Leonor Esteves Caldeira*, Maria Inês T. Silva*, Elisa Pedro, Joana Cosme

Hypersensitivity to *Vespa velutina nigrithorax*: an emerging problem in Portugal?

Immunoallergology Service, Centro Hospitalar Universitário Lisboa Norte, EPE, Lisbon, Portugal
*The authors contributed equally to this work

Key words

Allergy; anaphylaxis; Asian wasp; Hymenoptera venom; Vespa velutina nigrithorax.

Corresponding author
Leonor Esteves Caldeira
Immunoallergology Service
Centro Hospitalar Universitário Lisboa Norte, EPE
Avenida Professor Egas Moniz
1649-035 Lisbon, Portugal
ORCID: 0000-0003-2347-4658
E-mail: leonorfsecaldeira@gmail.com

Doi
10.23822/EurAnnACI.1764-1489.279

To the Editor,

Vespa velutina nigrithorax (VVN), also known as "yellow-legged" Asian hornet, is an insect native of South-East Asia, naturally distributed in Southern China, India, Indochina and Indonesia. This wasp is very successful in colonizing new areas, currently widespread in other countries/continents where it is considered an invasive species (1, 2). It was introduced in Europe through France and was identified in Portugal for the first time in 2011, in the north-western province of Minho (3).

Since its introduction in Europe, it has been considered an economic and ecological threat because of its impact on biodiversity and beekeeping productions, and also a public health threat due to venom allergenic and toxic properties. The number of reported cases of anaphylaxis due to VVN is increasing (2, 4).

VVN venom extract has become recently available in Portugal during the year of 2021, improving the specificity of the diagnosis and aiding in the treatment of patients with severe systemic allergic reactions to VVN. Therefore, we aimed to characterize the sensitization profile of Portuguese patients who reported systemic reactions to VVN, observed in our Center, a specialized Hymenoptera venom allergy unit.

Skin prick tests (SPT) and intradermal tests (IDT) (Bial-Aristegui/Roxall®) were performed with VVN, *Vespula* spp. and *Polistes dominula* venom extracts. We also determined specific IgE (sIgE) (ImmunoCAP®) for *Vespa velutina*, *Apis mellifera*, *Vespula* spp. and *Polistes dominula* and molecular components (rApi m 1, rApi m 2, rApi m 3, rApi m 5, rApi m 10, rVes v 1, rVes v 5, rPol d 5).

To the present date, 7 patients (P) identified VVN as the insect responsible for the sting, 4 females (P1, P2, P6, P7) and 3 males (P3, P4, P5). Patients' data is represented in **table I**. Median age was 53 ± 22 years (range, 20-78 years). Four (57%) lived in a rural area, and 2 (29%) worked outdoors, presenting a high risk of exposure. All patients described immediate systemic reactions (< 15 minutes) after VVN sting. According to Mueller classification (5), 2 patients had a grade I reaction, 2 a grade III and 3 a grade IV.

All patients reported previous stings from other Hymenoptera, including common wasp, paper wasp and European honeybee, describing local mild reactions. One patient (P3) also reported previous VVN stings, referring former local exuberant reactions.

Three patients had positive SPT (venom 100 mcg/mL) and four had positive IDT to VVN (0.01-1 mcg/mL). Positive sIgE (> 0.35 kUA/L) was detected for VVN total extract in 5 patients (71%) (median, (interquartile range (IQR)), 5.74 (0.91-23) kUA/L); five (71%) were positive for *Vespula* spp. (6.45 (2.41-34.3) kUA/L) and all (100%) were positive for *Polistes dominula* (4.05 (1.33-18.1) kUA/L). Only one patient (P1) (14%) had positive sIgE to *Apis mellifera* (0.35 kUA/L). Three patients (43%) demonstrated sIgE positive (median, (IQR)) for rVes v 5 (14.6 (1.06-44.2) kUA/L) and rPol d 5 (12.9 (0.76-44.7) kUA/L) (**table I**).

The median value (IQR) of total IgE was 228 (18-278) IU/mL, and of basal tryptase was 4.95 (3.45-9.7) mcg/L. None had a basal tryptase level > 11.4 mcg/L.

One patient (P1) presented lip pruritus and angioedema during IDT (concentration of 1 mcg/mL), that resolved after treatment with intravenous corticosteroid and antihistamine.

