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Evaluation of the risk factors for the rate of allergic reaction after bee and vespid sting in adults – a systematic review of the literature

Opredelitev napovednih dejavnikov za oceno stopnje alergijske reakcije po piku čebele in ose pri odraslih – sistematični pregled literature

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Abstract

Background: Currently available tests are unable to distinguish between asymptomatic sensitization and clinically relevant Hymenoptera venom allergy. Our aim was to elucidate some of the possible markers, identified by different researchers, which could play an important role in determining the predictive factor for severe systemic reaction or local reaction in sensitized patients after a bee or vespid sting.

Methods: A systematic literature review was conducted for the period to 31 December 2017 in the bibliographic database PubMed. In the systematic review we included all types of epidemiological studies in which researchers identified some possible predictive markers that could be used to identify allergic patients' response to a bee or vespid sting with either local or severe systemic reaction.

Results: In the systematic review, 16 original articles were included in the final analysis. The analysis elucidated the prevalence for large local reactions and severe systemic reaction after a bee or wasp sting. There are some risk factors which could play an important role in the determination of further treatment.

Conclusions: There are few studies concerning predictive factors for determining the severity of allergic reaction after bee or vespid stings. Also, a verified predictive factor for prognosis still remains unidentified. Further reasearch in this field should include public health professionals as well as clincal allergologists.

Izvleček

Izhodišča: Trenutno dosegljivi testi za razlikovanje med asimptomatsko senzibilizacijo in klinično relevantno alergijo za strupe žuželk niso zanesljivi. Namen našega članka je opredeliti: a) možne napovedne dejavnike, ki so jih navedli raziskovalci pregledanih raziskav, in b) napovedne dejavnike, ki igrajo pomembno vlogo pri opredelitvi poteka hude sistemske ali blažje lokalne reakcije pri senzibiliziranih bolnikih za pik ose ali čebele.

Metode: Sistematični pregled literature obdobje do 31. 12. 2017 temelji v bibliografski bazi Pub Med. V sistematični pregled smo vključili epidemiološke raziskave, v katerih so raziskovalci proučevali možne napovedne dejavnike za opredelitev odgovora alergičnih bolnikov za strup čebele ali ose s težko sistemsko ali lokalno reakcijo.

Rezultati: V sistematični pregled je bilo vključenih 16 izvirnih raziskav. Analiza je osvetlila prevalenco alergijskih bolezni, težko lokalno reakcijo ter sistemsko reakcijo po piku žuželk, kot so osa, sršen in čebela. Nakazujejo se tudi pomembni dejavniki tveganja za razvoj težke alergijske reakcije po piku, ki jih moramo upoštevati pri napovedi izida nadaljnjega zdravljenja.

Zaključki: Raziskav na temo napovednih dejavnikov za težko alergijsko reakcijo za pik čebele in ose je malo. Pri nadaljnjem raziskovanju napovednih dejavnikov je treba uporabiti interdisciplinarni pristop, ki bo vključeval strokovnjake s področja klinične in javnozdravstvene medicine.

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1 Introduction

Insect stings from the order of Hymenoptera can cause a local reaction with painful swelling, that lasts for several hours, in a healthy person. On the other hand, people with insect venom allergy may experience more large local reactions and systemic symptoms, including anaphylaxis (1).

Insect venom allergy is more common in adults than in children due to exposure to stings and co-morbidities and due to taking certain medications (2). A systemic allergic reaction occurs in 0.3% to 3.3% of the population (1,3-9), and with children, in less than 1% of the population (5). 2.4% to 26.4% of the adult population (3,4) and 19% of children (5) have large local reactions after the stings of these insects. In Central Europe, allergic reactions after insect stings are mainly due to bee and wasp stings, less often involving hornets and only very rarely involving bumblebees (10). Clark and Camargo (11) state that about one-quarter of anaphylaxis-related deaths can be attributed to insect sting allergy.

Symptoms of an allergic reaction after an insect sting vary from an large local reaction at the site of the sting (swelling at the site of the sting with a diameter of more than 10 cm, lasting more than 24 hours), to a milder systemic reaction manifested by generalized redness, itching, urticaria and angioedema. Typical symptoms of a moderate reaction are dizziness, shortness of breath, and nausea, whereas with a severe reaction, the patient may experience shock with loss of consciousness or even respiratory or cardiac failure. Fear of further severe allergic reactions usually has a negative effect on the quality of life (11-14).

