

Natural history of Hymenoptera venom allergy in Eastern Spain

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Summary

Introduction The natural history of stings, the clinical reaction of the patient and *in vivo* and *in vitro* tests are necessary parameters to assess before initiating Hymenoptera venom immunotherapy. In the decision to initiate immunotherapy with Hymenoptera venom, it is not usual to evaluate the natural history of the disease, which seems to be self-limiting and therefore of variable clinical significance.

Objectives Our aim was to determine the natural history of Hymenoptera hypersensitivity over 4 consecutive years in a rural Mediterranean population.

Methods An epidemiological study of Hymenoptera sting reactions and possible sensitivity was carried out in 145 randomly selected subjects out of a rural Mediterranean population of 600. Seventy-two subjects, including those with a history of anaphylaxis, completed the 4-year study. The nature of their clinical reactions, age, sex, history of atopy, profession, family history of reactions to Hymenoptera insects, time elapsed since the last sting, number of stings and specific IgE and IgG were determined (the latter, to the three most important insects in the area: *Apis mellifera*, *Polistes dominulus*, and *Vespula germanica*).

Results Of the 72 subjects, four subjects had systemic reactions (SR), 23 had large local reaction (LLR) and all the others (117) was minor local reactions. None who had experienced an SR had a repeat SR when re-stung over the 4-year study. Of those with LLR, 12 subjects had the same type of reaction and 11 experienced more mild local reactions when re-stung. In the SR and local reaction groups, IgE to honey bee (Hb) increased significantly during the study period, whereas in those with only LLR, specific IgE to wasp (*Polistes*) decreased. Specific IgG to *Polistes* and *Vespula* (wasps) decreased significantly, whereas there was no change in the specific IgG to Hb in any of the groups. The number of stings per year decreased at the end of the study in all groups, but positive-specific IgG was higher in subjects with the greatest number of stings. On multivariate analysis using logistic regression, the existence of specific IgE to bee venom, male sex, being an agricultural worker, age of over 16 years and more than five stings per year are seen as individual or co-factors for developing SR or LLR.

Conclusions The prevalence of SR was 2.8% in our Mediterranean population. The evolution of IgE and IgG throughout the 4-year study differed depending on the Hymenoptera studied. Adult male agricultural workers are at greater risk of having SR or LLR, especially when they have specific IgE to Hb and suffer from more than five stings every 4 years.

Keywords epidemiological study, Hymenoptera venom allergy, immunotherapy, natural history, risk factors

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Introduction

The decision to start immunotherapy with venom is taken based on the severity of the reaction and the presence of IgE antibodies to the venom of these insects. However, the natural history of the disease should also be taken into account. We should determine the risk a person runs of

being re-stung, together with the allergic reaction it may cause [1], which depends mainly on the individual's lifestyle [2].

Systemic reactions (SR) occur in a very small percentage (0.15–3.3%) compared with the IgE sensitization found in the general population, by skin tests and/or RAST, which may reach from 7% to 25%, even without a history of clinical reactions [3].

Therefore, the presence of IgE positive to the venom of these insects has a limited positive predictive value, and the characteristics of those patients who remain sensitized and subsequently develop an SR are still not clear [4–7].

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In Spain, most allergic reactions to Hymenoptera stings are produced by bee (*Apis mellifera*) and wasp (*Vespula germanica* and *Polistes dominulus*) stings, with a variable degree of cross-reactivity between these two species of vespids [8–10]. *P. dominulus* is more common in the Mediterranean area of Spain, where we carried out our study.

The aim of this study was to investigate the natural history of Hymenoptera venom allergy in a Mediterranean population exposed to the stings of these insects, in order to analyse the evolution of sensitivity over time and determine whether the severity of the reactions caused by re-stings is related to the nature of the initial reaction. It was also our objective to confirm the hypothesis of certain authors [1, 7] concerning the self-limiting nature of this type of disease and determine the significance of the presence of specific IgE with no clinical consequences.

