Original Article

Epidemiological factors on Hymenoptera venom allergy in a Spanish adult population

L. A. Navarro, A[a]. Peláez[b], F. de la Torre[c], J. M[a] Tenias Burillo[d], J. Megías[e], I. Martínez[f]

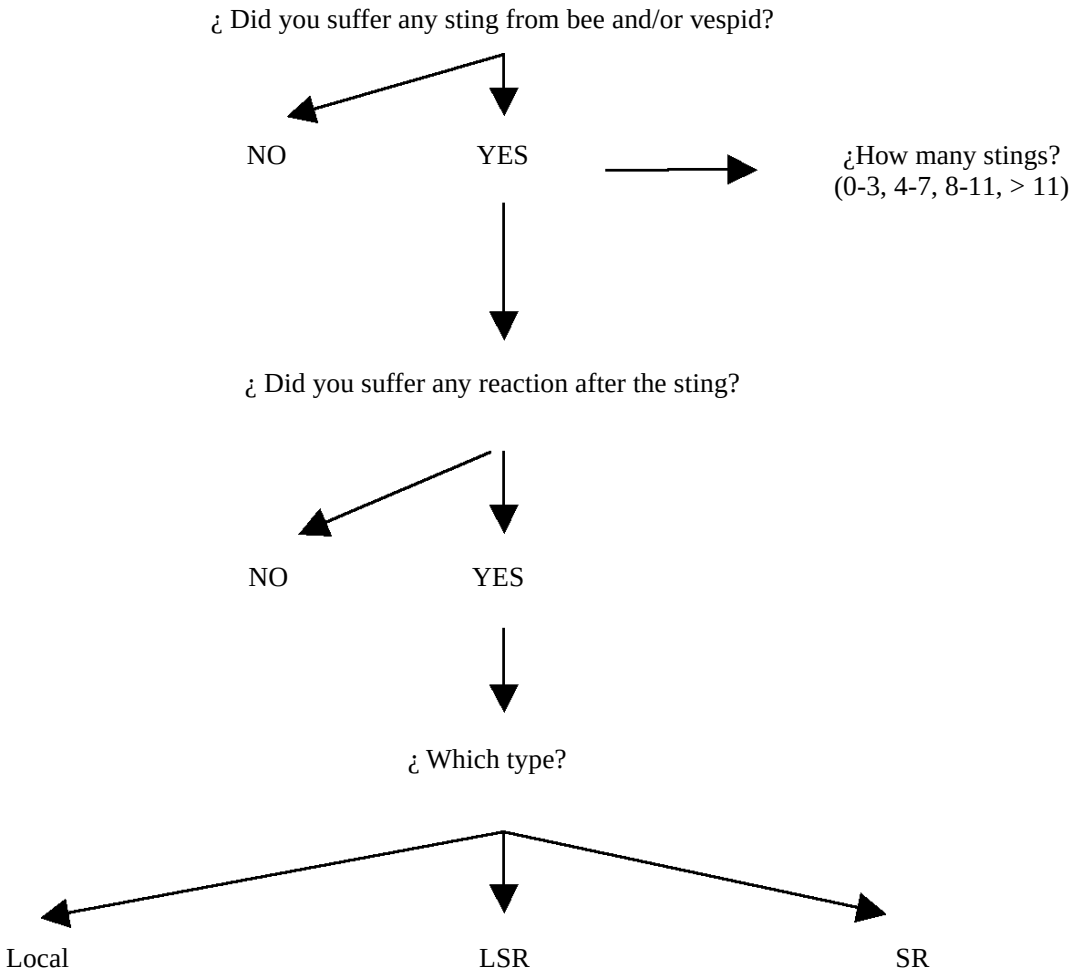
[a] Unidad de Alergia. Servicio de Medicina Interna. Hospital de Xàtiva (Spain) - [b] Servicio de Alergia. Hospital Clínico Universitario. Avda. Blasco Ibáñez, 17, 46010 Valencia (Spain) - [c] ALK-ABELLÓ , S.A. Miguel Fleta, 19, 28037 Madrid, Spain - [d] Dpto. Medicina Preventiva, Hospital Lluis Alcanys, Xàtiva (Spain) - [e] Dpto. Médico Ford España, Valencia (Spain) - [f] Servicio de Medicina Intena. Hospital de Xàtiva (Spain).

