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Title: Epidemiology of Hymenoptera venom allergy in the Valencia Fire Brigade (Spain).

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Clinical Implications: Firefighters in Valencia (Spain) are highly exposed to Hymenoptera stings and develop local and systemic reactions with a higher frequency than other exposed populations. People at risk must be identified and provided with adequate protective measures, including venom immunotherapy.

The prevalence of Hymenoptera venom allergy (HVA) correlates with the number of stings.¹ On the Spanish Mediterranean coast, the most prevalent Hymenoptera insects are *Apis mellifera*, *Polistes dominula*, and *Vespula germanica*². In this setting, firefighters are responsible for removing wasp nests and beehives around cities, increasing their exposure to stings (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) and their risk of an allergic reaction. Little research has been published on Hymenoptera stings in this population.

We conducted a poster campaign and survey to assess the prevalence and characteristics of HVA in firefighters in the city of Valencia (Spain). All participants completed a questionnaire eliciting detailed information about symptoms after stings, and an allergist interviewed them to corroborate the data provided.

Participants were classified as allergic and non-allergic, depending on the presence or absence of self-reported symptoms compatible with an allergic reaction after the sting.³ Severity was graded according to the Müller classification.⁴ Clinical manifestations, such as rhinitis, asthma, or cutaneous reactions were recorded. Participants underwent venom skin prick and intradermal tests (0.01 µg/mL, 0.1 µg/mL, and 1 µg/mL) and determination of specific immunoglobulin E (sIgE) to *Apis mellifera*, *Polistes dominula*, and *Vespula germanica*. We used a logistic regression to assess risk of HVA in firefighters as an adjusted odds ratio (OR) with 95% confidence interval (CI) (see this article's Online Repository at www.jaci-inpractice.org for more information on

statistical methods used). The Ethics Committee of the Elche University General Hospital (Spain) approved the study.

Of the 413 firefighters recruited, 93.2% completed the questionnaire (382 men and 3 women; mean age 43.9 ± 10.1 years, 95% CI 42.9–44.9). Most participants (95.3%) had received at least one sting. The prevalence of HVA based on clinical history alone was 19.74% ($n = 76$). Thus 54/385 (14%) had LLR and 22/385 (5.7%) had SR.

All cases classified as allergic, plus 96/309 participants classified as non-allergic (as selected through simple random sampling), underwent diagnostic tests. Sixty-two (81.5%) of the allergic firefighters showed sensitization (for sIgE alone in 3 (4%), for an intradermal reaction alone in 24 (31.5 %), and for both tests in 35 (46%), compared to 40 (41.7%) non-allergic participants. In the latter group, results were positive for sIgE alone in 3 (3.1%) cases, for an intradermal reaction alone in 18 (18.8%), and for both tests in 19 (19.8%). In the bivariate analysis between both groups (allergic and non-allergic) we show that allergy firefighters have a higher probability of having ID, sIgE or both positive tests, with an OR=7.24 (CI 3.5-15); OR=3.7 (IC 1.92-7.1) and OR = 7.9 (IC 3.7-16.9); $p < 0.01$, respectively.

In a subgroup of 51 highly exposed firefighters, the prevalence of allergic reactions was 39.2% ($n = 20$): 15 (29.4%) were LLRs and 5 (9.8%) SRs; the other 31 experienced only minor local reactions. Were selected thirty-six of these firefighters (20 allergic cases and 16 non-allergic cases) for allergic work-up. The other 15 were included in the group of 309 subjects without any allergic reaction. The frequency of sensitization in this subgroup of 36 firefighters was 35.3% (Table 1), and the asymptomatic sensitization was of 50%. These differences of asymptomatic

sensitization among different population are in concordance with the prevalence of HVA (See Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Participants presenting any type of allergic reaction had experienced more stings per year. Those who suffered SRs were working 7 years longer than those with LLRs ($p = 0.008$). (see this article's Online Repository at www.jaci-inpractice.org for more information on statistical methods used). The most common culprit insect identified was *A. mellifera* (28.8%), followed by *P. dominula* (12.4%) and *V. germanica* (7%).

Intradermal tests showed a closer association than sIgE levels with symptoms. We observed no relationship between levels of venom sIgE and the severity of reaction (LLR or SR). Venom sIgE levels to *A. mellifera* and *P. dominula* were correlated to how recent the sting was.

Based on the positive diagnostic test results in 62/76 of the participants reporting HVA-compatible reactions (LLR and SR), the questionnaire showed a sensitivity of 85%, a specificity of 58%, a positive predictive value of 61%, and a negative predictive value of 83.6% (OR 7.6; $p < 0.001$).

An allergic disease diagnosed by history and confirmed by Allergist interview (allergy rhinitis, bronchial asthma and atopic dermatitis) was diagnosed in 45/76 (59%) allergic cases and 34/96 (35.4%) non-allergic controls. The prevalence of allergic disease was 2.6 times higher in the group classified as allergic (LLR and SR together) according to the questionnaire.