When comparing the group with mild systemic reactions to VVN sting (Muller grade I), including P1 and P7, with the group of patients with severe reactions (Mueller grade III/IV), including P2, P3, P4, P5 and P6, there was no statistically significant difference ($p > 0.05$) in mean values of sIgE for VVN total extract, *Vespula* spp., *Polistes dominula,* rVes v 5 and rPol d 5. Additionally, no significant differences were demonstrated between mean total IgE and tryptase values and reaction severity.

In P1 and P3, with anaphylactic reactions after an Hymenoptera sting, with documented IgE sensitization to VVN and considering their risk of being re-sting given their professional and leisure activities, we considered to prescribe VVN immunotherapy, which they are about to start. P2 refused immunotherapy and P4 started immunotherapy with *Vespula* spp. whole extract venom. Taking into consideration patients' sensitization profile (**table I**), the remaining patients were not proposed to immunotherapy with VVN whole extract venom.

VVN anaphylactic reactions are increasing in the southern regions of Portugal. With the introduction of VVN extracts, the patients' diagnosis and treatment will be increasingly targeted and specific (4, 6-8). As well as in other studies, patients more prone to Hymenoptera stings and, therefore, more prone to allergic reactions, are the ones with outdoor jobs/hobbies (4, 6, 8). Levels of sIgE to VVN were low, according to other studies, and not directly related to reaction severity (4, 6). Also in those studies, sIgE to VVN tended to be lower than Vesp v 5, which also occurred in our study, with its equivalent Ves v 5 (8).

To date, VVN venom has not been fully studied, and only the whole venom extract is commercialized. However, in the context of research, two main allergens have been described: Vesp v 5 corresponding to antigen 5, with a homology of more than 75% with antigen 5 of *Vespula* spp. and *Polistes dominula*, and Vesp v 1 corresponding to A1-phospholipase, with a homology of about 70% with A1-phospholipase of *Vespula* spp., and *Polistes dominula* and in less degree with *Apis mellifera*. These findings suggest cross-reactivity of VVN with the most common vespids (2, 4, 6-9). And in fact, the majority of patients had, to some extent, sensitization to *Vespula* spp. or *Polistes dominula* whole venoms (100% of patients) or their recombinants rVes v 1, rVes v 5 and rPol d 5 (n = 6, 85.7%).

Similarly, to other studies, all patients had already been stung by other Hymenoptera (*Vespula* spp., *Polistes dominula* and *Apis mellifera*), this being the probable route of sensitization by cross-reactivity, due to high homology of major allergens, as explained above (2, 4, 6-9), as they had never been stung by VVN. With exception for P3, who have also been stung previously by VVN and has negative values for rVes v 5 and rPol d 5, raising the major possibility of genuine sensitization to VVN venom.

A recent study from an Insect Allergy Specialized Clinic North of Portugal shows similar data in 6 patients with anaphylaxis to VVN sting. All tested patients had positive results to Ves v5 and Pol d5, and two thirds were positive to Ves v1 (10).

In some studies, published before VVN venom immunotherapy was available, patients were treated with *Vespula* spp. venom immunotherapy. According to these data, *Vespula* spp. venom immunotherapy seemed to be effective and safe in patients with VVN anaphylactic reactions (2, 4, 7-9). New studies are now arising with targeted immunotherapy for VVN.

This study has some limitations. First, the identification of VVN was based on patients reports, although all are linked to these activities (as a hobby like a hunter, or professionally like a VVN nest destroyer from the civil defense team), live in a rural environment or photographed the insect, decreasing the risk of misidentification. Second, the small sample, which could limit the extrapolation of results. And third, the fact that recombinant allergens are not yet commercially available, which limit the validation of cross-reactivity and/or genuine sensitization.

Anaphylactic reactions to VVN venom are becoming an emerging problem in Portugal, mainly in southern areas, furthest from Spain. All physicians working in this area are committed to their patients, and a new era of Hymenoptera allergy treatment is beginning.

Nonetheless, the authors suggest that it has an important added value in clinical practice, providing a real-world evidence for the scientific community, the biggest one described so far in our country.

Fundings

None.

Contributions

LEC, MITS: study design, data collection, analysis and interpretation, writing - original draft, writing - review and editing. EP: writing - review and editing. JC: study design, data collection and interpretation, writing - review and editing.