Abstract: *Background:* The prevalence and risk factors of hymenoptera venom allergy (HVA) have been studied in several countries. However, there are few studies on the general population and these have very variable results. *Methods:* An observational, prospective and cross-sectional study was carried out on a sample of 1064 subjects in a total working population of 7887 subjects (Ford factory, Spain) in order to know the prevalence of HVA in this population and the influence of several risk factors in its development.
Results: The rate of exposure to stings was 84.1 % (ci 95 %: 81.8 – 86.3 %). The prevalence of HVA was 7.6% (ci 95 %: 6.1 – 9.4%), with local severe reactions (LSR) in 5.3% (ci 95 %: 4 – 6.8%) and systemic reactions (SR) in 2.3% (ci 95 %: 1.5 – 3.4%). More than 82 % of individuals over 20 years had already had some exposure, a figure that did not change in the age groups of older decades. In our study, the prevalence of HVA was not dependent on either age (similar age in all groups), sex: for LSR OR 2.75 (ci 95 %: 0.37 – 20.30), for SR OR 0.54 (ci 95 %: 0.12 – 2.38), or atopy OR 0.96 (ci 95 %: 0.50 – 1.83); SR being more frequent among the residents of rural habitats, with ranges approaching statistically significant levels OR 2.15 (ci 95 %: 0.95-4.81). The number of stings was larger in HVA group with respect a control group. The degree of venom sensitization measure by skin test and CAP-RAST was more intensive in SR group versus LSR group. Among vespids, sensitization to Polistes was more frequent than Vespula.
Conclusions: HVA in our sample has a similar prevalence to other countries located in similar geo-climatic environments. Rural habitat and the number of stings suffered along life are risk factors of HVA development.

Key words: Hymenoptera Venom Allergy, prevalence, risk factors, Spanish population.

Introduction

The *Hymenoptera venom* allergy (HVA) has been widely studied, both from a physiopathologic and from a therapeutic point of view. In addition, various epidemiological studies have been performed in different countries in which allergic reactions to hymenoptera stings affect the population at a rate between 2.8 % [1] and 28.7 % [2]. This wide range can be attributed to differences in the study method applied by the authors and to the presence of different clinical profiles encompassed by the definition of the reactions to hymenoptera stings. According to the clinical response to a hymenoptera sting, subjects can be divided into three groups: Firstly, sensitised nonallergic subjects who have no symptoms after being stung. Secondly, those suffering a local severe reaction (LSR), which affects between 1.5 % [1] and 26.4 % [2] of the population. And thirdly, those suffering a systemic reaction (SR), which affects between 0.35% [3] and 6% [4] of the population. However, even when employing similar methodologies, different authors still produce results that disagree with each other. A main differentiating factor is the existence of a different geographical environment. For this reason it does not seem appropriate to transfer conclusions from one country to another. However, studies carried out on the general adult population are few and prevalence figures are not available for many countries. It should



LSR: Local Severe Reaction (> 10 cm and > 48 h)
SR: Systemic Reaction.

also be remarked that although this pathology causes tens of deaths per year [5] (and possibly many more), several authors have complained of the scarce attention given to this problem by health services [6, 8]. In Spain, with the exception of two studies carried out on selected large populations [2, 9] there are no data on the degree to which the general population is affected.

Objectives

To carry out an epidemiological study of this problem in the general adult working population in Spain with a sufficiently large sample. Firstly to try to obtain results on prevalence; secondly, how a series of variables that depend on the environment (geographical situation, habitat and number of stings suffered along life) and on the individual (age, sex and atopy) act as risk factors; and thirdly we will then carry out an allergy study on the affected individuals to know immunological characteristics of several HVA manifestations.

