38(4):385–8

Title page

Title

Hymenoptera venom allergy: work disability and occupational impact of venom immunotherapy

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allergy, disability, hymenoptera, immunotherapy, venom.

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ABSTRACT

Objectives: Little is known about the Hymenoptera venom allergy impact on work ability and the effect of venom immunotherapy (VIT) on work. The objective of this study was to evaluate the prevalence and predictors of work disability in patients treated with VIT and the effects of VIT on occupational functioning.

Methods: 181 patients, aged 18–71, treated with VIT while working, were investigated by questionnaire. Subjects were classified into employed and self-employed and, based on work exposure to Hymenoptera, into three risk categories, high risk, occasionally high risk, and low risk. Work disability was defined as having to have changed jobs/tasks and/or suffered economic loss because of Hymenoptera venom allergy. Predictors of work disability were assessed in logistic regression models.

Results: 31 (17%) patients reported work disability. Being self employed and having the severe reaction at work were associated with work disability ($p<0.01$). Having a high-risk job for exposure to Hymenoptera was a significant predictor of work disability (OR 2.66, 95% CI 1.04-6.75). 24% of patients referred a positive effect of VIT on work. Determinants of the positive effect of VIT on work were having a high risk job for exposure to hymenoptera (OR 3.60, 95% CI 1.52 - 8.51) and having already concluded VIT (OR 2.82, 95% CI 1.30- 6.14).

Conclusions: Hymenoptera venom allergy could determine work disability. Patients with Hymenoptera venom allergy having a high risk job for exposure to Hymenoptera seem to have higher risk of work disability and refer more frequently a positive effect of VIT on work.

WHAT THIS PAPER ADDS

► Hymenoptera venom sting is recognized as a risk factor for relevant, often life-threatening, allergic reactions but little it is known about the socio-economical effects of hymenoptera venom allergy. In the present study, for the first time, work disability and occupational effects of venom immunotherapy were studied in a group of patients in working age.

► The results suggest that Hymenoptera venom allergy has an impact on work through causing work disability.

► Self-employed workers and workers at high risk of sting seem to be at higher risk of work disability related to Hymenoptera venom allergy. Type of job was also a predictor of a positive effect of VIT on work.

LIMITATIONS

► The small number of subjects could be considered a shortcoming of this survey

► The questionnaire has never been used in other studies

INTRODUCTION

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may affect the emotional, social and occupational behaviour of the affected individual.[6] Recently a disease-specific questionnaire, the Vespid Allergy Quality of Life Questionnaire, was designed and validated for assessing health-related quality of life in patients with anaphylactic responses following yellow jacket stings. The survey showed that patients experienced quality of life impairment especially because of the emotional distress associated with having to be constantly on the alert while leading their everyday "normal" lives.[7]

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2) Did you change your job tasks because of Hymenoptera sting reaction?
3) Did you suffer economic loss because of Hymenoptera sting reaction?

The definition of work disability was formulated on the basis of previous surveys about work disability, widely available in the literature [8,9]. To assess the effect of VIT, specific questions were asked about a possible positive, negative or indifferent effect of the treatment on work. Since there were not other questionnaire about this topic, a panel of allergologists and occupational physicians reviewed and proposed the questions used in this study about possible indicators of a treatment-related positive effect, such as not having changed jobs or tasks and feeling safer at work, or indicators of a negative effect, such as economic loss, changes of job or task and changes in working time. Subject with negative or indifferent effect of VIT on work were classified as not having a positive effect on work.

The study protocol was approved by the Ethical Committee of Umbria Region (CEAS). All the patients gave their informed and written consent to participate in this study.

Statistical analysis

Differences between patients with and without work disability were evaluated by Chi-square test or Fisher's exact test, as appropriate, for categorical variables, and using Mann-Whitney U-test or *t*-test for continuous variables. Predictors of work disability and positive or negative VIT effects on work were assessed in logistic regression models, adjusted for gender and age, choosing as independent variables those showing a different distribution across the groups in the univariate analysis. The goodness of fit of the logistic regression models was confirmed by the Hosmer-Lemeshow test.[10] All the analyses were performed using SPSS statistical software, version 20.0 (SPSS, IBM Corporation, New York, NY, USA).