Table I *- Demographic, clinical and laboratory data of studied patients.*

Patient (P)	Gender	Age, years	Mueller classification	SPT, mm (papule diameter)	IDT, mm (papule diameter)	sIgE (kUA/L)	
P1	F	53	Grade I	*Vespa velutina*: 6 *Vespula species*: negative *Polistes dominula*: negative	*Vespa velutina* 0.01 µg/mL: 10 0.1 µg/mL: 12 1 µg/mL: 14 *Vespula species* 0.01 µg/mL: negative 0.1 µg/mL: negative 1 µg/mL: 10 *Polistes dominula* 0.01 µg/mL: 13 0.1 µg/mL: 10 1 µg/mL: 20	*Vespa velutina*: 23.7 *Apis mellifera*: 0.97 *Vespula species*: 52.2 *Polistes dominula*: 58.4	rApi m 1: 0.03 rApi m 2: 0.12 rApi m 3: 0.01 rApi m 5: 18.5 Api m 10: 0.01 rVes v 1: 13.4 rVes v 5: 44.2 rPol d 5: 44.7
P2	F	78	Grade III	*Vespa velutina*: 8 *Vespula species*: negative *Polistes dominula*: 6	*Vespa velutina* 0.01 µg/mL: 12 0.1 µg/mL: 18 1 µg/mL: 20 *Vespula species* 0.01 µg/mL: 10 0.1 µg/mL: 18 1 µg/mL: not done *Polistes dominula* 0.01 µg/mL: 14 0.1 µg/mL: 16 1 µg/mL: not done	*Vespa velutina*: 5.74 *Apis mellifera*: 0.27 *Vespula species*: 16.4 *Polistes dominula*: 7.69	rApi m 1: 0.02 rApi m 2: 0.01 rApi m 3: 0.01 rApi m 5: 0.01 Api m 10: 0.01 rVes v 1: 0.37 rVes v 5: 14.6 rPol d 5: 12.9
P3	M	28	Grade IV	*Vespa velutina*: 8 *Vespula species*: negative *Polistes dominula*: negative	*Vespa velutina* 0.01 µg/mL: 8 0.1 µg/mL: 10 1 µg/mL: 12 *Vespula species* 0.01 µg/mL: negative 0.1 µg/mL: negative 1 µg/mL: 12 *Polistes dominula* 0.01 µg/mL: negative 0.1 µg/mL: negative 1 µg/mL: negative	*Vespa velutina*: 22.3 *Vespula species*: 6.45 *Polistes dominula*: 1.57	rVes v 1: 2.33 rVes v 5: 0.04 rPol d 5: 0.03
P4	M	69	Grade IV	*Vespa velutina*: negative *Vespula species*: negative *Polistes dominula*: negative	*Vespa velutina* 0.01 µg/mL: negative 0.1 µg/mL: 8 1 µg/mL: 12 *Vespula species* 0.01 µg/mL: negative 0.1 µg/mL: negative 1 µg/mL: 9 *Polistes dominula* 0.01 µg/mL: negative 0.1 µg/mL: negative 1 µg/mL: 8	*Vespa velutina*: 0.13 *Apis mellifera*: 0.16 *Vespula species*: 1.00 *Polistes dominula*: 0.54	rApi m 1: 0.00 rApi m 2: 0.01 rApi m 3: 0.02 rApi m 5: 0.85 Api m 10: 0.07 rVes v 1: 0.20 rVes v 5: 1.06 rPol d 5: 0.76

→

Patient (P)	Gender	Age, years	Mueller classification	SPT, mm (papule diameter)	IDT, mm (papule diameter)	sIgE (kUA/L)	
P5	M	35	Grade IV	*Vespa velutina*: negative *Vespula species*: negative *Polistes dominula*: negative	*Vespa velutina* 0.01 µg/mL: negative 0.1 µg/mL: negative 1 µg/mL: negative *Vespula species* 0.01 µg/mL: negative 0.1 µg/mL: negative 1 µg/mL: 12 *Polistes dominula* 0.01 µg/mL: 8 0.1 µg/mL: 12 1 µg/mL: 20	*Vespa velutina*: 0.4 *Apis mellifera*: 0.14 *Vespula species*: 0.19 *Polistes dominula*: 4.05	rApi m 1: 0.00 rApi m 2: 0.01 rApi m 3: 0.00 rApi m 5: 0.68 Api m 10: 0.08 rVes v 1: 1.61 rVes v 5: 0.00 rPol d 5: 0.00
P6	F	74	Grade III	*Vespa velutina*: negative *Vespula species*: negative *Polistes dominula*: negative	*Vespa velutina* 0.01 µg/mL: negative 0.1 µg/mL: negative 1 µg/mL: negative *Vespula species* 0.01 µg/mL: negative 0.1 µg/mL: negative 1 µg/mL: negative *Polistes dominula* 0.01 µg/mL: 10 0.1 µg/mL: 12 1 µg/mL: 14	*Vespa velutina*: 1.41 *Apis mellifera*: 0.01 *Vespula species*: 3.82 *Polistes dominula*: 18.1	rApi m 1: 0.01 rApi m 2: 0.01 rApi m 3: 0.01 rApi m 5: 0.03 Api m 10: 0.00 rVes v 1: 4.31 rVes v 5: 0.01 rPol d 5: 0.02
P7	F	26	Grade I	*Vespa velutina*: negative *Vespula species*: negative *Polistes dominula*: negative	*Vespa velutina* 0.01 µg/mL: negative 0.1 µg/mL: negative 1 µg/mL: negative *Vespula species* 0.01 µg/mL: negative 0.1 µg/mL: negative 1 µg/mL: negative *Polistes dominula* 0.01 µg/mL: negative 0.1 µg/mL: negative 1 µg/mL: negative	*Vespa velutina*: 0.24 *Apis mellifera*: 0.08 *Vespula species*: 0.08 *Polistes dominula*: 1.33	rApi m 1: 0.01 rApi m 2: 0.02 rApi m 3: 0.02 rApi m 5: 0.00 Api m 10: 0.01 rVes v 1: 0.02 rVes v 5: 0.01 rPol d 5: 0.00

