

Epidemiologic Observations on *Hymenoptera* Allergy in Spain: The Alergológica-2005 Study

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■ Abstract

Background: To date there has been an absence of nation-wide epidemiologic studies on insect allergy in Spain.

Objectives: To measure the frequency and to determine the characteristics of *Hymenoptera* hypersensitivity in a Spanish population at a particular point in time and compare with the data obtained in a similar study carried out in 1992.

Material and Methods: An observational, prospective and cross-sectional study (Alergológica-2005) was carried out all over Spain.

Results: The number of patients included in the study was 4991, of whom 77 (1.54%) were diagnosed with insect sting allergy. This represented an increase of 0.7% compared to Alergológica-1992. The honey bee was responsible for 45.5% of reactions, *Vespula* spp for 27.3% and *Polistes* spp for 23.4%. 64.9% of reactions were systemic. The group with *Hymenoptera* allergy had a predominance of males (69.1% vs. 42.7% in the general sample, $P < .0001$), older patients (median age 37.4 vs. 32.1, $P < .013$), and homes in rural zones (33% vs. 18.3%, $P < .004$). The median of days necessary to reach a diagnosis was lower ($P < .0001$). This population needed assistance in emergency units and hospitalisation more frequently. They had a low score on the mental component of the quality of life questionnaire.

Conclusions: There was an increase in cases diagnosed with insect allergy with regard to Alergológica-1992. The typical patient profile is of a man, living in a small village, working outdoors with significant exposure to insect stings and in contact with farm animals, without atopic diseases. Bees and wasps are equally responsible of the stings. The need of emergency assistance in those patients is higher and the waiting time to be attended by an allergist is shorter.

Key words: Hymenoptera. Allergy. Epidemiology. Cross-sectional study.

■ Resumen

Antecedentes: Ausencia de estudios epidemiológicos nacionales sobre alergia a picadura de insectos en España.

Objetivos: Medir la frecuencia y conocer las características de la alergia a himenópteros en una población española en un determinado momento y comparar los datos con los obtenidos en un estudio similar de 1992.

Material y Métodos: Un estudio prospectivo observacional y transversal (Alergológica 2005) se llevó a cabo en España.

Resultados: El número de pacientes incluido en el estudio fue de 4991, de los cuales 77 (1,54%) fue diagnosticado de alergia a picadura de insectos, con un incremento del 0,7% respecto a Alergológica-1992. La abeja fue responsable del 45,5% de las reacciones, *Vespula* spp del 27,3% y *Polistes* spp del 23,4%. El 64,9% de las reacciones fueron sistémicas. En el grupo con alergia a himenópteros había predominio de varones (69,1% contra 42,7% en la muestra general, $P < 0,0001$), de mayor edad (edad media 37,4 contra 32,1, $P < 0,013$), y domicilio en zonas rurales (33% contra 18,3%, $P < 0,004$). La media de días necesarios para obtener un diagnóstico fue menor ($P < 0,0001$). Esta población necesitó asistencia en urgencias y hospitalización más a menudo. Tiene, además, una puntuación baja en el componente mental del cuestionario de calidad de vida.

Conclusiones: Hay un aumento de los casos diagnosticados con alergia a picadura de insectos respecto a Alergológica-1992. El perfil del paciente es el de un varón que vive en una pequeña población, que trabaja al aire libre y tiene una exposición importante a picaduras de insectos, con contacto con animales de granja, y sin antecedentes de atopia. Abejas y avispas fueron igualmente responsables de las picaduras. La necesidad de asistencia urgente en estos pacientes es mayor y la lista de espera para ser atendido por un alergólogo, menor.

Palabras clave: Himenópteros. Alergia. Epidemiología. Estudio transversal.

Introduction

Insect stings usually cause transient local inflammation and occasional toxic reactions. However, allergic hypersensitivity can result in more severe local reactions or generalized systemic reactions. Just one insect sting may provoke a severe allergic reaction, which can be furthermore fatal, in a previously sensitized person [1]. Particularly, *Hymenoptera* are the insects that cause the most frequent, relevant and dangerous reactions. The allergic reaction may be caused by stings from a number of species in this insect order, occurring only in individuals who have previously been sensitized to *Hymenoptera* venom.

Strong local reactions are usually late-phase immunoglobulin E (IgE)-mediated allergic reactions, with severe swelling (>10 cm in diameter) developing over 24 to 48 hours and resolving in two to seven days. Systemic reactions also are IgE mediated and may cause one or more signs and symptoms of anaphylaxis, including generalized rash, angioedema, throat tightness, dyspnea, dizziness, and hypotensive shock.

