

EUROPEAN HORNET (VESPA CRABRO) STING : A NEW RISK FACTOR FOR LIFE-THREATENING REACTION IN HYMENOPTERA ALLERGIC PATIENTS ?

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Summary

■ **Background :** Severity of a previous reaction, adult age, male gender and honeybee sting are risk factors for severe systemic reactions after hymenoptera stings. The aim of the study was to assess the association between the *Vespa crabro* sting and severe systemic reactions.

■ **Methods :** One hundred fifty seven hymenoptera allergic patients with a positive case history for systemic reactions were selected on the basis of unequivocal identification of the stinging insect. In 97 patients the culprit insect was *Vespula spp.*, in 35 was *Vespa crabro* in the remaining 25 patients was *Apis mellifera*. The relative risk for a life-threatening reactions after a sting was evaluated for each hymenoptera species.

■ **Results :** While the percentage of life-threatening reactions was similar both in *Apis mellifera* (24%) and in *Vespula spp.* Allergic patients groups (27.8%), a very high prevalence (81.2%) was documented in *Vespa crabro* allergic patients group. The relative risk for life-threatening reactions after a *Vespa crabro* sting was about three times higher ($RR = 2.74 - CI\ 95\% 1.93-3.89 - R < 0.0001$) than it was for a honeybee or yellow jacket sting. The increase of the risk for life-threatening reactions after a *Vespa crabro* sting was independent from the age of patients.

■ **Conclusion :** *Vespa crabro* sting seems to be a new risk factor for life-threatening reactions after hymenoptera sting.

Key-Words : Hymenoptera hypersensitivity - European hornet - *Vespa crabro*, anaphylaxis..

INTRODUCTION

The prevalence of systemic reactions after a hymenoptera sting varies between 0.15-3.3% (1). The disease tends towards a spontaneous self-limitation and the tendency to relapse varies from 21-73% (1, 2, 3). The prevalence of severe allergic reactions is about 25% of systemic reactions (4).

Risk factors for severe reactions are the severity of the previous reaction, adult age, male gender and type of stinging insect (1). An elevated serum baseline tryptase level has also been suggested and is presently under investigation (4).

In the general population the prevalence of sensitization to vespids is greater than to honeybee ; nevertheless the honeybee sting is a risk factor for severe

systemic reactions and in particular the re-occurrence of a severe systemic reaction after a honeybee sting is higher than that to a sting from a vespid (1, 3).

The three common species of vespid found in Europe are the Yellow jacket (*Vespula spp.*), Wasp (*Polistes spp.*) and European hornet (*Vespa crabro*).

Some differences in venom sensitivity have been documented in populations exposed to different species of vespids, but a link between a specific species and reaction severity has not been reported (5, 6).

The role of *Vespa crabro* stings in life-threatening reactions has been suggested but the risk was considered low as this insect is rare (7, 8).

In a perspective national survey performed in Italy in September 1999, involving 23 Casualty Departments, 56 systemic severe reactions (classes III-IV, Mueller) caused by insect stings were reported.

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According to the patients' identification the culprit insects were honeybee 2 (3.5%), wasp/yellow jacket 14 (25%), European hornet 15 (27%), unidentified insect 25 (44.5%) (9).

In spite of the limits in culprit insect identification, this data is consistent with a previous observation and underlines the threat that *Vespa crabro* represents in Italy (10).

The present study was therefore designed to evaluate the role of the European hornet in severe sting reactions.

The data obtained seem to confirm that the European hornet sting is a risk factor for life-threatening reactions.

SUBJECTS AND METHODS

SUBJECTS

One hundred and sixty two hymenoptera-venom-allergic patients, with a systemic reaction and who had positively identified the culprit insect were evaluated.

The identification of the culprit insect was obtained by matching the results of the skin test, patient information concerning the features of the sting and of the stinging insect as well as patient's insect identification by an entomological collection.