Material and methods

Subjects

A prospective epidemiological study was carried out in a rural population in which the clinical reactions produced by Hymenoptera stings were evaluated over 4 consecutive years.

A sample of 145 subjects was randomly taken from a rural population of 600 inhabitants, aged between 3 and 90 years old, situated 10 km. from the Mediterranean Sea, in order to evaluate the prevalence of Hymenoptera sting allergy. Of these 145 subjects, 72 were followed up for 4 years, including all those who had experienced an SR and large local reaction (LLR), together with a control group who had no significant clinical reaction.

Questionnaire and skin tests

Interviews were carried out each year in spring and summer by an allergist in the local doctor's surgery. The questionnaire comprised 25 questions related to the signs and symptoms caused by the stings, type of reaction, culprit insect and date of the last sting.

Regarding the type of clinical reaction, we used Müller's classification [2] for SR and LLR. We calculated the number of stings at the beginning of the study by taking the average of the number of stings in the last 10 years. Subsequently, we found the yearly average of the number of stings during the 4 years of the study.

The skin tests with venom were carried out in the second and fourth year, at the same time of the year, using bee, *Vespula* and *Polistes* venom from America, supplied by DHS-Bayer® (DHS-Bayer Pharma, Allergy division, Stallergenes Group, Paris, France), because there was no standardized venom available for *P. dominulus* skin tests. We followed the manufacturer's dilution instructions and used the maximum concentration of 1 µg/mL. Histamine was used as the positive control and saline solution as the negative control. The criteria for positivity were determined in accordance with previous studies [11, 12] in which the immunological bases for their acceptance were established.

Determination of specific immunoglobulin E and immunoglobulin G

After the interview, we took 20 mL venous blood sample from each subject at the beginning of the study and during each year of the follow-up period. The serum was kept at -20°C ready for use. Determination of specific IgE was carried out twice using the Phadebas RAST® Pharmacia kit (Pharmacia Diagnostics AB, Uppsala, Sweden) with our own cellulose discs sensitized with the venom of the above-mentioned insects, collected personally by our group as described previously [8]. Briefly, sacs with the venom of *V. germanica* and *P. dominulus* were removed from the insects' abdomens, leaving their other anatomical structures intact. The venom was extracted with a needle and syringe, and filtered through a Millipore filter. The optimum allergen concentration per disc was determined using serial dilutions of 1/10 venom protein, starting with an initial concentration of 5 mg/mL. The background activity was estimated using the assay buffer only (bovine serum albumin 1% + Tween 0.1% and phosphate-buffered saline). The number of counts bound was corrected by subtracting the background counts and expressed as a percentage of the total number of counts added [8].

Atopy was – according to Phadebas RAST® Pharmacia – defined as the presence of specific IgE in the sera of the follow-up sample of at least one of the five most important allergens in our region: *Dermatophagoides pteronyssinus*, olive pollen, grass pollen, Russian thistle pollen and cat epithelium. In addition, we identified the clinical manifestations shown by the subjects such as rhinitis, asthma or some type of skin allergy.

Specific IgG was determined in the samples taken in the second and fourth year of follow-up using our own ELISA with anti-IgG marked with alkaline phosphatase from DAKO laboratories (DAKO Corp., Carpinteria, CA, USA). Venom from the three insects, obtained as described above, was added to 96 pin Nunc plates for 1 h and incubated at 37°C at concentrations of 2 µg/mL for bee and 10 µg/mL for the two vespids. Sera with an optical density of 2 standard deviations above the mean optical density of a pool of negative sera were considered positive [13]. The intra-assay coefficient of variation was less than 20%.

Statistical analysis

A bivariate analysis was carried out to compare the group that had experienced clinical manifestations (SR and LLR) and the group that had experienced only a minor local reaction (MLR). For the qualitative variables, we used the χ^2 test and Fisher's exact test, and for the quantitative variables the Student's *t*-test or Mann–Whitney *U*-test, respectively, depending on whether the variables had a normal distribution or not.