Material and methods

Sample evaluation

1.-Choosing the sample.

We define an a priori representative group of the adult working population as that formed by healthy individuals of working age (18-65 years of age). In accordance with the sampling theory for finite populations, an homogeneous population was sought that was sufficiently large for the study, avoiding possible exposure biases due to the professional activity (beekeeper or beekeeper relative, woodsman, farmer, or any activity related to working in the country). Therefore we chose the working population of a car factory (Ford Spain) located in an industrial complex in the province of Valencia, in a geographical environment with a gentle climate and with a high environmental humidity typical of the Mediterranean area. In 1997 the factory had 7887 workers of both sexes, most of them living in the same province.

2.-Sample size

The calculations were made for a safety level of 95 % (error a<0.05). As no epidemiological study has been carried out on the Spanish working population, the work by Golden [6] was chosen. In this work the prevalence of this type of hypersensitivity in a population of industrial workers was calculated. The prevalence depended on whether the author determined the hypersensitivity using cutaneous tests or RAST. According to the first method the prevalence was 17 % for wasp or bee venom, while with the second method the prevalence rose to 26 %. In accordance with these figures, two assumptions were put forward for the purpose of calculating the sample size. These are now discussed.

a.- Assuming the 17% figure, and the largest difference allowed with the population of 2.5 %, the resulting size is 867 subjects. If we increase the sample by 20 % to account for possible losses, the final figure is 1041.

b.- With a prevalence of 26% and a maximum allowed difference with the population of 2.9 %, the necessary sample size is 879 subjects. We oversize the sample by 20%, as in the previous case, and we arrive at a final sample of 1064. Taking into account that both figures are very similar, this last figure was selected as sample size.

3.-Design and stratification.

The sample is stratified according to the three criteria shown below:

1.-Sex: males/females.

2.-Age (years): separated by decades, (20-30, 31-40, 41-50, 51-65).

3.-Habitat. Using similar criteria to those of previous studies (9), this is divided into:

– Urban: municipalities around the metropolitan area of the city of Valencia and/or areas with more than 50000 inhabitants.

– Rural: municipalities of less than 50000 inhabitants and outside the aforementioned metropolitan area.

4.-Clinical review of the sample

A questionnaire was drawn up with personal data (age, sex, usual place of residence). It included questions on whether the individual had been exposed or not to stings, how many stings, when did he/she suffered the last sting and possible reactions after a sting (LSR and SR). Figure 1. The LSR were defined as the appearance of erythema and oedema greater than 10 cm in diameter, lasting for 24 hours, but which may last up to 5 days, covering part or the whole of the limb (2 or more joints) or the face. The SR were defined as anaphylactic cutaneous symptoms, and/or respiratory symptoms, and/or digestive symptoms, and/or cardiovascular symptoms appearing immediately after the sting, according to the Mueller criteria [10]. Doctors from the company that owned the factory filled out the questionnaires in a consecutive fashion, coinciding with the annual medical check-up of 1997.

5.-Allergy study

Each questionnaire was then reviewed by an allergist, and classified according to history (based on the Mueller criteria) into individuals affected by LSR and those affected by SR. Five people with SR were removed to continue immunological study: two refused to participate, and three because they had received previous treatment with immunotherapy. Among subjects that denied LSR and/or SR a control group with a double size than HVA subjects was selected. We studied the presence of specific IgE from hymenoptera in all people that reported LSR and/or SR reactions and in the control group by two methods: in skin by intradermal tests with extracts of Polistes, Vespula and Apis mellifera venoms , using concentrations of 0.01 mg/ml, 0.1 mg/ml and 1 mg/ml (ALK-ABELLÓ Pharmalgen), and in serum by serological technique (CAP-RAST Pharmacia®). Results of skin test were measured by the Norman scale [11].

Table 1. List of the distribution of variables between sample and province of Valencia.