The European hornet in particular is easily distinguished from other vespids by its size, which is about three-four times greater than that of the *Polistes spp.* or *Vespula spp.*, by its distinctive brown and orange colours and by its very painful sting.

If there was any doubt as to the identification of the insect the patient was not enrolled in the study.

The degree of severity of the systemic reactions was classified as per Mueller's classification (11).

Intracutaneous skin tests were performed to the forearm with increasing venom dilutions ranging from 0.001ug to 1ug/ml to diagnose venom allergy.

The following Hymenoptera venoms were used : *Apis mellifera*, *Vespula spp.*, *Polistes spp.* (Alk-Abello-Denmark, Stallergènes-France), *Vespa Crabro* (Anallergo- Italy).

Since allergy to *Polistes spp.* was positively diagnosed in only 5 patients and this group was too small for statistical analysis the patients were not included in the study. Elevated serum baseline tryptase level was not evaluated.

METHODS

Statistical analysis WAS performed on a Macintosh computer using an InStat 2.03 (GraphPad Software 1994) software package.

The t-test and chi-squared test were used in descriptive analysis of patients and the results are reported as mean $\pm$ standard deviation (SD).

For each stinging hymenoptera species the relative risk of a life-threatening reaction (Class IV as per the Mueller classification) was calculated against the sum of milder systemic reactions (Classes I, II, III as per the Mueller classification).

As age is a well known risk factor for severity of Hymenoptera sting reactions, thus interfering with the results, the patients were arbitrary divided into two age groups (< 50 years), (> 51 years) and the same analysis was repeated for each age group.

Data were reported as relative risk (RR) and 95% confidence interval (CI).

The significance was ascribed for $P < 0.05$ (two tailed-test).

RESULTS

The characteristics of our sample of patients are described in table 1. Consistent with the usual epidemiological appearance of this disease a higher prevalence of venom allergy in male than in female and a higher prevalence of allergy to vespids than to honeybee was observed.

No significant difference in gender percentages in each group was documented (Chi-square 1.34 $P = 0.51$). Severe systemic reactions represent 37.5% of systemic reactions resulting from a sting, the vast majority of which were caused by vespids (45.7% *Vespula spp.*, 44% *Vespa crabro*), and the remaining 10.3% by honeybees.

The percentage of life-threatening reactions was very high in the *Vespa crabro* allergic patients group (81,25%), while was similar both in honeybee allergic group (24%) and in *Vespula spp.* allergic group (27,8 %) (Chi-square 25.995 $P < 0.0001$).

In those patients who have had a systemic reaction, the risk of a life-threatening reaction is about three times higher (RR = 2.74 - CI 95% 1.93-3.89 - $R < 0.0001$)

for the *Vespa crabro* sting than it is for the honey bee or yellow jacket sting. There are no significant differences between the last two insects (table 2). The mean age of the patients allergic to *Vespa crabro* was higher than that for the other two groups of allergic patients (*Vespa crabro* vs *Vespula spp* $P < 0.001$ and *Vespa crabro* vs *Apis m.* $P < 0.02$) (table 1), but this factor does not seem to play a determining role in reaction severity. Indeed, the relative risk for severe systemic reactions after a *Vespa crabro* sting is more than double compared to honeybee or yellow jacket stings in both the < 50 years age group ($RR = 2.83$ - CI 95% 1.62-4.49 - $P = 0.0065$) and in the > 51 years age group ($RR = 2.39$ - CI 95% 1.45-3.95 - $P = 0.0008$). No differences between yellow jacket and bee stings was confirmed (table 3).

DISCUSSION

Our results clearly confirm the role of the European hornet in life threatening reactions after stinging. Moreover the results seem indicate that *Vespa crabro* allergy is having more impact than *Polistes spp* and honeybee allergy in the general population, at least in Italy.

The epidemiological features of our patients (age, gender distribution, sensitivity distribution between vespid and honeybee, prevalence of severe allergic reaction within a systemic reaction after a sting) are consistent with the usual features of hymenoptera allergic patients. The most important difference is the very high prevalence (81%) of a life-threatening reaction after a sting from the European hornet.