Insect sting allergy may develop at any age, and usually manifests after several uneventful stings [2-8]. It is known that strong local reactions are more frequent than systemic reactions, and range from 2.4% [2], 5.3% [5], up to 26.4% [4]. In children the prevalence yielded by one study is 19% [6] and in beekeepers as high as 38% [7].

The prevalence of systemic anaphylactic sting reactions in several epidemiologic studies ranged from 0.3% to 7.5% [2-8]. Systemic reactions among beekeepers are more frequent, and fall between 14% and 43% [9, 10]. In children, prevalence rates of systemic reactions are lower [6, 11, 12], ranging from 0.15% to 0.3%. Compared with adults, children have a higher frequency of isolated cutaneous reactions to insect stings and a lower frequency of vascular symptoms and anaphylactic shock.

The incidence of insect sting mortality seems to be low, ranging from 0.03 to 0.48 fatalities per 1 000 000 inhabitants per year [13-16]. However, the true number may be underestimated since the presence of venom-specific IgE has been reported in 23% of post-mortem serum samples taken from subjects who had died outdoors suddenly and inexplicably [17] between May and November. Surprisingly, around 40% [18] to 85% [13] of the subjects with fatal reactions after *Hymenoptera* stings had no documented history of previous anaphylactic reactions.

Hymenoptera venom allergy is rather well known, its diagnostic methodology has been also well defined and its therapeutic approach has been established in a European consensus. However, it is very important to recognize both the risk factors and the real magnitude of this health problem. Zone, climate, temperature, insect behavior and personal exposure will influence the risk of receiving a sting. Certain occupations or activities are associated with an increased risk of *Hymenoptera* stings, e.g. gardeners, farmers, beekeepers (and their family members), greenhouse workers, food handlers, bakers. Beehives or wasp nests located in the vicinity of dwellings, work places and also outdoor sports, have to be taken into account as risk factors.

Systemic allergic reactions to *Hymenoptera* stings are estimated to occur in about 2.5% of Spanish adults [3-5]. In 1992, the Spanish Society of Allergy and Clinical Immunology

started a trial in order to obtain accurate information on the epidemiologic, clinical and socioeconomic characteristics of the allergic patients in Spain that culminated in *Alergológica-1992* [19]. In 2005, our Society repeated this observational, prospective, and cross-sectional study on a sample of 4991 subjects seen in allergic clinics and selected at their first interview. The prevalence of *Hymenoptera* venom allergy and the influence of several risk factors in its development were also evaluated, and compared with the data obtained more than ten years before [20]. This trial was carried out by allergists from every part of Spain throughout two selected periods of 2005. The subjects were asked specific questions and also to describe their symptoms and the culprit insects. A final diagnosis of *Hymenoptera* venom allergy was made in 1.54% of these patients.

In this article we will discuss the risk factors and the population data of our recent trial.

Material and Methods

An observational, prospective and cross-sectional study was carried out on a sample of 4991 subjects. The aim of the study was to measure the frequency and characteristics of *Hymenoptera* hypersensitivity in a Spanish population at a particular point in time, and compare this to the data obtained from a similar study carried out in 1992: *Alergológica-1992* [19]. All the data on the methods used are described previously [21]. The qualitative variables were studied by calculation of relative frequencies (%); the quantitative variables were described using medians and measurements of dispersal. The differences between qualitative variables were described using the chi-square test and the comparison of the average values of quantitative variables was made through the student t test or non-parametric analysis of variance (the Kruskal-Wallis test).

Results

The total number of patients included in the study was 4991, of whom 77 (1.54%) were diagnosed with insect sting allergy. This represented an increase of 0.7% compared to *Alergológica-1992*.

The honey bee was responsible for 45.5% of reactions, *Vespula* spp for 27.3% and *Polistes* spp for 23.4%. 18.7% of the cases were bee-keepers or their family members. 64.9% of reactions to stings were systemic and 35.1% were large local reactions (Table I). Eighteen patients had suffered more than one sting reaction during the previous year. On 54.5% of occasions the reactions happened in the summer and 29.3% in the spring. Sixty-one of the 77 cases had suffered, previously to the present reaction, reactions with *Hymenoptera* stings: 62.3% local reactions and 19.5% general reactions (15 systemic reactions: 8 of grade 1, 3 of grade 2, 4 of grade 3 and 2 of grade 4).

Twenty-five cases were admitted to the emergency department and were treated with epinephrine; three (8.8%) were admitted to hospital. In the treatment of acute reactions,

Table 1. Type of Reaction

	N	%
Local	27	35.1
Systemic (Müller)	50	64.9
Grade 1	11	22.4
Grade 2	22	44.9
Grade 3	8	16.3
Grade 4	8	16.3
Total	77	100

71.4% of patients received antihistamines and 77.9% corticosteroids; and in 55.8% of cases epinephrine for self-injection was prescribed after the reaction. Immunotherapy was prescribed in 49.4% of the patients. The schedules of immunotherapy used were conventional in 55.3%, cluster in 31.6% and rush in 13.2%.