		SAMPLE n (%)	**PROVINCE n (%)**
AGE (years)	20-30	819 (11)	365518 (27)
	31-40	210 (19)	333492 (25)
	41-50	491 (46)	275194 (22)
	51-65	244 (22)	346517 (26)
SEX	MALE	1015 (95)	654978 (49.5)
	FEMALE	49 (5)	665743 (50.5)
HABITAT	URBAN	621 (58.4)	788507 (59.7)
	RURAL	443 (41.6)	532214 (40.3)

The work census for the province of Valencia in 1996 indicated 1320721 inhabitants.

Table 2. Distribution of exposure (at last one sting) in the sample.

		PREVALENCE % (CI 95%)	P
AGE (years)	20-30	82.2 (74.1 - 88.6)	0.008
	31-40	91.9 (87.4 - 95.2)	
	41-50	82.0 (78.3 - 85.3)	
	51-65	82.7 (77.6 - 87.0)	
SEX	MALE	84.5 (82.2 - 86.7)	0.09
	FEMALE	75.5 (61.1 - 86.7)	
HABITAT	URBAN	82.8 (79.6 - 85.7)	0.15
	RURAL	86 (82.4 - 89.1)	

CI: confidence interval p = p value

CAP-RAST results were positive when specific IgE levels measured were above 0.35 (kU/l) [12]. The same venoms were used for skin testing and CAP (Apis mellifera for bee and Polistes spp and Vespula spp for vespids). In both groups the presence of atopy was determined by clinical history from allergic rhinitis and/or asthma and/or eczema coinciding with positive cutaneous tests to the aeroallergens habitually found in the study area of study (Dermatophagoides, cat and dog epithelium, Parietaria, grasses, Olea and Alternaria). Identification of the responsible insect was carried out using both the information offered by patients and the outcome of skin tests and/or CAP.

Statistical analysis

The prevalence of allergic reactions of the SR and LSR type, and the confidence interval (ci) at 95 % (exact binomial method) were calculated. For each independent variable, the change of prevalence in the different categories was estimated by calculating the prevalence odds ratio (POR or simply OR). This association measure was chosen as the most adequate one for prevalence studies, as it provides the best estimate of the incidence ratio [13].

Table 3. Comparative paired analysis from the number of stings suffered between HVA and control group`.

Nº of stings	Control (n = 155)	HVA (n = 76)
0 to 3	78 (50.3%)*	21 (27.6%)
4 to 7	43 (27.7%)	20 (26.3%)
8 to 11	28 (18.1%)	25 (32.9%)
> 11	6 (3.9%)	10 (13.2%)**

*, ** p < 0.001

Table 4. Prevalence odds ratio (POR) of allergic reactions by age in the logistic regression model.

	Allergic reactions (LSR and/or SR)
Age (years)	POR (ci 95%)
20 – 30*	1
31 – 40	0.73 (0.30 - 1.1)
41 – 50	1.17 (0.55 – 2.50)
51 – 65	0.86 (0.36 – 2.01)

* Class reference.

Table 5. POR of allergic reactions by sex and habitat in the logistic regression model.

	Sex*	Habitat**
Reaction	POR (ci 95%)	POR (ci 95%)
LSR	2.44 (0.33 - 18.18)	1.24 (0.72 - 2.15)
SR	0.50 (0.11 - 2.20)	2.10 (0.92 - 4.76)

* Class reference: woman. ** Class reference: urban habitat.

Table 6. POR of allergic reactions by atopy and number of stings in the logistic regression model.

	POR
Atopy	
No	1
Yes	0.96 (0.50 - 1.83)
Number of stings	
0-3	1
4-7	1.45 (0.68 - 3.08)
8-11	3.48 (1.81 - 7.49)
> 11	5.68 (1.78 - 18.10)

The analysis strategy was based on the prevalence of the association measures for each variable (risk factor) in raw form without adjustment, and then, in order to control the possible influence of the remaining variables, a non-conditional logistic regression model was fitted.

The correlation between skin tests and CAP was made using the Spearman test, through their statistical Rho.

The calculations were carried out with the Epi Info 6.04 program (CDC, OMS) and the SPSS Windows Version 6.1.3 statistical package.

