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RISK FACTORS ASSOCIATED WITH SEVERE SYSTEMIC ALLERGIC REACTION AFTER WASP STING IN SUBJECTS WITH A HISTORY OF EUROPEAN HORNET STING ALLERGY

DEJAVNIKI TVEGANJA, POVEZANI S TEŽKO SISTEMSKO ALERGIJSKO REAKCIJO (SAR) PO PIKU OSE PRI OPAZOVANCIH S SAR PO PIKU EVROPSKEGA SRŠENA V ANAMNEZI

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ABSTRACT

Aim: To make the treatment approach in patients suffering a European hornet sting allergy reaction more personalized, preparing them also for possible future risks.

Methods: In Slovenia an extended retrospective observational cohort epidemiological study about the natural history of Hymenoptera venom sensitivity is in progress. The study is based on data from the healthcare records of the University Clinic Golnik (UCG) and data collected by a questionnaire sent to patients from May 2019 to April 2021. For a pilot study, we selected patients who were referred to UCG because of an allergic reaction to European hornet sting and had been re-stung later by a wasp (n=68). The association between severe systemic allergic reactions (SSAR) after wasp sting and potential risk factors in subjects with a history of hornet sting allergy was assessed univariately using the likelihood ratio test.

Results: Among 68 European hornet allergic patients 27 reacted with an SSAR and 41 reacted with a mild SAR. Among 27 patients with SSAR, 4 reacted with an SSAR also to a subsequent wasp sting. Among 41 patients with a mild European hornet sting SAR nobody reacted with an SSAR to a subsequent wasp sting. The association between the severity of the wasp SAR reaction in European hornet allergic patients was statistically significant (p=0.022).

Conclusion: Our results suggest that patients with severe European hornet SAR should be considered for wasp venom immunotherapy or prophylactic prescription of epinephrine auto-injector as they are at risk for an SSAR also after wasp string.

Keywords:
Hymenoptera allergy
European hornet sting
Wasp sting
Severe systemic allergic reactions
Healthcare
Public health

IZVLEČEK

Namen: *Prilagoditi vodenje in zdravljenje bolnikov z alergijsko reakcijo po piku evropskega sršena in jih podučiti o morebitnih tveganjih ob naslednjem piku kožekrilca.*

Metode: *Na Univerzitetni kliniki za pljučne bolezni in alergijo, Golnik (UKG), Slovenija se izvaja obsežna opazovalna kohortna epidemiološka raziskava o naravnem poteku alergije po piku žuželk iz rodu Hymenoptera, ki temelji na podatkih iz podatkovne baze UKG in podatkov pridobljenih iz vprašalnika, ki se je pošiljal bolnikom od maja 2019 do aprila 2021. V pilotno študijo smo vključili tiste bolnike, ki so reagirali z alergijsko reakcijo po piku Evropskega sršena in jih je kasneje pičila osa (n = 68). Za oceno povezanosti med opazovanci s težko sistemsko alergijsko reakcijo (SSAR) po piku ose pri opazovancih z alergijsko reakcijo po piku evropskega sršena v anamnezi in potencialmi dejavniki tveganja smo uporabili univariatno statistično metodo.*

Rezultati: *68 bolnikov je imelo alergijsko reakcijo po piku evropskega sršena. 27 jih je reagiralo s težko SAR in 41 z blago. Med 27 bolniki s težko SAR po piku sršena, so 4 bolniki reagirali s težko SAR po kasnejšem piku ose. Med 41 bolniki, ki so po prvem piku Evropskega sršena reagirali z blago SAR, nihče ni reagiral s težko SAR po kasnejšem piku ose. Rezultati so pokazali močno povezanost med težko SAR po piku evropskega sršena in težavnostjo SAR po ponovnih pikih ose (p = 0,022).*

Zaključki: *Vodenje in zdravljenje bolnikov s težko SAR po piku Evropskega sršena naj vključuje imunoterapijo s strupom ose ali profilaktično nošenje avtoinjektorja z epinefrinom za samopomoč, kar je izjemnega pomena zaradi življenje ogrožajoče nevarnosti ob morebitnem piku ose.*

Ključne besede:
alergija po piku kožekrilcev
pik evropskega sršena
pik ose
težka sistemska alergijska reakcija
zdravstvena oskrba
javno zdravje

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1 INTRODUCTION

Insect venom allergy is the most common cause of anaphylaxis in adults. In Europe about two thirds of sting-induced anaphylaxis is due to stings of Vespidae family insects (1). The wasp (Vespula germanica) and European hornet (Vespa crabro) belong to the Vespidae family. Throughout Europe, the genus Vespula is more common than Vespa (2). Wasps behave more aggressively and enter the human environment to find food, so their stings are more common. In contrast to this, European hornets have eating habits that are not associated with a human lifestyle. Their behaviour is less aggressive, unless they are disturbed in the vicinity of their nests. However, their stings can be more health-threatening to humans than wasps' stings (3).