Diagnostic tests (15) are required with individuals who have experienced a severe systemic reaction after the sting. There are several tests that can detect allergic sensibilization. Evidence of sensibilization is important because, based on this data, recommendations are made to patients to urgently reduce the chance of sting recurrence. In patients with severe reactions, the allergen is selected for treatment with specific immunotherapy, which prevents allergic reactions after a possible sting recurrence. There is currently no test that could be used to predict the likelihood and severity of a possible systemic reaction after an insect sting recurrence.

Systemic mastocytosis is also among

the risk factors for a severe reaction. Mastocytosis is a group of disorders characterized by the accumulation of mast cells in various organs. Insect sting allergy and severe systemic reactions are more common in patients with this rare disease. Current epidemiological data suggest that 50% of patients with mastocytosis experience anaphylaxis after an insect sting. Niedoszytko et al. (16) report on two simple procedures, used in clinical practice for screening for systemic mastocytosis: a thorough examination of the skin to detect cutaneous mastocytosis, and a measurement of basal tryptase concentration, which is correlated with mast cell load. Alvarez-Twose et al. developed the predictive model "Spanish Network on Mastocytosis" (Red Española de Mastocytosis [REMA]), which from clinical data (male sex, systemic reaction with impaired consciousness and without skin signs) and from laboratory data (elevated basal tryptase) the presence of clonal mast cells or systemic mastocytosis in patients who have experienced anaphylaxis with 92% sensitivity and 81% specificity (18).

In Slovenia, 400 to 500 new patients are examined every year due to a systemic reaction after an insect sting. Because diagnostic tests for insect sting allergy are not sensitive and specific enough, overdiagnosis can lead to allergy diagnosis in patients who are only sensitized but not allergic, and inadequate diagnosis that underestimates the need to avoid stings even the need for immunotherapy in patients who are likely to have a severe reaction after a possible subsequent sting (19-21). A major public health challenge is the reduced quality of life of those who are in constant fear of a new systemic reaction after a possible recurrence (11). Confino-Choen et al. report that patients who have experienced anaphylaxis suffer from stress that can last for years or a lifetime and negatively affect their quality of life. In the study, there were more than 12% of such cases, all of whom had confirmed anaphylaxis. Patients reported intrusive and distracting thoughts associated with an event they could not control. As many as 36% had debilitating thoughts and this proportion did not depend on the age, sex, or education of a patient. However, new research findings are the basis for the introduction of measures such as: better education and health promotion for these patients, and on the other hand, better awareness of doctors about the emotional consequences their patients might suffer and the need for possible psychological support for these patients (11).

In Slovenia, beekeeping has a long tradition, and the bee is a symbol of diligence, skill, and care for others. According to the Slovenian Beekeepers' Association, there are around 8,000 active beekeepers in the country (16).

The purpose of our systematic review is to identify and evaluate conventional parameters and methods such as skin tests, specific IgE, IgG4, and total IgE antibodies, and other risk factors for severe allergic reaction after wasp, bee, or hornet stings.

2 Methods

2.1 Sources of scientific articles

We performed a systematic review of the literature in the PubMed bibliographic database in the period from the first publications in this field of research to 31 December 2017 (22).

2.2 Methods of scientific article identification

We searched for Scientific articles were with the following keywords and Boolean operators: ([insect venom AND predictive factor]; [insect venom AND risk factors]; [insect venom AND predict]) throughout the text. When search-

ing, we limited ourselves to all original articles in English.

2.3. Methods of scientific article selection for inclusion in the systematic review

Scientific articles were included in the analysis based on the following inclusion criteria:

- scientific articles describing the definition study of a predictor of a severe or mild systemic reaction in patients allergic to Hymenopteran stings;
- scientific articles examining the definition of prognostic factors such as levels of specific IgE against insect venoms, total IgE, specific IgG and IgG4 against insect venoms, and skin test results for allergies caused by insect venoms;
- scientific articles examining allergic reactions and predictors of bee stings in beekeeper populations by countries/regions of the world;
- scientific papers that have identified a prognostic factor for milder/more severe systemic reaction or anaphylaxis after Hymenopteran sting.