Results

Distribution of the variables in the sample

The sample of 1064 subjects showed a clear male predominance (Table 1), and slightly more than half the subjects lived in urban areas, but the habitat distribution of the sample and the population from the province of Valencia were similar. The average age was 43.4 years (standard deviation 8.6 years; range from 21 to 67 years of age). The percentage of women was similar in both the rural habitat (22/443: 5%) and the urban one (27/621: 4.3%) and the average age was similar to that of the males: 42.7, compared to 43.4 for males.

Rates of stings in the sample

Given that not all those interviewed had been stung by hymenoptera, we studied their distribution in the sample: 84.1 % (ci 95 %: 81.8 to 86.3 %) had been stung at least once during their lives and the distribution was different according to age, sex or habitat. The maximum exposure occurred in the 31-40 age group, with statistically significant differences with respect to the rest. The rate for the remaining groups was very similar. Table 2. The history of at last one sting was greater in males and in rural habitats although not in a significant fashion. Comparative paired analysis showed that in HVA group, the number of stings was significantly higher than the control group. Table 3.

Allergic reactions to hymenoptera stings

Allergic reactions affected 81 of the 1064 subjects interviewed, with a prevalence of 7.6 % (ci 95 %: 6.1 to 9.4%). LSR occurred in 56 subjects, 5.3% (ci 95 %: 4 to 6.8%) and SR in 25, 2.3% (ci 95 %: 1.5 to 3.4%). All systemic reactions were accompanied by skin symptoms (urticaria and/or angioedema). Six subjects, 0.6% (ci 95 %: 0,3 to 0,9%) suffered an anaphylactic shock.

The mean age was similar in the group of subjects with SR (42.4 years), LSR (42.9 years) and in the group of subjects who did not suffer allergic reactions after a sting (43.8 years). A logistic regression model that included variables of age, sex, habitat, atopy and number of stings was applied.

The number of stings that occurred throughout life was significantly higher in the HVA group in comparison with the control group. No differences were observed regarding age, sex or atopy. The presence of atopy was similar among the HVA group as compared with the control group (26/76, 34.2% vs. 45/155, 29%). The number of patients with atopy was similar among those who suffered LSR or SR (8/20 vs. 18/56, p=0.7). Concerning the habitat, higher rates of prevalence of the two types of reaction were observed close to the statistical significance (p=0.08) in the rural habitat (however more intensely regarding SR). Tables 4, 5 and 6.

Allergy study

In the total sample, cutaneous tests resulted in more positive cases than CAP (86% -65/76- vs. 67% -51/76, p<0.03). In all patients with SR, both cutaneous tests and CAP were positive. A reaction to bee sting was identified in 31/76 subjects: 21/56 LSR and 10:20 SR. Reactions to wasps (Polistes and/or Vespula) were identified in 52/76, 42/56 LSR and 10/20 SR. Seven subjects presented with severe local reactions by wasps and bees. Of the 31 honeybee allergic patients, skin tests were positive in 27 (87%) and CAP was positive in 23 (74%). In the 52 wasp allergic patients, these figures were 42 (81%) and 33 (63%) respectively. The presence of venom sensitisation was significantly greater in the subjects with SR. Table 7. At the same time the degree of sensitisation, measured by the response to skin tests, was significantly greater in the subjects with SR than in those who suffered a LSR. Table 8. Most of the LSR and SR due to vespids were caused by Polistes. Table 9.

The correlation between skin tests and CAP was statistically significant both for LSR and for SR, and higher in SR. Table 10.

The interval since the last sting in SR was similar than LSR (4 years vs 5 years), (p>0.05). In subjects with negative skin tests (only in LSR group), the average interval between the last sting reaction and the time at which these individuals were studied was 9.8 years. On the contrary, for subjects with positive skin tests this interval was 2 years. This difference was statistically significant (p<0.05).