RESULTS

All 181 patients treated with VIT while working answered the questionnaire. Among them 68% were still undergoing VIT and 32% had concluded the therapy. The mean age was 49 years, 19% were female and more than half of the subjects lived in the countryside. Thirty-one patients (17%) reported work disability. No patient reported a complete work change because of Hymenoptera

venom allergy, ten (5%) reported having had to change job tasks, and 25 (14%) reported economic loss because of Hymenoptera venom allergy, four (2%) reported both conditions. The characteristics of the study population, classified according to work disability due to Hymenoptera venom allergy, are shown in table 1. No differences were found in distribution of gender, residence, mean age, stinging insect, and severity of the allergic reaction between the two groups. In subjects with work disability, Vespula was responsible for 45% of the reactions, and 45% experienced a systemic allergic reaction grade 4, according to Mueller's classification.

Fourteen patients (45%) with work disability and 26 (17%) without work disability experienced a sting reaction to Hymenoptera during shift ($p<0.01$). Subjects with work disability were mostly workers at high risk of work exposure to Hymenoptera while subjects without work disability were mostly at low risk (68% *vs.* 41%, $p<0.001$) (table1).

Table 1 Characteristics of the patients with Hymenoptera venom allergy treated with venom immunotherapy (VIT), with or without work disability

		Subjects with work disability n=31	Subjects without work disability n=150	*p* value
Female, n (%)		6 (19.4)	37 (24.7)	NS
Age, mean ± SD		49.4±9.9	47.1±10.9	NS
Living in the countryside, n (%)		20 (64.5)	98 (65.3)	NS
VIT, n (%)				
	Ongoing	21 (67.7)	101 (67.3)	NS
	Concluded	10 (32.2)	49 (67.3)	
Treated with VIT for, n (%)				
	Apis mellifera	11 (35.5)	48 (32)	NS
	Vespula sp.	14 (45.2)	52 (34.7)	NS
	Polistes sp.	3 (9.7)	38 (25.3)	NS
	Vespa crabro	3 (9.7)	12 (8)	NS
Type of VIT extract				
	Aqueous	23 (74.2)	104 (69.3)	NS
	Depot	8 (25.8)	46 (30.7)	
Mueller reaction grade, n (%)				
	I	6 (19.4)	27 (18)	NS
	II	4 (12.9)	30 (20)	
	III	7 (22.6)	30 (20)	
	IV	14 (45.2)	63 (42)	
Ever stung before the reaction, n (%)		26 (83.9)	110 (73.3)	NS
Other severe hymenoptera reactions, n (%)		1 (3.2)	12 (8)	NS
Years after the first severe reaction, mean ± SD		9±6.7	7.1±5.7	NS
Having the severe reaction, n (%)				
	at work	14 (45.2)	26(17.3)	<0.01
	during sport	1 (3.2)	4 (2.7)	NS
	during hobby activity	9 (29)	52 (34.7)	NS
	at home	6 (19.4)	44 (29.3)	NS
	in car/motorcycle	3 (9.7)	24 (16)	NS
Work-related risk of exposure to Hymenoptera, n (%)				
	High	21 (67.7)	53 (35.3)	<0.01
	Occasionally high	5 (16.1)	35 (23.3)	
	Low	5 (16.1)	62 (41.3)	
Self-employed worker, n (%)		16 (51.6)	42 (28)	<0.01

NS = not significant; SD = standard deviation.

Forty-four subjects (24%) reported a positive effect of VIT on work, 93 no impact (51%) and 44 negative (24%). The characteristics of the population, classified by the presence or absence of the positive impact of VIT on work, are displayed in table 2.