From the analysis, we excluded scientific articles that:

- included animal research;
- described a prognostic factor for an allergic reaction after insect stings during and after immunotherapy;
- have focused on predictors of allergic reactions after the sting of other insects and not bees, wasps, bumblebees or hornets;
- have focused on prognostic factors for allergic reactions after insect stings only in children and adolescents.

2.4. A data set, relevant to the systematic review

For each included scientific article, we defined the following data: lead author and year of publication, purpose of research, concept of epidemiological research, data collection methods, observed population, research environment, results and main findings.

2.5 Methods of data analysis and synthesis

Based on the data set, the synthesis identified the most commonly used research concepts in scientific articles, data collection methods, the most frequently observed population group and the research environment. The results were presented descriptively, but where it was stated, we also presented measures of correlation (e.g., PR - prospect ratio) between the observed phenomena.

3 Results

3.1 The process of scientific article selection for systematic review

Based on the selected search strategy and defined criteria, we included 16 original scientific articles in the final review (23-38). Figure 1 presents the process of scientific article selection for systematic review.

3.2 Description of the main features of the research

Appendix 1 presents the results of the analysed scientific articles according to the purpose of the research, the epidemiological concept of the research, the data collection methods used, the observed population/environment and a summary of the main findings.

3.3. Assessment of insect sting exposure (bee, wasp, hornet)

Eight retrospective observational cohort studies (26,28-31,34,36,37) and eight

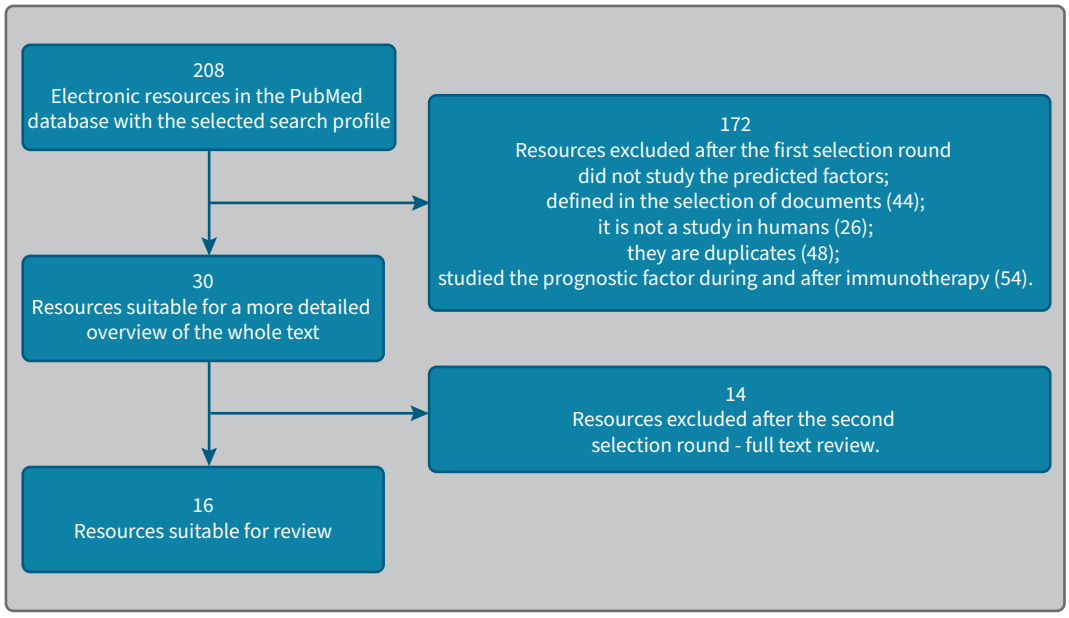

Figure 1: The process of scientific article selection for systematic review (22).

