

Large Local Reactions to Hymenoptera Stings Negatively Affect Quality Of Life to the Same Degree as Systemic Reactions

Sánchez-Morillas L¹, Alfaya Arias T², Martínez San Ireneo M³, Domínguez Noche C⁴, Vega Gutierrez JM⁵, Vega Castro A⁶, Moreno Mata E⁷, Marqués L⁸, Fuentes Ferrer M⁹, Ruiz-León B¹⁰, Hymenoptera Allergy Committee of the SEAIC

¹Allergy Department. Hospital Universitario Clínico San Carlos, IdISSC, ARADyAL RD16/0006/0009 Madrid

²Allergy Department. Hospital General Universitario de Ciudad Real, Hospital Universitario Fundación Alcorcón

³Allergy Department. Hospital Virgen del Valle, Toledo

⁴Allergy Department. Hospital Virgen del Puerto, Plasencia

⁵Allergy Department. Hospital Universitario Río Hortega, Valladolid

⁶Allergy Department. Hospital Universitario de Guadalajara, Spain. ARADyAL Spanish Thematic Network and Co-operative Research Centre RD16/0006/0023

⁷Allergy Department. Hospital General La Mancha Centro, Alcázar de San Juan, Ciudad Real

⁸Allergy Department. Hospitales Universitarios Santa María y Arnau de Vilanova, IRB Lleida, Lleida

⁹Preventive Medicine Department. Hospital Universitario Clínico San Carlos, IdISSC, Madrid

¹⁰Allergy Department. Hospital Universitario Reina Sofía, Córdoba, Spain. Allergy Network ARADyAL RD16/0006/0018, Instituto de Salud Carlos III, Madrid; Instituto Maimónides de Investigación Biomédica de Córdoba, Córdoba

Corresponding author:

Leticia Sánchez-Morillas

Allergy Department. Hospital Universitario Clínico San Carlos, IdISSC, ARADyAL RD16/0006/0009 Madrid, Spain

Email: lsanchezmorillas@hotmail.com

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0688

Key words: Allergy to Hymenoptera. Quality of life. Hymenoptera stings. Large local reactions. Systemic reaction.

Palabras clave: Alergia a himenópteros. Calidad de vida. Picaduras de himenópteros. Reacción local aumentada. Reacción sistémica.

Reactions to Hymenoptera stings usually produce pain, pruritus, erythema and mild inflammation at the site of the sting. Some patients present a large local reaction (LLR) which leads to inflammation greater than 10 cm in diameter which lasts over 24 hours up to 5-10 days [1].

Quality of life questionnaires are useful tools in daily clinical practice. In the case of Hymenoptera allergy, Elberink et al [2] developed a quality of life questionnaire for patients with SR following Hymenoptera stings (VQLQ) which showed a deterioration in the quality of life.

Between 2008 and 2015, the Hymenoptera Allergy Committee of the Spanish Society of Allergology and Clinical Immunology (SEIAC) undertook the translation into Spanish and the subsequent cultural adaptation of the VQLQ, as well as a cross-sectional and longitudinal validation of the questionnaire [3,4]. The questionnaire was validated in patients allergic to *Apis*, *Vespula* and *Polistes* (HiCaVi). The HiCaVi consists of 14 questions each with 7 possible answers and yields a score of between 1 and 7, representing low to high quality of life.

The hypothesis of our study is that the quality of life of patients with LLR is also impaired. Furthermore, we sought to compare our findings with those of patients with SR due to allergy to Hymenoptera venom.

Between 2016 and 2018, the Hymenoptera Allergy Committee of SEAIC conducted a multicenter study in 9 hospitals in Spain. A cross-sectional observational study was performed which included consecutive patients older than 14 years who attended Allergy departments reporting a LLR following a Hymenoptera sting in the previous two years. Professional beekeepers were excluded. After statistical analysis, we performed a post-hoc comparison with an historical control group of patients with SR included in the cross-sectional and longitudinal validation of the original questionnaire.

The study was approved by the Ethics and Research Committees of the participating hospitals. All patients were informed and gave their consent to participate in the study signing a written informed consent.

Qualitative variables are presented with their distribution as absolute and relative frequencies. Quantitative variables are summarized with means and standard deviations or medians and interquartile ranges when the data did not follow a normal distribution.

Qualitative variables were compared using the Chi-squared test or the Fisher exact test, when necessary. Comparison of means between two independent groups was made using the Student *t* test. For all tests the significance level was set at 0.05. Data processing and analysis was carried out using the statistical software package SPSS v21.0.

A total of 186 patients with a mean age of 43.87 years (SD 14.99) were included in the study. The results are included in Supplementary Table.

The mean score on the HiCaVi for the whole group was 4.1 (SD 1.53). We found no significant differences when we analyzed the questionnaire scores by age, gender, culprit insect, place of residence or location of the reaction. However, significant differences were found for the type of reaction as those patients with an immediate reaction had a significantly lower score than patients with a delayed reaction (immediate reactions 3.87 vs delayed reactions 4.36 $P = 0.031$).