The mean age of European hornet allergic patients is higher than the mean age of the yellow jacket and honeybee allergic patients, thus questioning the role of European hornet sting in this result.

Indeed the age is a well known risk factor for life threatening reactions after insect sting, because of the coexisting cardiovascular disease and their treatment (1).

The persistence of the highest risk for life threatening reactions after European hornet sting seems independent from age of patients (table 3) and is consistent with an effective role of European hornet sting in such result.

The European hornet (*Vespa crabro*) is present in Europe and also on the east coast of North America where it was accidentally introduced by man in 19th century.

It is the least common vespid but its presence in the environment varies from country to country and from year to year. Also the exact geographical distribution of the insect in Europe is not well known.

Specific sensitivity to venoms in populations exposed to different vespids revealed the minor impact of the European hornet in Spain, while a greater role of the same insect was noted in south-east France (Marseille) and in Italy (5, 6, 7).

The extensive cross-reactivity between *Vespula spp* and *Vespa Crabro* venoms (12, 13) and the lack of specific diagnostic tools for *Vespa Crabro* until up to a few years ago, meant that only *Vespula spp* diagnostic tools were available, thus underestimating the specific role of the European Hornet in epidemiological studies performed in countries belonging to the mediterranean basin (14, 15, 16).

The cause of the link between life-threatening reactions and a *Vespa crabro* sting is unknown, though there is speculation that the composition and/or the dose of venom injected could be involved.

The main components of *Vespa crabro* venom, hyaluronidase, phospholipase A and B and Antigen 5 are structurally homologous to corresponding proteins in other vespid venoms. The sequence homology of major allergens is around 70% (7, 12, 13). Two specific biologically active peptides were isolated from *Vespa crabro* venom : mastoparan, which degranulates mast cells, and crabrolin, which enhances phos-

Culprit Hymenoptera	Patients no.	Male/Female Ratio	R4/R1+R2+R3 #	Mean Age± SD
<i>Vespula spp.</i>	97	68/29	27/70	41 ± 16 years*
<i>Vespa Crabro</i>	35	27/08	26/09	56 ± 13 years* §
<i>Apis Mellifera</i>	25	20/05	06/19	47 ± 12 years §
Total	157	115/42	59/98	

Table 1 : Demographic characteristics of the patients and relationship with culprit insect.

R4/R1+R2+R3 : proportion of class IV Mueller reaction versus classes I + II + III Mueller systemic reactions ($P < 0.0001$ Chi-square test).

* $R < 0.001$, § $R < 0.02$ (student t test).

pholipase activity but a relationship between these peptides and reaction severity has never been documented (7).

The amount of venom proteins injected per sting and reaction severity have been suggested as a possible cause in different level of reaction severity, particularly at re-sting, between honeybee and yellow jacket (17).

Culprit Hymenoptera	Relative risk
<i>Vespa crabro</i> versus <i>Apis Mellifera</i>	3.09 (CI 95% 1.49-6.3) p = 0.0002
<i>Vespa crabro</i> versus <i>Vespula spp.</i>	2.66 (CI 95% 1.83-3.88) p < 0.0001
<i>Vespa crabro</i> versus <i>Apis Mellifera</i> + <i>Vespula spp.</i>	2.74 (CI 95% 1.93-3.89) p < 0.0001
<i>Vespula spp.</i> versus <i>Apis Mellifera</i>	1.15 (CI 95% 0.53-2.49) R = 0.80 n. s.

Table 2 : Role of the stinging hymenoptera in life-threatening reaction. Relative risk and confidence interval of severe systemic reactions class IV Mueller versus classes I + II + III Mueller systemic reactions depending on stinging insect.