prospective observational cohort studies were included in the systematic review of the literature according to the epidemiological concept (23-25,27,32,33,35,37). Among retrospective observational studies, there are four studies, two in Finland (30,31), one in the United Kingdom (37) and one in Turkey (34), that could be used to clarify the risk factor for systemic reactions to bee venom of the observed population of beekeepers. In all four studies of beekeepers, a dedicated questionnaire, which was published in beekeeper association newsletters or on the World Wide Web, was used to assess bee sting exposure and certain risk factors (sex, age, duration of beekeeping, co-morbidity, atopy…) for severity of the allergic reaction. In a study by Annila et al. (31), data on observed risk factors were obtained using the questionnaire and sIgE testing for bee venom and skin prick allergy tests before and after the beekeeping season. In the next three retrospective cohort studies, the general population in Sweden (28) and the population of allergic patients admitted to the University Clinic of Bern in Switzerland over the last five years (36) were observed, as well as the population sensitized to bees or wasp venom in the Netherlands (29). In a study by Björnsson et al. (28), serum sIgE was measured to determine the prevalence of sensitized adults. They also used a dedicated questionnaire on insect stings and the severity of the reaction and the observed risk factors (atopy, sex, age, location of the area in Sweden). Richter et al. (36) measured the levels of basal serum tryptase concentration together with the assessment of atopy, age and sex to assess cIgE, sIgE exposure. In a retrospective cohort study, Blaauw et al. (29) asked patients about the reaction after a previous Hymenopteran sting and then performed a provocation test in the intensive care unit and measured the severity of the reaction. In prospective observational cohort studies, eight studies (23-25,27,33,38) measured the immune response with sIgE, sIgG, cIgE, skin prick tests and compared the severity of the previous reaction, sex, age, atopic constitution, location and number of previous stings, and time interval from previous allergic reaction with the result of a bee or wasp provocative sting. In a

prospective cohort study by Golden et al (32), sensitization to insect venoms of volunteers was measured for five to nine years, followed by sensitization with skin prick tests and sIgE, and natural insect stings were recorded. In a cohort study, Pucci et al. (26) monitored subjects with insect stings, who were exposed to a resting in less than two months, and measured intradermal skin tests and sIgE and difficulty to reaction rate. Another cohort study (35) evaluated a skin prick test to assess exposure, but in this study, there was a greater emphasis on measuring baseline serum tryptase and the age of patients.

3.4. Measuring skin and serological tests for insect (bee, wasp, hornet) sting allergy

3.4.1 Skin tests

Poison concentrations of 1 to 100 µg/ml are used for skin prick tests. For intradermal skin tests, 0.02 ml at a toxin concentration of 0.001 to 1 µg/ml is injected on the volar side of the forearm. The intradermal test is positive if the diameter of the urticaria is 5 mm or more. Even at 100 µg, the sensitivity of the skin prick test is much lower than with the intradermal test, so it makes sense to do an intradermal skin test with a negative prick test (27,38).

3.4.2 Allergen-specific IgE (sIgE)

The systemic allergic reaction is mediated by sIgE. The most characteristic symptoms during an allergic reaction after an insect sting are: urticaria, angioedema, bronchospasm, and anaphylactic shock. In the first days after the sting, sIgE for insect venom may be low or undetectable. Usually, sIgE get elevated days or weeks after the sting. In patients in whom sIgE are not detectable, the tests should be repeated after a few weeks. A double-positive diagnostic test for both bee and wasp venom is common and results from double sensitization or cross-reactivity between some epitopes of both venoms. A particular problem of cross-reactivity is sIgE antibodies against hydrocarbon epitopes (CCD), which have no clinical significance. Most double-positive patients are, however, sensitized to both toxins (37). The inhibition test helps us to distinguish between cross-reactivity and double sensitization (27,38).

3.4.3 Allergen-specific IgG (sIgG)

SIgG levels reflect allergen exposure. High levels of sIgG antibodies have been found in the highly exposed population of beekeepers, and also in patients on venom immunotherapy. However, in studies in which immunotherapy patients underwent an insect bite provocation test, it was not possible to demonstrate that the protective effect of immunotherapy coincided with the concentration of sIgG antibodies (sIgG-4) or the ratio of sIgG- and sIgE-antibodies. Routine evaluation of sIgG is not used in the diagnosis of allergy to insect venoms (27,38).