The results from the quality of life questionnaire for the patients with LLR (4.1 [SD 1.53]) were compared with those obtained from the 186 patients with SR included in the cross-sectional and longitudinal validation of the questionnaire (3.86 [SD 1.55]). This yielded a nonsignificant difference of means of 0.23 ($P = 0.145$).

The results of our study show that patients with LLR due to Hymenoptera stings have a reduced quality of life. This loss of quality of life is similar to that experienced by patients who have SR to insect stings.

The prevalence of LLR ranges from 2.4 to 26.4% of the general population depending on the series consulted and is lower in children and higher in professional beekeepers (38%) [1,5]. Such variability may be related to the lack of homogeneity in the definition of LLR, the methodology used and the population studied [1,6].

It is estimated that the risk of developing a SR following a LLR is relatively low, ranging from 2 to 24%. Given the low risk, the indicated treatment is symptomatic and immunotherapy (IT) is not routinely recommended [1,7,8]. IT may be recommended in patients with a high exposure to stings, those who live far from healthcare facilities or in those whose fear of a new sting may affect their quality of life [9-10]. Therefore, measuring quality of life in clinical daily practice may prove useful in the initial

approach and in the decision of what treatment to implement in patients with a LLR following a Hymenoptera sting.

The lower score significant in immediate reactions may be due to the fact that patients perceive a reaction that occurs closer in time to the insect sting as being more dangerous, however they probably received early treatment too. The reactions that occurs several hours after the sting is seen as being more innocuous, even though in both cases the score obtained is low.

When we compared the results from the quality of life questionnaire, the patients with SR obtained a slightly lower score than patients with LLR although the difference was not statistically significant.

Our study has some limitations, mainly related to the clinical management of this type of patient. As we have mentioned, treatment of patients with LLR is symptomatic and therefore performing *in vivo* and *in vitro* studies does not form part of daily clinical practice. However, given that the objective of our study was different, such data have no effect on our overall conclusions. Furthermore, ours was a multicenter study conducted in centers in Spain. Therefore, further studies are required at the international level to confirm our findings.

This is the first controlled study to directly examine the difference in quality of life between patients with LLR and SR and to establish that both groups experience a reduction in their quality of life. The use of quality of life questionnaires in these patients may help in their initial assessment and support the decision to implement specific treatment with immunotherapy.

Funding

The authors declare that no funding was received for the present study.

Conflicts of interest

Dra. Alfaya T declares personal fees of ALK-Abelló, outside the submitted work. The rest of authors declare that they have no conflicts of interest.

Acknowledgments

The study is carried out within the framework of the hymenoptera allergy Committee of the SEAIC.

References

1. Bilò MB, Martini M, Pravettoni V, Bignardi D, Bonadonna P, Cortellini G, et al. Large local reactions to Hymenoptera stings: outcome of restings in real life. *Allergy*. 2019;74:1969-76.
2. Oude Elberink JNG, deMonchy JGR, Golden DBK, Brouwer JLP, Guyatt GH, Dubois AEJ. Quality of life in yellow jacket allergic patients. Development and validation of a health-related quality of life questionnaire in yellow jacket allergic patients. *J Allergy Clin Immunol*. 2002;109:162-7.

3. Armisen M, Guspi R, Alfaya T, Cruz S, Fernández S, Domínguez-Noche C, et al. Cross-sectional validation of a quality of life questionnaire in Spanish for patients allergic to hymenoptera venom. *J Invest Allergol Clin Immunol*. 2015;25(3):176-82.
4. Alfaya T, Vega A, Domínguez-Noche C, Ruiz B, Marqués L, Sánchez-Morillas L. Longitudinal validation of the Spanish Version of the Health-Related Quality of Life Questionnaire for Hymenoptera Venom Allergy (HRQLHA) *J Invest Allergol Clin Immunol*. 2015;25(6):426-30.
5. Sturm GJ, Varga EM, Roberts G, Mosbech H, Bilo MB, Akdis CA, et al. EAACI guidelines on allergen immunotherapy: Hymenoptera venom allergy. *Allergy*. 2018;73(4):744-64.
6. Biló MB, Bonifazi F. The natural history and epidemiology of insect venom allergy: clinical implications. *Clin Exp Allergy*. 2009;39:1467-76.
7. Tripolt P, Arzt-Gradwohl LA, Cerpes U, Laipold K, Binder B, Sturm GJ. Large local reactions and systemic reactions to insect stings: similarities and differences. *PLoS one*. 2020;16:15(4).e0231747.
8. Bilo MB, Pravettoni V, Bignardi D, Bonadonna P, Mauro M, Novembre E, et al. Hymenoptera venom allergy: management of children and adults in clinical practice. *J Invest Allergol Clin Immunol*. 2019;29(3):180-205.
9. Golden DB, Kelly D, Hamilton RG, Craig TJ. Venom immunotherapy reduces large local reactions to insect stings. *J Allergy Clin Immunol*. 2009;123:1386-90.
10. Severino MG, Cortellini G, Bonadonna P, Francescato E, Panzini L, Macchia D, et al. Sublingual immunotherapy for large local reactions caused by honeybee sting: a double-blind placebo-controlled trial. *J Allergy Clin Immunol*. 2008;122:44-8.