Table 2 Characteristics of the patients with regard to the impact of venom immunotherapy (VIT) on work

		Impact of VIT on work		
		Positive n=44	Negative or indifferent n=137	p value
Female, n (%)		12 (27.3)	31 (22.6)	NS
Age, mean ± SD		49.7±11.7	46.8±10.3	NS
VIT, n (%)				
	Ongoing	22 (50)	100 (73)	<0.01
	Concluded	22 (50)	37 (27)	
Treated with VIT for, n (%)				
	Apis mellifera	11 (25)	48 (35)	NS
	Vespula sp.	17 (38.6)	49 (35.8)	NS
	Polistes sp.	13 (22.7)	31 (22.6)	NS
	Vespa crabro	6 (13.6)	9 (6.6)	NS
Mueller reaction grade, n (%)				
	I	7 (15.9)	26 (19)	NS
	II	6 (13.6)	28 (20.4)	
	III	12 (27.3)	25 (18.2)	
	IV	19 (43.2)	58 (42.3)	
Ever stung before the reaction, n (%)		38 (86.4)	102 (74.5)	NS
Other severe Hymenoptera reactions, n (%)		2 (4.5)	11 (8)	NS
Years after the first severe reaction, mean ±		7.7±5.4	7.3±6.1	NS

SD			
Having the severe reaction at work, n (%)	17 (38.6)	23 (16.8)	<0.005
Work-related risk of exposure to Hymenoptera, n (%)			
High	28 (63.6)	46 (33.6)	<0.01
Occasionally high	5 (11.4)	35 (25.5)	
Low	11 (25)	56 (40.9)	
Self-employed worker, n (%)	20 (45.5)	38 (27.7)	<0.05

F = female; NS = not significant; SD = standard deviation

Subjects reporting a positive effect of VIT on work were more frequently at higher risk of work exposure to hymenoptera, self employed workers and have experienced the allergic reaction at work (table 2). Evaluating the same characteristics presented in table 2, there were no significant differences between those with a negative impact of VIT and the other participants (those with a positive o indifferent impact on work).

In the logistic regression analysis, adjusted for gender and age, significant predictor of work disability was having a high-risk job for exposure to Hymenoptera (OR 2.66, 95% CI 1.04-6.75)(table 3).

Table 3. Predictors of work disability among patients undergoing Hymenoptera venom immunotherapy (VIT), adjusted for gender and age

	OR	95% CI	
Having the severe reaction at work	2.306	0.909	5.852
Workers at high risk of exposure to Hymenoptera	2.655	1.044	6.754
Self-employed workers	2.079	0.883	4.892

CI = confidence interval; OR = odds ratio

Working in a high-risk job for exposure to Hymenoptera was a determinant of the positive effect of VIT on work (OR 3.60, 95% CI 1.522 - 8.508) as well having already concluded VIT (OR 2.82, 95% CI 1.30- 6.14) (table 4).

Table 4. Predictors of the effect of venom immunotherapy (VIT) on work, adjusted for gender and age

Positive VIT effect	**OR**	**95% CI**	
VIT concluded	2.822	1.296	6.144
Having the severe reaction at work	1.777	0.721	4.384
Workers at high risk of exposure to Hymenoptera	3.599	1.522	8.508
Self-employed workers	1.323	0.601	2.912

CI = confidence interval; OR = odds ratio

DISCUSSION

Hymenoptera venom allergy and work disability

In this study a not negligible percentage of patients with severe Hymenoptera venom allergy requiring VIT reported work disability. Our main finding is the association between occupational characteristics (jobs at a high risk of exposure to Hymenoptera) and work disability related to Hymenoptera venom allergy.

Our results suggest that presence of systemic Hymenoptera allergy can lead to occupational problems, especially when the severe reaction took place during work. This was consistent with the data in the literature.[6]

In our study the percentage of workers at high risk of sting (beekeepers, farmers, truck drivers) was slightly higher (41%) compared with workers occasionally at risk (22%) or those with low risk of sting (37%). Working in these high-risk jobs for sting was a significant risk factor for work disability. These findings support the hypothesis that Hymenoptera venom allergy could be considered an occupational disease.[1]