3.5 Methods of analysis of the association of skin and serological tests for insect bites (bee, wasp, bumblebee, hornet) and other risk factors and severity of allergic reaction

Univariate analysis using t-test and $\chi 2$ test was used in several studies to analyze the association between the severity of an allergic reaction after a Hymenopteran sting and a predictive risk factor (skin tests, serum tests: sIgE, cIgE, sIgG) to assess the association of dependent and independent variables. (23-30,34,36-38). Some studies have used other tests to assess associatin: Mann-Whitney test (24,25,27,33), Kruskall-Wallis non-parametric test (38), Kendall correlation (33), Fischer test (23,32), Wilcoxon test (32) and Kolmogorov-Smirnov test (37). The

level of statistical characteristic was determined at $p < 0.05$ in all studies. One study (32) determined only the natural frequency of sensitization and allergic reactions with simple descriptive statistics.

Multiple logistic regression was used in most studies (27,28,30-32,34,36,37). Odds ratios (OR) and a 95% confidence interval (CI) were determined. The level of statistical characteristic was determined at $p < 0.05$ in all studies.

4 Discussion

4.1 Discussion of the results of the systematic review

Insect stings can cause an allergic reaction, sometimes even the most severe – anaphylactic reaction (36). In Europe, most stings are attributed to wasps and bees, and to a lesser extent, hornets, and bumblebees (37). In our systematic review of the literature, we focused on original scientific articles that define the prevalence of varying degrees of allergic reactions and some possible predictive factors for the severity of an allergic reaction.

4.1.1 Sensitization to insect stings

The prevalence of sensitization (determined by a positive skin test or the presence of sIgE in serum) has been investigated and ranges between 9.3% and 27% (36). Several epidemiological observational studies point out that this characteristic depends on the level of exposure to the stings; in Sweden, where the population is less exposed to insects, a lower level of sensitization is recorded compared to other European countries (28). In a specific population, such as beekeepers, who are exposed to many stings in a short time, the risk of sensitization increases (30,31,34,37). The higher prevalence of sensitization in men can be attributed to the fact that men spend more time outside due to work or physical activity outside, which increases the risk of insect stings (27,28,37). Also, the higher frequency of wasp sensitization compared to bees in the general population can be attributed to the fact that wasp stings are more common than bee stings. Wasps behave more aggressively and are significantly more prone to appear in the human environment, as they can be found next to human food and waste. Bumblebees and bees have different eating habits that are rarely associated with the human lifestyle. Their behaviour is less aggressive, unless we disturb them in the vicinity of their hive (28). One of the most interesting questions about the natural course of asymptomatic sensitization remains open as a risk factor for the first severe reaction or death after an insect sting in people who are unaware of their condition (32,38).

4.1.2 Large local reaction

The prevalence of a large local reaction varies in the general population. It was researched that it stands at between 2.4% and 26.4% (38). In beekeepers it is at about 38% (30,31). The reason for such differences is unknown; however, it has been suggested that this is influenced by methodological aspects in defining the reaction or exposure to insects. Some research has pointed out that patients with a large local reaction have the same reaction after a provocation test with a sting. The risk of reacting with a systemic reaction after a re-sting is small, from 5% to 10%. Paradoxically, the risk of a systemic reaction after a recurrence for patients with a large local reaction is even lower than in sensitized asymptomatic patients (17%) (32). Although epidemiological studies suggest a clear difference in the natural course between a large local reaction and a systemic reaction, standard diagnostic methods (skin tests, sIgE) are not sensitive enough to determine the difference between the two (38).

4.1.3. Asymptomatic sensitization or systemic reaction

The prevalence of asymptomatic sensitization in Central Europe in the general population is about 30%. The prevalence of systemic response in the general population is the subject of various studies that have reported results ranging from 0.15% to 3.3% (28,38). The degree of variability of this phenomenon is probably due to two influencing factors: the mode of data collection and the degree of sting exposure.

The difference in the prevalence of allergy to insect stings in the general population between northern and southern Europe correlates well with the presence of insects in the environment (28). Moreover, the high prevalence of systemic reactions in beekeepers, which is between 14% and 42%, clearly confirms the influence of this factor (30,31,34,37). They found an inverse relationship between the number of stings in one year and the prevalence of systemic reactions (31,34). This probably suggests that a certain number of stings per year elicit tolerance. The high prevalence of systemic reactions in beekeeping family members and amateur beekeepers bitten by insects more frequently than the general population is consistent with this claim (38).