Discussion

Interest in the epidemiology of HVA began in the United States in the seventies, and extended to Europe and Australia in the eighties and nineties as this pathology was shown to be a frequent health problem in the population, although the studies did not manage to pin down the precise scope of the problem. Such discrepancies are interpreted in the first studies by remarkable differences in design from the methodological point of view [7]. In fact, in the first cross-sectional studies of the questionnaire type [14,15], it was possible to show that there was a low bias in the

Table 7. Relation between the type of reaction and the presence of sensitisation to *hymenoptera venom (Polistes and/or Vespula and/or Apis).*

	Specific IgE serum		Skin tests	
	LSR	**SR**	**LSR**	**SR**
Negative	25 (21.4%)		11 (20%)	
Positive	31 (78.6%)	20 (100%)	45 (80%)	20 (100%)
P	0.0008		< 0.03	

Table 8. Relation between the degree of sensitisation measured by skin tests to *Apis* and/or *Polistes* and/or *Vespula*, and the type of reaction.

Skin tests	**LSR**	**SR**	**p**
Negative	11 (20%)	0 (0%)	< 0.01
Positive (1 μg/mL)	18 (34%)	8 (40%)	ns
Positive (0.1 μg/mL)	21 (37%)	5 (25%)	ns
Positive (0.01 μg/mL)	5 (9%)	7 (35%)	< 0.01

ns. not significant.

Table 9. Skin tests to *Polistes* and *Vespula* in wasp allergic patients.

Skin tests	**LSR**		**SR**	
	Polistes	***Vespula***	***Polistes***	***Vespula***
Negative	14 (33%)	28 (66%)		6 (60%)
Positive	28 (67%)	14 (34%)	10 (100%)	4 (40%)
P	< 0.005		< 0.006	

Table 10. Correlation between outcomes of skin tests and CAP.

	Type of reaction	
	LSR	**SR**
Apis	0.514	0.828
Polistes	0.455	0.755
Vespula	0.585	n.s.

Correlation significant ($p<0.05$) above 0.3. n.s. = not significant.

results, as the specialists who designed the study did not participate in the interview and also LSR was not included as HVA. However, in the last two decades, although the discrimination is already specialised, a variety of methods for the studies (population type and their size, data collection methods, species of hymenoptera studied, age and/or sex distribution of the population, etc.) still exists. In the light of this the broad range of results is not surprising, that prevalence figures for HVA vary so widely (1.5-26.4 % in LSR, and 0.35-6 % in SR). An analysis of the many publications existing shows that even with a very similar methodology important differences are still observed, which implies the existence of other distortion factors. For this reason it does not seem reliable to extrapolate the results from one country to another where no studies have been carried out. Apart from selected population studies [2, 9,16], no work has been carried out in Spain.

We have found a prevalence of HVA (SR and/or LSR) of 7.6% in adult population (ci 95 % 6.1-9.4), very similar to the 7.7 % found by Grigoreas [17] in Athens (Greece), or to 8.6 % in Marseilles (France) found by Charpin [7]. In these studies the methodology and geo-climatic environment are similar. In Italy, Incorvaia [18] found a lower rate (5.1%), but this rate is from the recruited population. Studies carried out under the influence of a continental climate show lower figures, such as the work by Müller in Switzerland [1] with 2.8 %, or Herbert [19] in Canada (3.5%). Golden [6] and Muñoz Lejarazu [16] carry out their studies in Atlantic climate areas with much higher results, 21.9 % and 19.9 %, respectively, although this Spanish study was not carried out in the general population. In a climate of high humidity in Japan, Shimizu [4] describes a very high prevalence of 30 % for HVA in a control group of workers in the urban environment and only makes reference to allergy to yellow-jacket.

Regarding SR the prevalence rate was 2.3 % (ci 95 %: 1.5–3.4), in good agreement with studies [17, 18] [20, 22] carried out with similar methodology and climate, with data that oscillate between 1.9 % found by Charpin [8] and 3.1% found by Grigoreas [17], and similarly to Fernández [2] in the south-east of Spain. Schäfer [23] in a rural medium and Golden [6] found similar figures (3.3%). Shimizu [4] in Japan, with 6%, found very much higher results. Studies performed in continental climates [19, 24] however, offer lower figures in the region of 1.2-1.5 %.