Personal antecedents of asthma were observed in 6.7% of the cases, rhinitis in 5.3% and atopic dermatitis in 4%. There were no histories of food allergy.

The diagnostic tests used in the study of these patients were clinical histories, skin tests and quantification of specific IgE to *Hymenoptera* venoms. The sting challenge was not used in any case.

The patients with *Hymenoptera* allergy had a low score (25th percentile), compared with the general sample, in the mental component of the quality of life questionnaire.

Comparison with the Main Sample

Several differences between the main sample of the study and that with allergy to venoms were found and these are summarized in the Table 2.

The group with *Hymenoptera* allergy were mainly males (69.1% vs. 42.7% in the general sample, $P < .0001$), they were older (median age 37.4 vs. 32.1 years, $P < .013$), they lived in rural zones (33% vs. 18.3%, $P < .004$) and lived in contact with animals more frequently (54.7%, with stables at home in 17.3%

of cases). The waiting list to be attended was lower in patients with *Hymenoptera* allergy. In the first month after the reactions, 50% of cases were attended by an allergy specialist, and up to 85% in the second month. The median of days necessary to reach a diagnosis was 22.7, with a minimum of 1 and a maximum of 120. This fact revealed a significant difference ($P < .0001$), with respect to the main sample.

Most patients came from rural areas which showed a significant difference to the main sample ($P < .0004$). The explanation for this could be that this factor increased sting exposure.

It should be noted that 36.8% were referred from the emergency department and 73.5% came to the emergency department because of an allergic reaction (31.6% in the main sample) and 8.8% were admitted to the hospital (2.6% in the main sample).

Discussion

The prevalence of *Hymenoptera* venom allergy in Spain is 2.5% for systemic reactions and ranges from 2.4% to 5.3% for large local reactions. There is asymptomatic sensitization in 16.4 – 28.5% of the population [3-5].

If we compare these data with those obtained from the sample, we can easily conclude that there is a misdiagnosis of this type of allergy and a clear increase with regard to previous research (*Alergológica*-1992)[19]. This misdiagnosis is probably because those patients are never seen by an allergist. This can be a consequence of the illness itself, as it is most frequently acute and self-limited in time. Furthermore, allergy to insect stings is rather unknown among other specialists, including doctors from emergency units.

There are several factors that influence the risk of receiving a sting. The prevalence of *Hymenoptera* venom allergy is greater in men, median age, and in rural areas. The typical patient profile is of a man, living in a small village, working outdoors (farmer, building worker or gardener) with a greater exposure to insect stings. Another contribution to these results is the fact that beekeepers (and their family members) are a working group at risk, and they usually live in rural areas. Thus, in patients with insect allergy we find a higher frequency of people living in houses, rather than apartments, with cowsheds and in contact with farm animals.

Table 2. Comparison with the Main Sample*

Characteristics	General Sample (Without Venom Allergy)	With Venom Allergy	P value
N	4914	77	
Age	Median age 32.1; SD 18.4	Median age 37.4; SD 18.6	<.013
Sex	Male 2078 (42.3%)	Male 53 (69.1%)	<.0001
Visits to ED last year	1319 (27.2%)	47 (64.4%)	<.0001
Hospital admissions last year	112 (2.3%)	3 (4.1%)	.24
Cohabitation with animals	42%	54.7%	
Rural habitat	876 (18.3%)	25 (33.3%)	<.004
Waiting list (days)	77.95 (SD 125.372)	47.99 (SD 60.282)	<.0001

ED indicates emergency department.

There are no other allergic diseases in these patients, as has been reported in previous studies [3, 5, 6].

There are a lower number of children in the sample with insect allergy than in the general sample. It is well known that insect allergy has a better prognosis in children than in adults [6]. However, due to the low number of epidemiologic studies that include children, we do not know if the prevalence of *Hymenoptera* allergy is lower at these ages. This low figure could be possibly due to a lower level of exposure (lower number of stings due to short time of exposure). In any event this fact was also detected in *Alergológica-1992*.

The severity of the reactions in these patients explains why they needed assistance in emergency units, have been hospitalized and many of them were referred from emergency doctors. It is important to note that in many cases the emergency health assistance is provided by doctors in rural areas, sometimes far from hospitals with difficult access to hospital facilities.