Regarding the method of data collection, the most commonly used tool is a questionnaire (26,28,30,31,34,37). Even if the questionnaires are the same, there are different assessments of individuals with what reaction they reacted to the sting. This phenomenon is mainly due to the way patients imagine a systemic reaction. Therefore, better control can be achieved through a survey conducted by a healthcare professional and through skin and serological tests to confirm the anamnesis, which allows us to have more realistic results. In addition, there is no uniform classification in the original articles for assessing the severity of a systemic reaction: it is mostly assessed according to Müller (24,25,27,29-31,35,36). There is another way to assess the significance of the disease, namely to count visits to the emergency department. However, this method has drawbacks, as only the most severe cases of a systemic reaction are treated in the emergency unit.

4.1.4 Diagnostic tests (skin tests, sIgE, cIgE)

17% of the population has positive skin tests with insect venom. The study confirmed that those allergic to wasp stings, with a positive history and a negative skin test, have systemic reactions in 22% (33). 10% of patients with negative skin tests or undetectable sIgE for insect venom react with anaphylaxis. However, it appears that in a fairly large proportion (17%) of patients with a positive skin test and a negative history, the possibility of a systemic reaction still exists, even more than 10 years after the evidence of positive skin tests (32). Skin tests become negative in 30% of patients after 2 years and in almost 50% after 3 years (32).

From 27.1% to 40.7% of the population have positive sIgE. Given the prevalence of those who react with a systemic reaction, the test is not sensitive enough to predict a systemic allergic reaction. SIgE synthesis immediately after the sting is usually transient.

The study also assessed cIgE levels and association with the systemic response. CIgE levels increased with age, but not statistically significantly. Higher levels of cIgE were compared with the difficulty of the systemic response, but no association was found (36). Higher levels of cIgE can perhaps also be attributed to atopy. Several studies have shown that atopy is associated with an increased risk of a systemic reaction after an insect sting (32).

4.1.5 Sting aetiology

Higher sensitization to wasp stings compared to bees in the general population can be attributed to exposure. Wasps

behave more aggressively and have a significant tendency to enter the human environment as they can be found next to human food and waste. Bumblebees and bees have different eating habits that are rarely associated with a person's lifestyle. Their behaviour is less aggressive, unless we disturb them in the vicinity of their hive (26).

4.1.6 Sex

In the first study (37), the female sex was statistically significantly characteristic of the severity of the systemic reaction following bee stings. This phenomenon can be attributed to sex hormones. Androgen receptors have recently been identified on human mast cells, with oestrogen responsible for accelerated, IgE-dependent mast cell activation. However, these hypotheses need to be confirmed. On the other hand, men are more exposed and consequently experience a higher number of stings; therefore, more of them experience a systemic reaction (27,28).

4.1.7.Age

In terms of age, people under the age of 20, especially men, are statistically significantly more likely to react with a systemic reaction than those between the ages of 20 and 45. This can be attributed to the fact of a different immune response (not yet fully explained) and to higher exposure (26). On the other hand, people over the age of 45 also react statistically significantly more often with a systemic reaction than those aged 20 to 45, and the cause is probably reduced cIgE levels in the young, co-morbidity in the elderly (medicines associated with cardiovascular disease, respiratory diseases) (26,28,37).

4.1.8.History of systemic reaction

The most important risk factor for recurrence of a systemic reaction is a history of a previous systemic reaction. In the reviewed literature, only one article evaluates the relationship between the difficulty of the first systemic reaction and the difficulty of the subsequent systemic reaction. In the article, the systemic reaction after the provocation test with insect venom was not more difficult than that described by the patients in their history; on the contrary, it was lighter (36). Unfortunately, the sample of patients was so small that the interpretation of the results is not reliable. In addition, subjective reporting of a history of systemic reactions may be misleading (excessive concern) and objective assessment by the physician in a hospital is milder, as the emotional state (release of neuropeptides or catecholamines) is different from that in nature (36). In the future, a large sample of the population should be assessed for the role of the severity of the history of systemic allergic reactions in predicting the severity of further systemic reactions after recurrent insect stings.