Logistic regression showed a statistically significant association between allergic symptoms following a Hymenoptera sting and receiving medical treatment, intradermal test results, and a history of allergies diseases (rhinitis, asthma, atopic dermatitis, food allergy and drug allergy). The other variables showed significant crude associations, but these associations did not hold after multivariable adjustment (Table 2).

Our results show a high prevalence of HVA in firefighters (19.7%), which is almost three times that seen in the general population in the same area (7.6%)⁵. This increased risk is due to the greater occupational exposure to stings, as indicated by the even higher prevalence of HVA and asymptomatic sensitization (50%) in the highly exposed subgroup. This figure compares to 50% in beekeepers and greatly surpasses the proportions observed in other groups (See Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Like other authors⁶, we found no differences between the levels of venom sIgE and the occurrence of LLRs or SRs. Those stung frequently produced higher levels of venom sIgE and could suffer SRs in a relatively short time. Indeed, people who had been stung in the previous few weeks had a higher risk of experiencing a new SR than those who did not have any recent stings⁷.

Firefighters with HVA were nine times more likely to present to medical services following a sting than non-allergic, suggesting that those visits are in relation with the hypersensitivity reaction severity (Table 2). More severe symptoms at 24 hours could indicate a selective HVA. This association has also been reported elsewhere⁵.

Firefighters have an occupational risk of HVA due to potential exposure to Hymenoptera stings. Other authors have suggested that venom immunotherapy must be indicated in case of continued exposure because this treatment is globally accepted as the treatment of choice in venom allergy⁸, helping to decrease occupational disability, anxiety, health impacts, and health care costs⁹.

Our results are the first to show that the estimated prevalence of HVA in the studied firefighters is 2-3 times higher than in the general population. Highly exposed subgroups have a four- to five-fold risk. This data may warrant further investigation of other population of firefighters.

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Table 1. Diagnostic test results in highly exposed subgroup of firefighters (N = 36)

	LLR cases	SR cases	Non allergic cases	Total
ID/sIgE tests	n (%)	n (%)	n (%)	n
Positives	14 (93.3)	4 (80)	8 (50)	26
Negatives	1 (6.7)	1 (20)	8 (50)	10
Total	15 (100)	5 (100)	16 (100)	36

LLR: large local reaction. SR: systemic reaction. ID: intradermal test to venom. sIgE: specific IgE to

venom

TABLE 2. Logistic regression analysis. Crude and adjusted associations between independent variables and clinical reaction to Hymenoptera sting

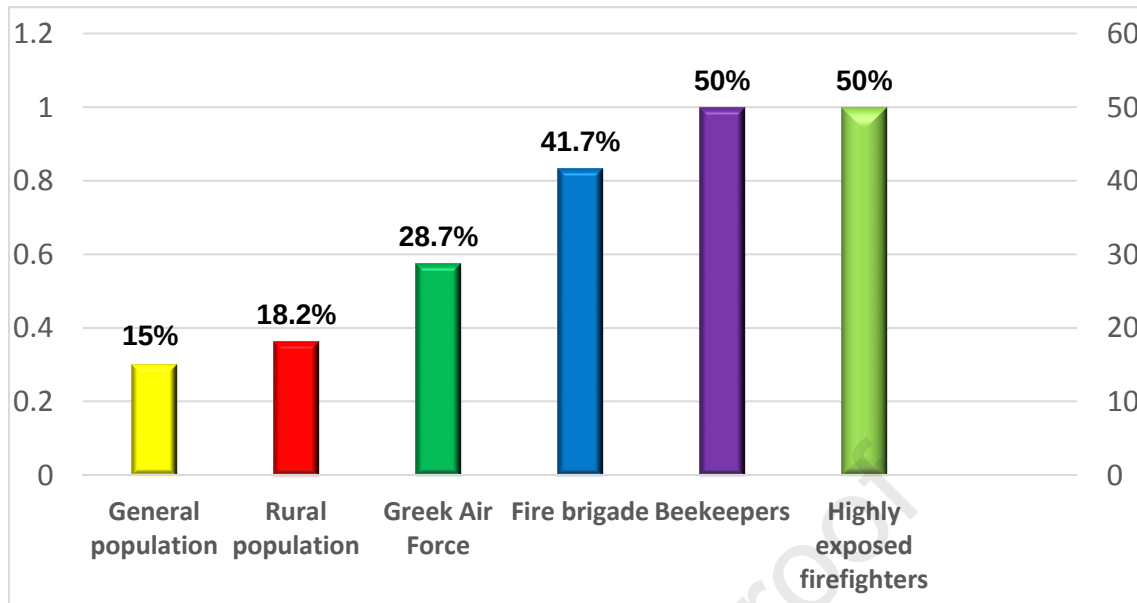
Independent variables	Allergic subjects, n (%)	Non allergic subjects, n (%)	ORc* (95% CI)	ORa** (95% CI)	P value
History of allergy	43 (55.8)	34 (34.2)	2.64 (1.43–4.88)	2.92 (1.34–6.37)	0.007
No allergies	33 (32.4)	69 (67.6)			
Positive ID test	59 (81.9%)	37 (38.1)	7.36 (3.56–15.23)	6.72 (1.88–24.08)	0.003
Negative ID test	13 (18.1%)	60 (61.9)			
Treatment	38 (50.7%)	9 (10.1)	9.13 (4.003–20.8)	10.14 (2.97–34.6)	< 0.001
No treatment	37 (49.3%)	80 (89.9)			