The molecular composition of both venoms is known in detail (4). The amount released in a wasp sting is much lower than in a European hornet sting. Wasps release 5-10 micrograms of venom per sting. The exact quantity of venom in a European hornet sting is not known. The dry weight of venom per sac in the European hornet was found to be 260 micrograms (5).
There is a marked cross-reactivity between wasp and European hornet venom. In fact, most of the genus Vespula allergens share a 95% homology in their amino acid sequence (6). As a consequence, diagnostic and therapeutic extracts also display a substantial cross-reactivity. The clinical relevance of this cross-reactivity is reflected in the fact that a patient primarily sensitized to wasp may experience an allergic reaction after being stung by a European hornet and vice versa, and further, a patient allergic to the latter can be adequately treated with wasp venom immunotherapy (VIT) (7).

Allergic reactions to Hymenoptera stings have varying levels of severity, being systemic (systemic allergic reaction – SAR) or local. This is not only true for the comparison between different individuals, as the grade of severity can also vary in each patient. About 1% of the population have anaphylactic reaction to Hymenoptera insect stings (8). The most important risk factor for severe insect sting anaphylaxis (anaphylactic shock or fatal/near fatal reactions), including malfunction of the respiratory system, is mast cell disease (mastocytosis or monoclonal mast cell activation syndrome). Other risk factors for severe SAR (SSAR) are older age, subsequent stings (after first SAR), a short interval (<2 months) between being re-stung, wasp or European hornet venom allergy (in contrast to honeybee venom allergy) and male gender, while the role of treatment with ACE inhibitors and beta blockers is debatable (9,10).

For patients who experienced a severe systemic IgE-mediated reaction to Hymenoptera sting, specific VIT is the therapy of choice (8). VIT has to be performed with culprit allergen after the sensitization is confirmed by positive skin test or specific IgE. Patients who experienced IgE-mediated reaction following the sting of a European hornet usually have positive skin tests and specific IgE to all vespid venoms (11), which means patients sensitised (and reacting) to vespid venom usually have positive tests to venoms of multiple vespid species, due to crossreactivity. According to data gained from the database of University Clinic Golnik (UCG) in Slovenia, about 280 new adult patients with systemic reaction after a Hymenoptera insect sting are examined every year.

This problem also has a public health dimension, especially in countries with a more spatially dispersed population such as Slovenia (12), which means a more rural population and thus greater exposure to Hymenoptera stings.

This study was launched with the aim of making the treatment approach in patients suffering a European hornet sting allergy more personalized, preparing them also for possible future risks. The objective was to at least roughly determine possible predictive factors for an SSAR after wasp sting in subjects with a history of European hornet sting allergy.

2 METHODS

2.1 Study design, study setting and time frame

In Slovenia an extended retrospective observational cohort epidemiological study about the natural history of Hymenoptera venom sensitivity is in progress. It is based on data from the healthcare records of the UCG and data collected by a questionnaire sent to patients from May 2019 to April 2021 (13). Initially a total of 3,689 patients were selected to enter the study. It was possible to deliver a questionnaire to 3,651 of them. Of these, 1,149 questionnaires were returned (response rate 31.5%), and 1,051 questionnaires were suitable for analysis. Among 1,015 respondents, 514 (48.9%) were referred due to allergic reaction after wasp sting, 410 (39.0%) due to honeybee allergic reaction, 103 (9.8%) due to European hornet allergic reaction and 24 (2.3%) due to both honeybee and wasp allergic reaction. For the purpose of this study, European hornet allergic patients re-stung by a wasp were selected.