4.1.9 Time from the previous tolerated sting to the repeated sting

A specific risk factor for the onset of the first systemic reaction is a reaction-free sting in the two previous months (26). The risk of a systemic reaction is increased by 58% compared to controls if the previous, tolerated sting occurred less than two months (26) prior to the first sting that had a reactive response. The absence of further stings can lead to tolerance. Persistent asymptomatic sensitization with no intermediate stings is likely to involve genetic factors, but the cause of persistence with sIgE has yet to be explained (32).

4.1.10 Sting frequency

A large number of simultaneous stings (<50) may sensitize and may be the reason that the next sting causes anaphylaxis. The frequency of stings can be one of the main factors: a very short interval

between stings (an interval within two to six months) can cause a systemic reaction (26). This is also reflected in beekeepers, as those patients who have worked in apiaries for a shorter time have had many more systemic reactions than those who have been beekeepers for several years. On the other hand, a higher number of stings, especially in beekeepers (> 100), has a protective effect, as it probably causes tolerance (31,34,37).

4.1.11 Atopy

Atopy is a risk factor for more severe systemic reactions after a bee sting. The risk of a systemic reaction is 4 times higher in atopic than in non-atopic beekeepers (32). 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. In atopic subjects, it showed a lower threshold in skin tests with insect toxins and a higher level of sIgE than in non-atopic patients (27,28,30,34). Genetic predisposition increased the risk of sIgE formation (38) in atopic patients.

Based on the results, we can conclude that the balance between environmental factors (sting frequency), age, and genetic factors (persistence of sIgE) is the reason for the prevalence of systemic allergic reactions to stings in the general population.

4.2 Limitations and strengths of the research

Our research has some limitations. First, it is a review of literature that is accessible and written in English and limited to the Pub Med database, making the results dependent on bias of choice. Second, there are few studies that have examined the predictive risk factor for the severity of an allergic reaction after bee, wasp, and hornet stings. In fact, upon review, there is no research that would evaluate an allergy after a bumblebee sting. In our systematic review, we included studies that had very different sizes of the observed population. We are aware that some studies are more credible due to the greater number of observed patients than those that studied the risk factor for developing an allergic reaction after an insect sting in a very small population group.

The strengths of the research are that we elucidated on which risk factors are indicated as important for the development of more or less systemic and large local reactions, and evaluated their shortcomings in treatment. Because the quality of life of at-risk patients can be severely reduced, studies can be a good foundation for health promotion in the field of bee and wasp sting allergy.

4.3 Significance of results for the public health profession and possibilities for further research

All efforts to define the prognostic factor for allergic persons for Hymenopteran stings are aimed at improving the quality of life of the affected person, reducing morbidity and, last but not least, reducing mortality resulting from the worst allergic reaction - anaphylactic shock. For both the patients and their families, the anaphylactic reaction after a bee or wasp sting is very traumatic. Scientists have found that patients with an anaphylactic reaction after an insect sting have a greatly reduced quality of life, especially due to the emotional stress associated with constant fear and alertness in normal life (40). A reliable predictive risk factor for the severity of an allergic reaction would certainly help physicians promote the health and better quality of life of people allergic to insect stings. Beekeepers require a special approach to health promotion. In some countries, preventive mea-

sures are already being implemented to improve their behaviour: instructions to reduce exposure to bee stings, self-medication in emergencies, consideration of immunotherapy with bee venom, and so on. (41)

Further research should focus on elucidating the natural course of allergic disease after insect stings, to shed light on the overall development of risk factors, and the right decision for further immunotherapy treatment, as patients are sometimes overdiagnosed or underdiagnosed.

5 Conclusion

There is currently no predictive factor that can predict the severity of an allergic reaction with certainty. However, some risk factors are already known (aetiology, sex, age, history of systemic reactions, recurrence of stings in the interval of two months, frequency of stings, atopy, genetic predisposition, systemic mastocytosis), which are advised to be discussed in the general population in preventing allergic reactions following a wasp or a bee sting. Promoting health on the natural course of the disease and on the effects of immunotherapy based on scientific findings would undoubtedly improve the quality of life of patients suffering from such problems.

6 Online appendix

Appendix 1: Scientific research that has studied a prognostic factor that would reliably show more severe systemic allergic reactions (anaphylaxis), or milder or major local allergic reactions after a wasp, bee or hornet sting. The file is available at the web link: https://doi.org/10.6016/ZdravVestn.2973.

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