In addition, in order to evaluate the evolution of sensitization over the 4 years, we used the Friedman non-parametric test for paired data to determine IgE, and the Wilcoxon test for two-paired samples to determine IgG.

Logistic regression analysis was performed to estimate the adjusted odds ratio (OR) when taking several variables into account. The OR with a 95% confidence interval (CI) was determined. A *P*-value less than 0.05 (two-tailed test) was

considered statistically significant. The results are presented as percentages and means (SD).

All the statistical analyses were carried out using the SPSS (Statistical Package for Social Sciences) program for Windows, version 6.0.1.

Results

Random sample

Of the first 145 subjects studied, 75 (51.7%) were men with an average age of 44.5 years (95% CI, 39.4–49.6), which was greater than that of the women – 35 years (95% CI, 29.9–40.2). The prevalence of clinical reactions in our sample according to the case histories is shown in Table 1a. The prevalence of SR and local reactions was similar among both sexes. However, there was a predominance of men who experienced an LLR (13.7% vs. 1.37%, $P < 0.001$).

Subjects sensitized to bee venom were older than those who were not sensitized (50 ± 17 vs. 38 ± 22 , $P < 0.05$), while with vespid venoms there were no differences.

Of the 145 initial subjects, 55 (38%) had specific IgE to at least one venom of the three insects: 22 to *A. Mellifera* (15.2%), 47 to *P. dominulus* (32.4%) and 28 to *V. germanica* (19.3%). Two of them (1.37%) had had an SR, 16 (11%) an LLR and 37 (25%) reported MLR.

Risk factors

Severity of the reaction We followed up 72 (49.6%) of the initial 145 subjects over 4 consecutive years. These included all those with an SR or LLR, together with a similar number of subjects with MLR.

Table 1a. Prevalence of clinical reactions (145 subjects)

Type of reaction	Sex	Age (years)	Responsible insect
4 SR (2.8%)	2 M (50%)	44–60	3 wasps and 1 wasp and bee
23 LLR (15.8%)	16 M (69.6%)	7–72	4 bees, 16 wasps and 3 of both
118 no reaction (81.4%)	57 M (48.3%)	2–91	6 bees, 95 wasps, 13 of both and 4 unknown

SR, systemic reaction; LLR, large local reaction; M, male.

Table 1b. Follow-up sample (72 subjects): subjects and clinical reactions

Initial reaction	Agricultural workers	Atopics	Re-stung reactions
Systemic reaction			
1 Type II	Yes	No	No reaction
2 Type II	Yes	Yes	LLR
3 Type III	No	No	No re-stung
4 Type IV	No	No	No reaction
23 LLR	13 (56.5%)	6 (26%)	12 LLR (52.17%)
45 no reaction	12 (28%)	10 (22%)	26 no reaction (57.8%)

LLR, large local reaction.

The clinical characteristics of the SR experienced by the four subjects (two men and two women), according to Müller's classification (4), are shown in Table 1b. Only three of them were re-stung by the same insect during this period and the re-stings experienced are shown in Table 1b.

At the end of the study, within the SR group, only one subject, who subsequently experienced LLR, had detectable specific IgE to the three insects, both according to RAST and the skin tests. In addition, this subject had positive IgG to the venom of both vespids. Only one of the other three subjects had positive IgG to both vespids.

None of those who had experienced an LLR had an SR when re-stung during the 4 years. At the end of the study, in this group one-half (12 subjects) had experienced the same type of reaction when re-stung, but the other half (11) experienced only MLR. In other words, about 50% changed to minimal local reactions during the study.

In the minor reactions group, there was a predominance of women. In this group of 45 subjects followed up over 4 years, 26 (57.8%) continued to have the same type of minimal local reactions as at the beginning of the study, and 19 (42.2%) were not re-stung (Table 1b).

Atopy Of the 72 subjects followed up, 17 (23.6%) were atopic. The mean age of atopic subjects was 30.4 ± 23 years less than those who were not atopic ($P = 0.04$, Mann–Whitney U -test). The distribution of atopy in the three groups is shown in Table 1b. Only nine (32%) of the 28 subjects with positive IgE to insect venoms in the first year were atopic.