Work disability and decreased work productivity usually occur also in other similar diseases such as asthma and allergic rhinitis, [9,11] especially if ocular symptoms are present.[12] In studies on respiratory work disability the exposure to the risk factors, such as irritants, is the most important predictor of work disability.[13] This was the finding also in this study, where workers most likely to be exposed to Hymenoptera were at higher risk of work disability. In other studies blue-collar workers have been reported to be at higher risk of occupational consequences of Hymenoptera venom allergy than white-collar workers;[6] similar in our study the category of workers at high risk of exposure to Hymenoptera referred more work disability (change work/task and/or economic loss) than the other two groups (occasionally at high risk, and at low risk). In this study the risk of work disability for self employed workers was not statistically significant as expected because some authors reported that employees were usually at higher risk of health-related job loss than self-employed workers.[14] The non-significant risk increase related to "having the reaction at work" could be explained by the obvious correlation between high-risk jobs for sting and the occurrence of reaction in a population characterized by severe allergic reaction to Hymenoptera venom.

Venom immunotherapy impact on work

VIT is globally accepted as the treatment of choice in venom allergy.[15]

Although 44 patients in the present study declared a negative effect of VIT on work, caused by changing working time and economic loss due to VIT, most of our subjects declared an indifferent effect of VIT on work. Subjects at high risk of sting reported a positive VIT impact on work. This

will support the accepted medical approach that occupation may influence the decision to initiate VIT, also for non-life-threatening reactions.[5]

Another predictor of a perceived positive effect from VIT was completion of treatment. Subjects who have already completed VIT are probably more aware of the long-term beneficial effects of treatment. They are less likely to report any drawbacks of VIT, such as the time spent in therapy, which can affect work and social life. A relevant number of participants reported a negative impact of VIT on work and even if we could not find any peculiar characteristic of this group, this finding deserves attention. To prevent this side effect of VIT related to the amount of time spent in therapy, it is important to underline that we have room for improvement, developing new forms and routes of VIT (e.g. sublingual VIT),[16] or more convenient regimens such as rush up-dosing, which may lead to improved patient compliance. Unfortunately some studies have concluded that the accelerated VIT protocols are associated with a significant increase in the incidence of systemic reactions compared with conventional protocols.[17] Moreover, such accelerated protocols may necessitate new allocations of medical services and further timetabling in relation to employment.[6] Another way to reduce the reported negative effect of VIT could be to improve information about the risks related to a new reaction to hymenoptera venom among patients selected for VIT, who are those at higher risk of severe reactions. During this study we had the impression that information about venom related life- threatening reaction is not homogenous in our group of patient. Stressing the efficacy of VIT for the prevention of life-threatening reaction could be a good strategy to improve the acceptance of this treatment. Venom immunotherapy could be considered a workplace intervention to reduce work disability, even if, as a result of the few available studies on work intervention to prevent work disability, no convincing conclusions can be drawn about the effectiveness of these interventions.[18]

Validity issues

The small number of subjects could be considered a shortcoming of this study, anyway the subject is novel, the disease is rare and in the literature previous reports on work disability with similar

numbers were already been published.[8,19] Since the existing questionnaire about quality of life in patients with Hymenoptera venom allergy does not take into account work disability,[20] we had to design our questionnaire, defining work disability as job/task change or economic loss due to the disease (in our case, Hymenoptera venom allergy).[8,19,21] We were aware of a possible recall bias, as reported in other questionnaire-based surveys. To minimize recall bias we also considered the entity of the allergic reaction according to the Mueller grading scale, as well as the presence of other severe reactions and the time from the severe reaction that push the subject to consult an allergologist. None of these variables had a significant effect on work disability. Furthermore, we preferred to use prompted questions, which are less prone to recall bias, especially for occupational exposures.[22]

CONCLUSIONS

This cross-sectional study suggests that Hymenoptera venom allergy has an impact on work through causing work disability. Having a high-risk job for sting appears to be a significant risk factor for work disability as well a predictor of a perceived positive impact of VIT on work. Therefore, for the prevention and treatment of patients we have to consider also the occupational burden of Hymenoptera venom allergy.,

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Competing Interests None.