CI: confidence interval; ORc/a: crude/adjusted odds ratio; ID: intradermal

Table E1. Sample studies of allergies to Hymenoptera venom in different groups of workers

Study (year)	Country	Workers, reported prevalence of allergic reactions
De la Torre-Morin F et al. (1995)	Spain	Beekeepers, 51.4%, SR 30%-60%
Pérez-Pimiento A et al. (2007)	Spain	Gardeners 39%, builders 17%, postmen 11%
Copertaro A et al. (2006)	Italy	Forestry workers 2% SR and 2% LLR
Incorvaia C et al. (2004)	Italy	Forestry workers, 4.5% SR and 9.8% LLR
Shimizu T et al. (1995)	Japan	Forestry workers, 24% SR
Yumeko Hayashi et al. (2014)	Japan	Foresters, 21.8% SR
Thong BY et al. (2005)	Singapore	Military forces, 61%
Kochuyt AM et al. (1993)	Belgium	Green workers and biologists
de Groot H et al. (1995)	Holland	Green workers and biologists
Arias Cruz et al. (2007)	Mexico	Veterinarians and biologists, 7.8% LLR
Cabrera et al. (2014)	Spain	Firefighters, 7.8% SR and 27.4 % LLR

LLR: Large Local Reaction; SR: Systemic Reaction

Figure E1.

METHODS

The study began with a poster campaign to inform and recruit firefighters of Valencia City along with the design of a survey for data collection. All participants completed a questionnaire administered by an Allergist that included items like age, sex and symptoms after the sting. This were classified in (local reaction, LLR [diameter of 10 cm or more], or SR as described. The severity of symptoms was graded according to the Müeller classification. Other variables included location of the sting, treatment, duration of reaction, estimated number of accumulated stings (exposure), date of the last bite, Hymenoptera species (if known), and presence of other allergies.

The study had two phases. The first was an exploration of the clinic-epidemiological characteristics of the study group, consisting of a medical interview to corroborate the data collected in the questionnaires. The second phase aimed to assess the prevalence of Hymenoptera allergy in the study cases. Data on two groups of participants were collected: “allergic cases” of active firefighters were those who performed all of their duties and suffered symptoms compatible with an allergic reaction after a Hymenoptera sting, and “non-allergic controls” of active Firefighters were those who have not experienced symptoms after the sting. Although any active Firefighter can make an Hymenoptera service and exposure to sting, this type of work was carried out by a specialized group of 51 Firefighters. All participants underwent diagnostic tests to assess sensitization to Hymenoptera venom. Prick and intradermal (ID) tests (0.01 – 0.1 – 1 µg/ml) and determination of specific immunoglobulin E (IgE) with *Apis mellifera*, *Polistes dominula* and *Vespula germanica* venoms were carried out. Results were analyzed in conjunction with total IgE levels. Criteria for diagnosis were made as described.

This study was approved by the Ethical Committee of the Alicante University General Hospital (Spain). As required, before undertaking the study, subjects were informed of the skin testing and blood sample and a written informed consent was obtained.

Statistical analysis Qualitative variables were presented as absolute and relative frequencies, and quantitative data are presented as mean $\pm$ standard deviation. Student t tests were used to assess the differences between groups. The χ^2 test was used to assess differences in bivariate analysis and to test for independence and calculate the odds ratio (OR). Spearman's rank coefficient tests were used to correlation between variables.

Logistic regression was performed to estimate the adjusted odds ratio (OR) and 95% confidence interval (CI), controlling for confounders. A two-tailed p value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the SPSS (Statistical Package for Social Sciences) program for Windows, version 22.0 (SPSS, IBM Corporation, New York, USA).

Repository Figure Legend:

Figure E1: Prevalence of asymptomatic sensitization in different occupational or geographical groups.

This figure shows the prevalence of HVA in the general population and high exposure workers (Perez-Pimiento AJ, Gonzalez-Sanchez LA, Prieto-Lastra L. Anaphylaxis to hymenoptera sting: study of 113 patients. *Med Clin* 2005;125:417-420; Thong BY, Leong KP, Chng HH. Insect venom hypersensitivity: experience in a clinical immunology/allergy service in Singapore. *Singapore Med J* 2005;46:535-539; Incorvaia C, Senna G, Mauro M, Bonadonna P, Marconi I, Asero R et al. Prevalence of allergic reactions to Hymenoptera stings in northern Italy. *Eur Ann Allergy Clin Immunol* 2004;36:372-374).