Only in the first and second year was a statistically significant association found between atopy and IgE positive to the most common insect in our area, *Polistes* ($P = 0.03$ and 0.015, respectively, χ^2 test), whereas this was not observed in the case of *A. mellifera* or *V. germanica*. Only at the end of the study was an association found between atopy and raised IgG to *Polistes* and *Vespula* venom ($P = 0.021$, χ^2 test).

Interval of time The group in which 3 years or less elapsed since the last sting had a significantly higher percentage of specific IgE to the venom of the three insects, both at the start and at the end of the study, according to skin tests ($P = 0.02$, χ^2 test) and RAST ($P = 0.02$, χ^2 test). But the number of subjects with positive RAST in this group decreased at the end of the study.

Specific IgG levels to all three venoms were similar in groups with different time intervals, both in the second and the fourth year. In other words, there were no significant changes in the IgG levels, which might mean that the time elapsed since the last sting does not determine drastic changes in this isotype of Ig, at least in a short period of time.

Number of stings There was a decrease in the number of stings every year until the end of the study, although this decrease was not statistically significant. The mean number of stings at the start was 1.87 compared with a mean of 1.51 at the end of the 4 years.

The groups with SR and LLR experienced a greater overall number of stings during the 4-year study compared with the group with MLR ($P = 0.003$, χ^2 test), which indicates that the former had a greater risk of re-exposure.

Based on the median of the overall number of stings accumulated over the 4 years, we divided the follow-up sample into more than five stings and five or fewer stings. We found an association between positive skin tests and RAST in the last year and more than five stings during the study period ($P = 0.001$ and 0.005 respectively, in the χ^2 test).

With regard to the number of stings and IgG values, only in the fourth year did we find an association between IgG levels and suffering from more than five stings during the study ($P = 0.009$, χ^2 test).

Age There was a significant percentage of sensitivity in the group of subjects aged between 50 and 60 years at the beginning of the study (Table 2).

Profession There were two clearly differentiated groups in our sample: one made up of 27 subjects (37.5%) who worked in the agricultural or related sector and the other consisting of 45 subjects (62.5%) with professions ranging from that of housewife, student, sewing machinist and clerk to fruit warehouse worker. In the first group, two subjects combined their normal activities with the seasonal exploitation of beehives (Table 3).

Family history of stings Of the 72 subjects studied, 15 (20.8%) had relatives with a history of clinical reactions in response to Hymenoptera stings. One family member had actually died as a result of an SR to a bee sting. However, the existence or not of a family history of stings was not related to either the type of reaction or specific IgE in any of the years of follow-up.

Evolution of sensitization

Specific Immunoglobulin E We found RAST positive to venoms in 28 subjects, which accounts for 38.8% of the sample of 72 subjects. Of these, two (7.1%) had experienced an SR, 16 (57.1%) had an LLR and 10 (35.7%) had had only a MLR. At least seven cases had RAST positive to the venom

of the three insects, 11 were positive to two types of venom and 10 to at least one venom.

In the group of subjects with an SR ($n = 4$), a significant increase in specific IgE to *A. mellifera* was seen over the 4 years ($P < 0.05$, Friedman test), with no significant variations in specific IgE to vespids (Fig. 1).

In the group of subjects with LLR ($n = 19$), only in the case of *P. dominulus* did specific IgE decrease significantly over the 4 years ($P < 0.05$, Friedman test), and it was not modified in the case of *V. germanica* or *A. mellifera* (Fig. 1).

In the MLR group ($n = 38$), we also observed a significant increase in the values of specific IgE to *A. mellifera* ($P < 0.001$, Friedman test), with no significant variations in the case of either vespid (Fig. 1).

Specific immunoglobulin G Considering the sample as a whole, the values of specific IgG to *A. mellifera* venom did not change over time, whereas in the case of vespids we found a significant decrease ($P < 0.001$, Wilcoxon test) from the second to the fourth year. However, IgG values of subjects who had more than fifth stings increased significantly in the fourth year irrespective of the culprit insect ($P < 0.001$, Wilcoxon test).