2.2 Data collection process, study instruments and inclusion criteria

For the purpose of a pilot study, we selected patients who were referred to UCG because of an allergic reaction to European hornet sting and had been re-stung later by a wasp. Only patients who were not treated with VIT and who returned a postal or online version of the questionnaire were included.

From the healthcare records we obtained the age, sex, geographical location of the patient and the culprit insect of the first reaction of the sting as well as the clinical history of each patient: (i) aetiology of the first sting/ stings, which was/were the cause of the allergy and admission to hospital, (ii) severity of the first SAR or large local reaction (LLR) (Mueller grading system), (iii) history of asthma, (iv) history of cardiovascular diseases, (v) atopic constitution (other allergies) and (vi) laboratory tests performed - sIgE for the bee venom and/or the wasp venom and/or the European hornet venom.

2.3 Observed outcome

The type of reaction and its severity after wasp sting which followed an allergic reaction to European hornet sting (Mueller grading system (14)) was assessed based on the question 'What were the signs of the allergic reaction', accompanied by a table explaining the signs of the subsequent allergic reaction. The patients could choose between five available answers from the table, which were converted into the severity of allergic reaction according to Mueller (from I to IV) or LLR. For the purpose of the analysis, we combined the answers into two categories: mild SAR after subsequent wasp sting reaction (Mueller grading system I and II) or LLR and SSAR after subsequent wasp sting reaction (Mueller III and Mueller IV). SSAR after wasp sting was chosen as the observed outcome (0-no, 1-yes).

2.4 Risk factors for severe SAR after wasp sting

For the purpose of analysis, all the variables were aggregated into two categories. Factors included in our analysis were socio-demographic: gender and age. The age of the patients was calculated from the year of birth until referral to the UCG for the assessment of the first European hornet sting and was aggregated into two categories (0 to 40 years old (0), 41+ years old (1)). Other factors associated with the type of reaction and its severity after a wasp sting that followed an allergic reaction to European hornet sting gained from the questionnaire or from the BIRPIS Hospital information system, were: carrying out farm work (0-no, 1-yes; questionnaire), type of living environment (0-rural, 1-urban; questionnaire), family history of Hymenoptera venom allergy (0-no, 1-yes; questionnaire), the time from visiting UCG to the next sting (0-2 years (0), >3 years (1); questionnaire), having asthma (0-no, 1-yes; BIRPIS Hospital information system), having other diseases (0-no, 1-yes; BIRPIS Hospital information system), concentration sIgE (<0.35-low, 0.36 to 3.49-moderate, >3.50-high (15), Hospital information system).

2.5 Methods of analysis

The association between SSAR after wasp sting and potential risk factors in subjects with a history of hornet sting allergy was assessed univariately using the likelihood ratio test.
In all statistical tests, $p \leq 0.05$ was considered significant. The IBM SPSS for Windows Version 27.0 (SPSS Inc., Chicago, IL, USA) software was used.

3 RESULTS

3.1 Sample description

The final sample included 68 European hornet allergic patients re-stung by a wasp, 50 (73.5%) men and 18 (26.5%) women. The majority of them were 41 years old or older (52.9%).

3.2 Results of the association analysis

There were 27/68 patients with an SSAR after a European hornet sting. Four (14.8%) of them reacted with an SSAR also to a subsequent wasp sting. One the other hand there were 41 patients with a mild European hornet sting allergic reaction and nobody reacted with an SSAR after a subsequent wasp sting (Table 1). The association between the severity of the wasp SAR reaction in European hornet allergic patients was statistically significant ($p=0.022$). This means that those who experience severe allergic reaction after a European hornet sting are more prone to react severely (Mueller grading system III or IV) after a subsequent wasp sting.

When considering other risk factors for the severity of the wasp SAR in European hornet sting allergic patients, none was statistically significantly associated with the observed outcome (Table 1). This means there were no associations between the severity of wasp sting reaction according to age, sex, farm work, living in a rural or urban area, Hymenoptera allergy in the family, the time of the next sting, having asthma or other diseases.

4 DISCUSSION

The results of our study suggest that a severe SAR after a European hornet sting can serve as a useful indicator that these patients might react with a severe SAR after a subsequent wasp sting. Among 103 patients referred due to allergic reaction after a European hornet sting, 66% self-reported being re-stung by a wasp, which is a very high prevalence. This indication is very important as management and treatment of the patient, which consist of wasp VIT or carrying of epinephrine autoinjection (EAI) for self-administrations, is of utmost importance to prevent severe reaction or even save their lives in the case of a possible subsequent wasp sting.