Papule diameter was expressed in millimeters (mm) and those with a diameter of 3 mm or more above the negative control were considered positive. Specific IgE was considered positive for values > 0.35 kUA/L. In skin prick tests, venom extracts were used in pure concentrations (100 µg/mL); IDT: intradermal tests; SPT: skin prick tests.

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. Perrard A, Arca M, Rome Q, Muller F, Tan J, Bista S, et al. Geographic variation of melanisation patterns in a hornet species: genetic differences, climatic pressures or aposematic constraints? PLoS One. 2014;9(4):e94162. doi: 10.1371/journal.pone.0094162.
2. Vidal C. The Asian wasp Vespa velutina nigrithorax: Entomological and allergological characteristics. Clin Exp Allergy. 2022;52(4):489-98. doi: 10.1111/cea.14063.
3. Feás Sánchez X, Charles RJ. Notes on the Nest Architecture and Colony Composition in Winter of the Yellow-Legged Asian Hornet, Vespa velutina Lepeletier 1836 (Hym.: Vespidae), in Its Introduced Habitat in Galicia (NW Spain). Insects. 2019;10(8):237. doi: 10.3390/insects10080237.
4. Vidal C, Armisén M, Monsalve R, González-Vidal T, Lojo S, López-Freire S, et al. Anaphylaxis to Vespa velutina nigrithorax: Pattern of Sensitization for an Emerging Problem in Western Countries. J Investig Allergol Clin Immunol. 2021;31(3):228-35. doi: 10.18176/jiaci.0474.
5. Mueller HL. Diagnosis and treatment of insect sensitivity. J Asthma Res. 1966;3(4):331-3. doi: 10.3109/02770906609106941.
6. Ruiz-Leon B, Serrano P, Vidal C, Moreno-Aguilar C. Management of Double Sensitization to Vespids in Europe. Toxins (Basel). 2022;14(2):126. doi: 10.3390/toxins14020126.
7. Rodríguez-Vázquez V, Armisén M, Gómez-Rial J, Lamas-Vázquez B, Vidal C. Immunotherapy with Vespula venom for Vespa velutina nigrithorax anaphylaxis: Preliminary clinical and immunological results. Clin Exp Allergy. 2022;52(2):345-7. doi: 10.1111/cea.14039.
8. Vidal C, Armisén M, Monsalve R, Gómez-Rial J, González-Fernández T, Carballada F, et al. Vesp v 5 and glycosylated Vesp v 1 are relevant allergens in Vespa velutina nigrithorax anaphylaxis. Clin Exp Allergy. 2020;50(12):1424-7. doi: 10.1111/cea.13738.
9. Tabar AI, Chugo S, Joral A, Lizaso MT, Lizarza S, Alvarez-Puebla MJ, et al. Vespa Velutina Nigritorax: A new causative agent for anaphylaxis. Clin Transl Allergy. 2015;5(Suppl 3):43. doi: 10.1186/2045-7022-5-S3-P43.
10. Miranda J, Mesquita AM, Plácido J, Coimbra A. Vespa velutina nigrithorax venom allergy: Real-life clinical practice. Ann Allergy Asthma Immunol. 2022;129(4):524-5. doi: 10.1016/j.anai.2022.07.020.