In the LLR group, the values of IgG to *Vespula* venom decreased significantly ($P = 0.004$, Wilcoxon test).

Also, in the MLR group, a significant decrease in the values of IgG to *P. dominulus* venom ($P = 0.0002$, Wilcoxon test) and *V. germanica* venom ($P = 0.0004$, Wilcoxon test) was found.

Table 2. Sensitivity according to age

Age (years)	Skin test+	RAST+	72 subjects
0–10	2	3	9
11–20	1	4	9
21–30	3	5	8
31–40	2	3	9
41–50	1	1	5
51–60	9	10	20
61–70	1	2	9
71–80	0	0	3

Table 3. Occupation in the 72 subjects

Profession	Number	Systemic reaction	Large local reaction	Local reaction
Agricultural workers	27*	2	13	12
Another professions	45	2	10	33

*Two subjects were beekeepers.

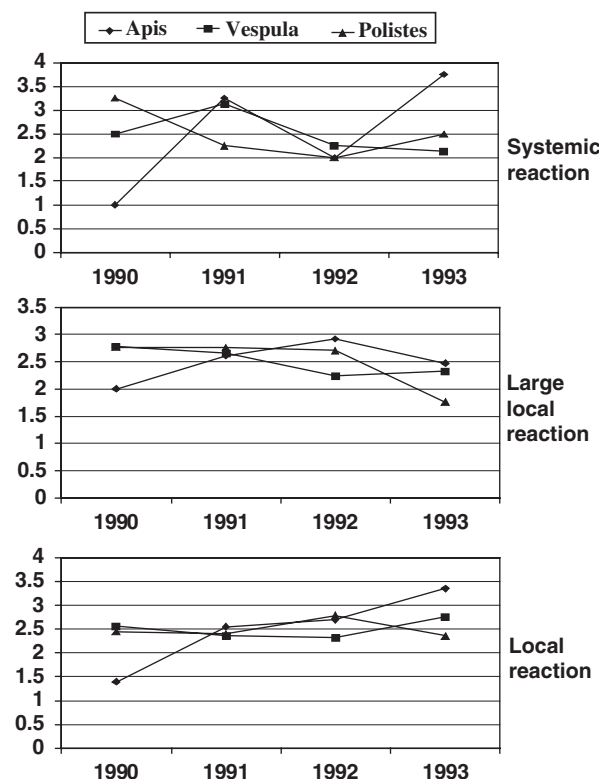


Fig. 1. Evolution of IgE sensitization to bee and vespids according to the type of clinical reaction over 4 years (Friedman test).

Asymptomatic sensitization The prevalence of asymptomatic sensitization – subjects with no significant clinical reaction but with positive specific IgE – in the initial sample was 25.51% (37 out of 145 subjects) according to RAST. In the follow-up sample, only 10 subjects (13.8%) exhibited these characteristics, and the number was reduced to six when they were studied by means of skin tests (8.5%). On RAST the evolution of this group of subjects according to the individual insect species shows that sensitization to *A. mellifera* increased at the end of the study from four to nine positive cases, in the case of *Polistes* it decreased from nine cases initially to four cases at the end and in the case of *Vespula* it also decreased from five to three cases.

However, asymptomatic sensitization as a whole is maintained with no great variations throughout the 4 years, starting with 10 cases in the first year, 13 in the second, seven in the third and 10 again in the fourth year. In our study, we observed that during the 4-year follow-up some subjects maintained the same sensitization as at the beginning, with no clinical changes despite being re-stung. On the other hand, other subjects became sensitized during these years but with no clinical consequences.

Multivariate analysis of risk factors

In order to evaluate the overall re-exposure risk, we carried out a multivariate analysis using logistic regression and creating an *ad hoc* model so as to calculate the probability of a subject having a significant clinical reaction in certain circumstances (Table 4).