Table 1. Results of analysis of association between severe SAR after a wasp sting in hornet sting allergic patients and selected risk.

Risk factor for SSAR after a wasp sting	Category	N_{tot}	N_{hornet}/N_{cat} (%)	p
Severe SAR after European hornet sting	No	68	0/41 (0.0%)	0.005
	Yes		4/27 (14.8%)	
Gender	Female	68	1/18 (5.6%)	0.945
	Male		3/50 (6.0%)	
Age	0-40	65	3/29 (10.3%)	0.203
	41+		1/36 (2.8%)	
Carrying out farm work	No	68	2/34 (5.9%)	1.000
	Yes		2/34 (5.9%)	
Type of living environment	Rural	68	2/45 (4.4%)	0.492
	Urban		2/23 (8.7%)	
Family history of Hymenoptera allergy	No	68	3/53 (5.7%)	0.885
	Yes		1/15 (6.7%)	
Time between two stings	0-2 years	68	0/25 (0.0%)	0.051
	>3 years		4/43 (9.3%)	
History of asthma	No	68	4/67 (6.0%)	0.727
	Yes		0/1 (0.0%)	
Accompanying diseases	No	68	4/60 (6.7%)	0.309
	Yes		0/8 (0.0%)	
Concentrations of sIgE	Low	68	1/7 (14.3%)	0.646
	Moderate		2/35 (5.7%)	
	High		1/26 (3.8%)	

Legend:
N_{tot}=total number of observations, N_{hornet}=number of subjects with severe European hornet systemic allergic reaction within the category; Ncat=number of subjects within the category; SSAR=severe systemic allergic reaction; concentrations of sIgE=<0.35-low, from 0.36 to 3.49-moderate, >3.50-high (15).

In the literature reporting on patients who experienced an SSAR after a hornet sting and were not treated with VIT, real-world evidence data about the course of the disease is scarce. Košnik et al. identified that wasp venom induces sensitization in the majority of patients with IgE-mediated allergic reaction to the venom from the sting of a European hornet. The data demonstrate that in Slovenia, the vast majority of patients with anaphylactic reaction to European hornet sting seem to be sensitized through previous wasp stings. Wasp venom was considered an appropriate immunotherapeutic agent for such patients, except for those with proven primary sensitization to specific epitopes of European hornet venom (16). Macchia et al. assessed in a prospective way the characteristics of re-stings and showed that in European hornet allergic patients both wasp and European hornet VIT are equally effective (17). Eržen et al. showed that patients with European hornet allergy and high basophil sensitivity (BAT) after stimulation with wasp venom are also at risk of developing a systemic reaction after a wasp sting. On the contrary, patients with low basophil sensitivity are likely to tolerate further wasp stings without an SAR. The BAT proved to be a helpful additional tool because of its high sensitivity and specificity, and it has predictive value for the severity of the reaction (18). In patients with low basophil sensitivity to wasp venom and considering the low probability of further European hornet stings in the general population in Central Europe, those patients could be offered a more personalized management plan and follow-up (19).

Risk factors associated with the severity of the SAR after subsequent stings are mainly described for wasp and honey bee stings, and are as follows: gender, age, beekeeping

or living next to a beehive, farm work, living in a rural area, genetic predisposition, the time from the first SAR to the next sting, asthma and other diseases, especially cardiovascular diseases. The results of our analyses show there is no association between selected risk factors and the severity of the SAR after a subsequent wasp sting in European hornet allergic patients.