LSR affected 5.3 % (ci 95 %: 4-6.8), and were twice as frequent as SR. The divergence in diagnostic criteria when determining LSR and the lack of studies in the general population might justify the broad variability in the results [4, 6, 17, 18, 21, 22]. Nevertheless climatic influence seems important too, since studies in Mediterranean populations establish a prevalence of 4.6% in Greece [17], 7.4% in the southern coast of France [8], or 4.3% in the southern coast of Australia [21]. Under continental influence, prevalence varies from 1.5% in Switzerland [1], to 2.3% in Canada [19]. The high rate obtained in Japan (24%) [4] is not comparable due to the same previous reasons (a climate of high humidity).

As the age increases from 20 years we see a slight non-linear and not-significant increase in the prevalence of LSR and SR. In addition, the average ages of subjects with reactions and healthy subjects are similar. The literature contains few and contradictory references about the age influence on the development of HVA [25, 27], and they are justified by assumptions of exposure that cause variations depending on whether the presence of allergic reactions or sensitisation to venoms is studied. On the other hand, Müller [7] suggests that since the probability of a greater number of stings increases as subjects get older, the number of reactions should also increase; recent publications establish a lower prevalence (0.35%) of SR in children [3] than our 2.3% in adults.

In our population the male group showed a somewhat greater prevalence of HVA, but not more significant than in women. These results are in agreement with authors who study groups with similar degrees of exposure to sting between sexes [14, 15, 17, 27]. A fit analysis between several studies with similar populations [6, 8, 21, 24, 25, 28, 29] shows that the greater rates both of reactions and of sensitisation in men are due more to the differences in exposure between sexes, than to sex itself as a risk factor. In our series SR appeared more frequently in women than in men, but the group of women was very small and our results were not conclusive.

SR to stings from hymenoptera occurred with greater frequency in a rural habitat but no statistical significance could be attached to this. Although there is no common criterion that acts as a habitat differentiator and the references are few and far between, several authors coincide that the prevalence (8, 16) and sensitization rate to hymenoptera venom [17] is greater in a rural environment than in an urban one.

The number of stings suffered along life seems the most important environmental risk factor for HVA development. Previous works in beekeepers [30], forestry workers [4] and several types of populations [7-9], also show that the prevalence of allergic reactions to hymenoptera venom is greater among subjects that have suffered a high number of stings. Almost one-third of subjects allergic to hymenoptera stings presented with signs of atopy. A similar figure was found in other studies, meaning which atopy is not a risk factor for the development of HVA [31]. According to the results obtained in our study, the majority of reactions in our area were mainly caused by Polistes. These findings are in agreement with previous studies [32].

We conclude that the age does not appear to be related to HVA in any of its manifestations. Of the three, the factor that has the greatest influence in the development of a reaction to stings of hymenoptera seems to be the rural habitat, with an overall increase in the risk close to 50%. As regards sex, we cannot draw definite conclusions given the small size of the female group in our study. After comparing our results with those of other authors we see the influence of climate, a factor that has not been sufficiently valued until now. We obtain prevalence rates very similar to studies of other countries with a Mediterranean climate. Thus, we see that the reactions are more frequent in countries with a Mediterranean climate with mild winters and hot summers and a larger number of days of sunshine in spring and autumn than in countries with continental climate where the temperatures are more extreme and there is less sunshine.

We can affirm that both in Spain and in other countries HVA affects a significant percentage of the population. Specifically, in the province of Valencia where the study was performed, by extrapolating the percentages to the total population of working age, the SR would affect 2.3%, which represents around 30000 inhabitants who should undergo at least an allergy evaluation. However, the low attendance rate at the allergy practices [16] generated by this pathology suggests that it is insufficiently studied and treated.

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Dr. Antonio Peláez, MD

Hospital Clínico Universitario
Sección Alergia Adultos
Avda. Blasco Ibáñez, 17
46010 Valencia. Spain
Tel.: +34963862649
Fax: +34963862649