Our model selects the initial variables, that is, those in the first year, and as predicting variables uses age (divided into 16 years or under and over 16 years), sex, profession, time elapsed since the last sting, atopy, family history of reactions to stings, number of stings (divided into five stings or fewer and more than five), specific IgE to the three insects in the first year, specific IgG in the second year and skin tests with venom of the three insects in the second year.

The variables that have a significant effect on whether there is a clinical reaction or not are: fewer than five stings ($P = 0.004$), RAST positive to *A. mellifera* venom ($P = 0.001$), male sex ($P = 0.005$), agricultural worker ($P = 0.01$) and an age of over 16 years ($P = 0.04$), as can be seen from the CI of the OR of these five variables. The upper limit of the variable number of stings is less than 1, indicating that fewer than five stings during the study period (4 years) is associated with a

low probability of experiencing a reaction if re-stung. On the other hand, the lower limit of the interval in the case of the variables RAST positive to bee, male sex, agricultural worker and age > 16 years is greater than 1, indicating that these variables are individual risk factors for developing a reaction to a re-sting. However, atopy did not seem to be a risk factor in our multiple logistic regression model.

The model determined by logistic regression creates a new variable from the interaction of an age of over 16 years with RAST positive to *A. mellifera* in the first year ($P = 0.001$), with an OR of 10.0221 and 95% CI of 2.45–40.9. Once again, because the lower limit of the interval is greater than 1, there is a greater risk of experiencing a reaction to a new sting when these two variables co-exist.

Discussion

Only a limited number of prospective studies on large populations have evaluated the prevalence of sensitization to Hymenoptera stings. One such study was carried out by Stuckey et al. [14] on an unselected population of 2429 subjects, in which he found 16% RAST positive to bee venom, and another by Golden et al. [6] where in a randomized sample of 269 subjects a 17% sensitization to at least one insect was found. In southern Spain, we found a prevalence of 16.4% in a rural population of 300 subjects [15].

The objective of this prospective study was to evaluate the natural evolution of clinical reactions to Hymenoptera stings and IgE-mediated sensitization to the venom of these insects in a sample of a population made up of adults and children who, as they live in a rural community 10 km from the Mediterranean Sea, are exposed to hymenoptera stings.

From the case histories, the prevalence of SR_s was 2.75% (four cases) in our initial sample of 145 subjects, representative of the municipality and randomly selected from the census. This figure is similar to that found in other studies carried out in other geographical areas of similar environmental characteristics [15]. In our study, an allergist interviewed the subjects each year, over a period of 4 years, in the local doctor's surgery. The subjects were asked specific questions and also to describe their symptoms and the culprit insects.

If we assume that specific IgE plays an essential role in the development of reactions to Hymenoptera stings, and given the good correlation between specific IgE levels and IgE linked to basophils in patients not undergoing immunotherapy [16, 13], then the severity of such reactions could be expected to decrease with time if specific IgE decreased since the last sting. This tendency, which has already been observed in other studies [17–19], was confirmed in our study, especially in the case of vespids.

Although the cases of SR in our study are too few to enable general conclusions to be drawn, the natural evolution of our subjects is consistent with the findings of other studies, both in the sense that immunologic sensitization decreases over time and that over 50% of the subjects who had previously experienced an SR did not have this type of reaction after being re-stung [1, 12, 17–19].

Table 4. Logistic regression analysis: variables that have an effect on the development of a clinical reaction

IV	BETA	SE	OR	CI	SIG
RAST+Hb	1.6448	0.6943	7.0564	1.96–25.4	0.01
Age > 16 years	1.5832	0.8059	4.8707	1.05–23.7	0.04
Male sex	1.4597	0.5240	4.3046	1.54–12.0	0.005
Agricultural worker	1.2347	0.5135	3.4375	1.26–9.40	0.01
No. of stings < 5	1.5032	0.5232	4.4960	0.0798–0.620	0.004

IV, independent variable; BETA, coefficient of regression; SE, standard error; OR, odds ratio; CI, confidence interval of the odds ratio of 95%; SIG, statistical significance.