The prevalence of SARs is generally higher for men than for women. Men are more exposed (outdoor workers, physical activity) and consequently experience a higher number of stings, and might therefore be at a higher risk for sensitization (9). Adults are more likely to have severe SARs after re-stings than children, and older adults (41+years old) have more severe SARs after being re-stung, which is related to comorbidity, especially the presence of cardiovascular diseases (20). As far as farm work is concerned, we presume that those engaged in this kind of work are more exposed to European hornet stings, because of their living habits. Like other social wasps, European hornets build communal nests by chewing wood to make a papery pulp, and are found mostly in rural areas (3). Epidemiological studies that have assessed sensitization to insect venom and atopy, which is the most well-known genetic factor, suggest causality. Data on the association between rhinitis, ocular symptoms, allergic asthma and insect sensitization is common. Atopic subjects have a lower threshold in skin tests with insect venoms and a higher level of sIgE than non-atopic patients (21). Genetic predisposition increased the risk of sIgE formation in atopic patients and in patients who have a history of allergic reaction to Hymenoptera stings in the family (22). Among other diseases which could possibly increase the severity of SAR after wasp stings, cardiovascular are the most important. In particular, these include medications for cardiovascular diseases (beta-blockers and ACE inhibitors) but to date not enough evidence-based studies on this topic have been published (9,10). As far as the time between first and subsequent Hymenoptera sting is concerned, the absence of further stings can lead to tolerance. Persistent sensitization with no intermediate stings is likely to involve genetic factors, but the cause of persistence of sIgE has yet to be explained (23).

Our study has some potential limitations. First, the data were collected in a self-reported survey, and thus the actual data in the whole cohort could be different. Greater control over the questionnaire results can be achieved with the supervision of an allergist. For these reasons, the data from the hospital information system of individual histories was extremely important in our study, as we had access to everyone's history concerning the characteristics of individual health status and of the first sting. Next, the number of patients who experienced an SSAR after a hornet sting and were subsequently stung by a wasp and had no VIT is very small, particularly patients with a European hornet sting SSAR. Next, our study included only patients without VIT. This means that most of the patients reacted with a mild SAR (Mueller grade I or II) or even with LLR after a European hornet sting. For some patients in our study group who reacted severely, VIT was advised. They refuse it for different reasons: not trusting the results of specific immunotherapy treatment, the distance to the clinic where treatment is provided, job commitments, not having time for other reasons and poverty. Through the protocol these patients are protected with an epinephrine auto-injector (EAI) (24). Finally, as there is no available literature about risk factors that could increase the severity of the SAR explicitly for European hornet, thus we could only presume these risk factors are similar to those from being stung by a wasp or honey bee.

This study has also some strengths. First, to the best of our knowledge this is the first assessment of possible risk factors for SSAR after a wasp sting in European hornet allergic patients. Next, the survey addresses multiple variables in one unique study, which is not usual for the retrospective studies already conducted in this field (16-18). Next, the study population covered all Slovenian patients referred to the hospital due to allergic reaction after Hymenoptera stings from 1997 to 2015, as the UCG was the only institution in Slovenia that covered diagnostic procedures and the treatment of this kind of allergy in adults. Finally, this study was a very long-lasting retrospective study.

This study has some important clinical as well as public health implications. Among the clinical implications, it is worth first mentioning that the study results indicated a strong association between an SSAR after a European hornet sting and severity of allergic reaction after a subsequent wasp sting. Management and treatment of patients with an SSAR after European hornet sting could be personalized using this knowledge. For example, this knowledge could be used in empowerment of such patients regarding the necessity of VIT or EAI use after structured training on how to use this kit, and other precaution measures (9). From a public health perspective, the results of our study can be very important in educating and empowering population groups that are at risk for Hymenoptera mites, such as children, adolescents and beekeepers (25, 26).

We are aware that this is only the beginning of research in this field. Although we showed that 15% of patients with severe European hornet allergic reaction will react with severe reaction also after a wasp sting, further studies are needed to identify biomarkers that could find those patients at risk. For example, BAT sensitivity which looks like a promising biomarker to predict the risk of severe reaction after a subsequent wasp sting should be measured.

5 CONCLUSIONS

The results of our study showed that an SSAR after a hornet sting is one of the risk factors for subsequent SSAR also after a wasp sting. They suggest that patients with an SSAR after a European hornet sting should be considered for wasp VIT or prophylactic prescription of EAI, as they are at risk for an SSAR also after a wasp sting. The awareness of this kind of possible treatment among healthcare providers, patients and the general public as well, should be improved in all steps in the procedures towards a healthier, better quality of life or even protection of their lives.

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CONFLICT OF INTERESTS

The authors declare that no conflicts of interest exist.

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ETHICAL APPROVAL

Ethical approval to conduct the study was obtained from the National Medical Ethics Committee of the Republic of Slovenia (NMEC), No. 0120-188/2017/4, Academic research.

AVAILABILITY OF DATA AND MATERIALS

All data and materials used in this study are available upon reasonable request of the corresponding author.

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