References

1 Bonadonna P, Schiappoli M, Dama A, et al. Is hymenoptera venom allergy an occupational disease? Occup Environ Med 2008;65(3):217–8.

2 Gregorian Ch, Galatas ID, Klamouris Ch, et al. Insect venom allergy in Greek adults. *Allergy* 1997;52:51–7.

3 Müller UR. Insect Sting Allergy. Stuttgart, Germany: Gustav Fischer, 1990.

4. Incorvaia C, Mauro M, Pravettoni V, et al. Hypersensitivity to hymenoptera venom: advances in diagnosis and implications for treatment. *Recent Pat Inflamm Allergy Drug Discov* 2011;5 (2):128–35.

5 Bonifazi F, Jutel M, Bilò MB, et al. Prevention and treatment of hymenoptera venom allergy. *Allergy* 2005;60:1459–70.

6 Kahan E, Ben-Moshe R, Derazne E, et al. The impact of Hymenoptera venom allergy on occupational activities. *Occup Med.*1997;47(5):273–6.

7 Bilo BM, Rueff F, Mosbech H, et al. Diagnosis of Hymenoptera venom allergy. *Allergy* 2005;60:1339–49.

8 Eisner MD, Yelin EH, Katz PP, et al. Risk factors for work disability in severe adult asthma. *Am J Med.* 2006;119(10):884–91.

9 Torén K, Zock JP, Kogevinas M, et al. An international prospective general population-based study of respiratory work disability. *Thorax* 2009;64:339–344.

10 Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol.* 1982;115(1):92–106.

11 De la HozCaballer B, Rodriguez M, Fraj J, et al. Allergic rhinitis and its impact on work productivity in primary care practice and a comparison with other common diseases: the cross-sectional study to evaluate work productivity in allergic rhinitis compared with other common diseases (CAPRI) study. *Am J Rhinol Allergy* 2012;26(5):390–4.

12 Virchow JC, Kay S, Demoly P, et al. Impact of ocular symptoms on quality of life (QoL), work productivity and resource utilisation in allergic rhinitis patients – an observational, cross sectional study in four countries in Europe. *J Med Econ.* 2011;14(3):305–14.

13 Murgia N, Torén K, Kim JL, Andersson E. Risk factors for respiratory work disability in a cohort of pulp mill workers exposed to irritant gases. *BMC Public Health.*2011;11:689.

14 Solomon C, Poole J, Palmer KT, et al. Health-related job loss: findings from a community-based survey. *Occup Environ Med.* 2007;64(3):144–9.

15 Ozdemir C., Kucuksezer UC, Akdis M, et al. Mechanism of immunotherapy to wasp and bee venom. *Clin Exp Allergy*. 2011;41:1226–34.

16 Bilò MB. Anaphylaxis caused by Hymenoptera stings: from epidemiology to treatment. *Allergy* 2011; 66(95):35–7.

17 Krishna MT, Ewan PW, Diwakar L, et al. Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and Clinical Immunology (BSACI) guidelines. *Clinical et experimental Allergy*. 2011;41(9):1201–20.

18 Van Oostrom SH, Driessen MT, de Vet HC et al. Workplace interventions for preventing work disability. *Cochrane database Syst Rev.* 2009 Apr 15;(2):CD006955.

19 Blanc PD, Ellbjar S, Janson C, et al. Asthma-related work disability in Sweden. The impact of workplace exposures. *Am J Respir Crit Care Med* 1999; 160(6): 2028–33.

20 Oude Elberink JN, de Monchy JG, Golden DB, et al. Development and validation of a health-related quality-of-life questionnaire in patients with yellow jacket allergy. *J Allergy Clin Immunol.*2002;109(1):162–70.

21 Omachi TA, Claman DM, Blanc PD, et al. Obstructive sleep apnea: a risk factor for work disability. *Sleep.* 2009;32(6):791–8.

22 Teschke K, Smith JC, Olshan AF. Evidence of recall bias in volunteered vs. prompted responses about occupational exposures. *Am J Ind Med.* 2000;38(4):385–8