We found a prevalence of LLR of 15.8%, which is very close to that reported in Golden et al.'s [6] study (18.6%), and somewhat lower than in other studies: 21% in Abrecht et al.'s [20], and 25% in Fernández et al.'s [15]. Our subjects who experienced this type of reaction, as occurred in the other studies mentioned, were mainly men (the ratio of men to women was 2:1), and this could be explained by their greater degree of exposure to Hymenoptera stings. In addition, those who experienced this type of reaction were also significantly older than those who had an MLR, and this may be a result of the life style of this rural population. None of these subjects experienced a systemic reaction when re-stung in our 4-year study, and this concurs with the general belief that the probability of experiencing an SR after having experienced an LLR is less than 5% [20].

We found no greater incidence of clinical reactions to Hymenoptera stings in atopic subjects; however, in the first 2 years of our study only – surprisingly not in the last two – we observed a greater number of subjects with specific IgE positive to *Polistes*. These observations might explain the apparent contradiction in the transversal studies of Golden et al. [6] and Miyachi et al. [21], who found a greater presence of specific IgE to bee or wasp stings in atopic subjects but maintain that the clinical manifestations of allergy do not appear to predict sensitization. Our findings may be in keeping with the observations of these authors concerning the greater production in atopic subjects of specific IgE to the most common species in each geographical region – in our case *Polistes* – but not on a yearly basis.

In the general population, some authors [5, 22, 23] find a prevalence of specific IgE (RAST and/or skin tests) to allergens of the venom of between 7% and 21%. However, this asymptomatic sensitization, which in our initial sample of 145 subjects reached 25.51%, does not imply that these subjects will experience an SR when they are re-stung. Furthermore, asymptomatic sensitization appears to vary depending on the season [24]. The same happens in our study, because the skin tests and blood collection took place in the same season each year, spring or summer.

Our results appear to confirm the belief that sensitization to vespid venom in patients with significant clinical reactions decreases with time, whereas in the case of bee venom sensitization remains the same as time goes by (27), irrespective of whether the reactions are significant or not. The significant increase in the values of RAST to bee in patients with an SR during the 4 years supports this idea. In fact, this increase is much more significant ($P = 0.0004$) in subjects with no clinical manifestation. On the other hand, we observed a significant decrease in the number of subjects sensitized to *Polistes* venom with an LLR.

In our study, we observed that during the 4-year follow-up some subjects maintained the same sensitization as at the beginning, with no clinical reactions despite being re-stung. On the other hand, others became sensitized during this time and showed no clinical consequences. Therefore, we can conclude that asymptomatic sensitization does not represent a clear risk of experiencing an SR to a future sting, at least in the case of vespids; however, the opposite could occur in the case of subjects sensitized to *A. mellifera*. The significant increase in the values of RAST to bee during the 4 years in patients with an SR supports this thesis, and this increase is

even more significant ($P = 0.0004$) in subjects with no clinical manifestation. On the other hand, we observed a significant decrease in the number of subjects sensitized to *Polistes* venom with an LLR. This would seem to confirm the belief that sensitization to vespid venom in patients with significant clinical reactions decreases over time, whereas in the case of bee venom, it remains constant [25, 26].

Finally, based on the results of the logistic regression analysis, which eliminates possible confounding factors, we can say that having fewer than five stings in 4 years has a significant effect on the probability of not having a clinical reaction. Conversely, it may be concluded that more than five stings would imply a greater risk of reaction. The presence of specific IgE to bee venom, male sex, being an agricultural worker and an age of over 16 years are also individual risk factors in themselves, as found in our study. This risk increases very significantly when specific IgE positive to bee venom co-exists with an age of over 16 years.

In conclusion, a better understanding of the natural history of Hymenoptera venom allergy indicates that these reactions tend to be self-limiting in many cases, and suggests that the follow-up of sensitized patients would enable us to better determine whether immunotherapy with venom or just preventive symptomatic measures were indicated.

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