Age ≤ 50 years		Age ≥ 51 years	
Hymenoptera	Relative risk	Hymenoptera	Relative risk
<i>Vespa crabro</i> versus <i>Apis Mellifera</i>	2.27 (CI 95% 0.91-5.65) R = 0.099	<i>Vespa crabro</i> versus <i>Apis Mellifera</i>	4.56 (CI 95% 1.26-16.4) p = 0.0011
<i>Vespa crabro</i> versus <i>Vespula spp.</i>	2.97 (CI 95% 1.64-5.36) p = 0.0057	<i>Vespa crabro</i> versus <i>Vespula spp.</i>	2.00 (CI 95% 1.19-3.35) p = 0.0066
<i>Vespa crabro</i> versus <i>Apis Mellifera</i> + <i>Vespula spp.</i>	2.83 (CI 95% 1.62-4.49) p = 0.0065	<i>Vespa crabro</i> versus <i>Apis Mellifera</i> + <i>Vespula spp.</i>	2.39 (CI 95% 1.45-3.95) p = 0.0008
<i>Vespula spp.</i> versus <i>Apis Mellifera</i>	0.76 (CI 95% 0.30-1.92) R = 0.76 (n. s.)	<i>Vespula spp.</i> versus <i>Apis Mellifera</i>	2.27 (CI 95% 0.59-8.76) p = 0.27 (n. s.)

Table 3 : Role of age and of stinging hymenoptera in life-threatening reaction. Relative risk and confidence interval of severe systemic reactions class IV Mueller versus classes I + II + III Mueller systemic reactions depending on stinging insect and age group.

Indeed, the venom dose injected by the honeybee is relatively high and constant having been calculated at $59 \pm 7 \mu\text{g}$ in one study and in $148 \mu\text{g}$ in a second study (18, 19).

On the other hand the dose of venom injected by *Vespa spp* is low and varies between 2-20 μg : the feeding habits of the insect immediately prior to stinging can reduce the amount of venom injected per sting (20).

The amount of venom injected in a single hornet sting is not known, but the quantity of venom collected from a single *Vespa crabro* was 0.92 mg, the dry weight of which was 260 μg . even if the total dose is not injected in a single sting the availability of this potentially high amount of venom could be involved in the severity of the reactions resulting from a sting (20).

Taken together such observations seem to suggest that it could be the amount rather than the composition of the venom injected that makes the European Hornet sting so dangerous.

Cross-reactivity between *Vespula spp* and *Vespa crabro* venoms is a further aspect amplifying the threat from *Vespa crabro*, because a sting from this insect can trigger a reaction in subjects previously sensitised to *Vespula spp*, which is the most common clinical condition (1). A recent study performed in Slovenia showed that 70% of 24 patients with anaphylactic reactions to a *Vespa crabro* sting had previously been sensitised to *Vespula spp* venom (8).

Further, the cross-reactivity of this venom affects the choice of venom immunotherapy, even though the homology of venoms it is not complete *Vespa crabro* allergic patients are usually treated with *Vespula spp* venom immunotherapy (8, 21).

Venom immunotherapy is extremely effective, and only about 5% remained unprotected upon a re-sting (21).

It has recently been demonstrated that the species of vespid can undermine the efficacy of immunotherapy, in particular the frequency and the severity of systemic reactions after a *V. maculifrons* sting is three times higher than those resulting from a *V. germanica* sting. It is thought that the variability of the injected allergen load per sting could be involved in this outcome (22).

In line with this observation, because of the amount of venom injected, the *Vespa crabro* sting could be a further risk factor deriving from the failure of *Vespula spp* venom immunotherapy.

In conclusion, the widespread presence of the European hornet in Italy, the large amount of venom it injects and the cross-reactivity between *Vespa crabro* and *Vespula* spp. venoms are probably involved in the high risk of life-threatening reaction after a *Vespa crabro* sting.

Further studies will be necessary to shed further light on the role of the European hornet in severe allergic reactions and its possible role in undermining the efficacy of *Vespula* spp. venom immunotherapy.

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