Hymenoptera allergy is treated only by allergists. Consequently, it is usual for cases of severe reactions, such as anaphylactic reactions, to be referred from emergency units. Furthermore, patients attended in emergency units normally present with more severe reactions.

The use of sanitary care was higher in this group than in the general population. If we accept that this is an under-diagnosed problem, the real use of those services should be higher. It is necessary that allergists dedicate time and effort to spreading the knowledge of this type of pathology among another colleagues who treat acute reactions, especially emergency and family doctors, so patients can benefit from an effective treatment and a correct diagnosis. If primary prevention is not possible (it is not possible to know who will develop a systemic reaction) we can avoid new reactions with immunotherapy.

The severity of the reactions and the sensitivity of allergists to this problem were the causes of the short waiting time for these patients; as it was essential to make a quick diagnosis and start the immunotherapy as soon as possible.

The diagnostic procedure in those patients is the same as in other allergic disorders. The history must be compatible: an acute allergic reaction after an insect (wasp or bee) sting, suggestive of an IgE-mediated mechanism. If so, then specific IgE, both *in vivo* and *in vitro* should be measured: skin prick and intradermal tests should be performed and serum specific IgE measured to confirm the diagnosis. The importance of the reaction and the risk of exposure determine the choice of which diagnostic tests to perform. Local reactions are not a subsidiary of immunotherapy [14], so in most cases diagnostic tests are ruled out and a preventive or symptomatic treatment against future stings is recommended. Sting challenge tests are not used as an initial diagnostic tool. They are not indicated in patients who have not been treated with immunotherapy [14].

Sensitization profiles vary depending on the geographical area (for *Polistes* and *Vespula*), the population included in the study and the existence of specific jobs such as beekeeping. They also depend on whether the three main venoms are used for the diagnosis: Honeybee, *Vespula* mix and *Polistes* mix. This last point is unknown because these data were not included in the questionnaire.

Previous epidemiologic studies in Spain show large

differences in the prevalence depending on the region studied: bee venom allergy ranges from 10.6% in Madrid to 57.7% in Galicia. In wasp allergy, we found 0.96% of *Polistes* allergic patients in Galicia versus 45% in Valencia [3-5, 22]. We can conclude that in this trial the proportion between bee and wasps is similar, possibly because the data come from the entire nation.

The type of reaction presented in different studies is variable and depends on the kind of population included. In this study there was a high prevalence of systemic reactions because patients were obtained from allergy outpatient departments and patients with severe reactions are most commonly referred to allergists. The results would be different if this epidemiologic study had been carried out in the general population.

Most of the patients who suffered a reaction previous to the generalized reaction experienced a strong local reaction. These data differ from other studies of the natural history of *Hymenoptera* allergy which conclude that strong local reactions do not develop into systemic reactions [3, 5, 14]. This controversial result can be explained by the fact that the method used in this trial was not adequate to evaluate the progression over time of this type of reaction. It was not a longitudinal study and the insect responsible for the previous reactions was not recorded and the size of local reactions was not described in detail.

Epinephrine is the drug of choice to treat IgE-dependent anaphylaxis. In generalized cutaneous reactions with bronchospasm, the use of β_2 -agonists, corticosteroids and antihistamines is accepted. The wide use of epinephrine in these patients reflected good compliance with these guidelines. Anaphylactic reactions have often been under-treated and it seems that we have improved in this aspect.

All patients who have suffered a generalized systemic reaction after a *Hymenoptera* sting should carry epinephrine for self-injection, especially in the warm season, where the risk of stings is higher. The situation is different when there is a local reaction, the systemic reaction is slight and the patient presents a low risk of new stings. In these cases, the indication for carrying epinephrine is not justified. Furthermore, these patients stop following this recommendation after a short time [14].

Immunotherapy is indicated in the case of systemic severe reaction and demonstrated allergy to the offending insect. It is also indicated if the reaction is slight or moderate and there are other risk factors. The indication for immunotherapy in this group follows these criteria, so most reactions are severe.

We should expect a higher frequency of cluster regimens, as experience with venom immunotherapy is greater with cluster regimens than in other kinds of extracts such as aeroallergens. The variability and geographical dispersion of the data analyzed could have had an influence on the unexpected and frequent utilization of prolonged protocols, whereas other Spanish allergists that treat a considerable number of patients with *Hymenoptera* venom allergy usually employ cluster regimens.

For most patients an allergic reaction after an insect sting is a traumatic event. The low score on the mental component on the quality of life questionnaire shows the emotional distress due to the fear of a new sting and a new reaction.

Patients are frightened of dying, so they do their utmost to prevent new stings. They alter their lifestyle (work, house, and daily activities). If changes are not possible, psychological impairments may result.

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