



Natural history of systemic reactions and risk factors in children and adults with Hymenoptera venom allergy

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Abstract

Purpose Stings by Hymenoptera usually cause just local reactions. However, in some cases, they can induce systemic symptoms and even fatal reactions. The natural history and the risk factors of severe systemic reactions are presented in this review.

Methods Both the natural history and risk factors of systemic reactions due to insect stings are unraveled. This publication is based on a selective literature search in PubMed, Web of Science, and EMBASE (until 30 July 2019). Recent publications about insect venom allergy in English journals were analyzed. This literature search included original and review articles and relevant abstracts of allergy congresses in English.

Results Risk factors are classified as follows: (1) patient-related, (2) allergen-related and (3) reaction-related and also risk factor associated to venom immunotherapy (VIT) are considered. Due to the scarcity of data about the suitability of premedication before and during VIT, a succinct table gathering available premedication invites further investigation.

Conclusions There is limited evidence with regard to the natural history of HVA both in adults and in chil-

dren. Several risk factors may influence the natural history of HVA, namely patient-related, allergen-related and reaction-related. Other factors are inherent to the use of venom immunotherapy (VIT).

Keywords Insect sting · Honey bee venom · Wasp venom · Mastocytosis · Anaphylaxis · Immunotherapy

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitors
cMCAS	Clonal mast cell activation syndromes
HVA	Hymenopteran venom allergy
IgE	Immunoglobulin E
IS	Insect sting
ISM	Indolent systemic mastocytosis
ISMs–	Indolent systemic mastocytosis without skin lesions
LLR	Large local reactions
PoCHVAQoLS	Parents of Children with Hymenoptera Venom Allergy Quality of Life Scale
QoL	Quality of life
REMA	The Spanish network of mastocytosis

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sIgG4	Specific immunoglobulin G4
SPT	Skin prick testing
SR	Systemic reactions
SSR	Severe systemic reactions
VIT	Venom immunotherapy

Introduction

Stings by Hymenoptera, namely bees, wasps, yellow jackets, hornets and ants, usually cause local reactions. However, in some cases, they can induce systemic symptoms and even fatal reactions [1–3]. Insect stings by Hymenoptera species are very common; data indicate that 56.6–94.5% of the general population has been stung at least once in their lifetime [4].

Reactions to hymenopteran venom are also responsible both for decreased quality of life and significant anxiety about future stings [1, 3]. The results of the quality-of-life questionnaire validation studies have demonstrated that a well-tolerated sting challenge test improves the quality of life of venom-allergic patients by reducing the anticipatory anxiety associated with the fear of being stung [5, 6].

In recent years, recombinant technologies have represented a great advance in the diagnosis of hymenopteran venom allergy (HVA), as they may provide a profile of sensitization profile to specific allergens. Moreover, molecular diagnosis helps to discriminate between true sensitization and cross-reactivity in multiple-venom sensitization, which is crucial in order to prescribe the appropriate venom immunotherapy (VIT) [7, 8].

Systemic reactions (SR) due to HVA affect between 2.3 and 2.8% of the rural population in Spain and may lead to potentially life-threatening anaphylaxis [8]. In Europe, the rate of self-reported severe systemic reactions (SSR) in European epidemiological studies ranges from 0.3 to 7.5% in adults, and up to 3.4% in children [1]. Severe SSR are less frequent in children and appears to be rare in children of preschool age (<5 years) [1].

Methods

This article is based on a selective literature search in three electronic databases: PubMed, Web of Science and EMBASE (until 30 July 2019). The following keyword algorithm was used: (“hypersensitivity venom” [MeSH]) OR (“hypersensitivity venom” [Journal]) OR hypersensitivity venom [Title/Abstract]. We manually included other articles that were missed by the initial search after selecting the terms: venom, insect venom allergy, hymenoptera venom allergy, wasp venom allergy, bee venom allergy, allergy; immunotherapy, subcutaneous immunotherapy, risk factors, pretreatment, premedication, children, adults and mastocytosis.

This literature search included original and review articles as well as abstracts of allergy congresses in English.

Risk factors with regard to insect venom allergy in adults

Several risk factors may be distinguished in adults (Table 1).

Patient-related risk factors

Age

Elderly patients with HVA and pre-existing cardiovascular disease have an increased risk of a fatal sting reaction [1]. Young people pose a lower risk of anaphylaxis [9].

Male gender

Male sex has been recently identified as a risk factor for severe anaphylactic reactions independent of the elicitor [10].

These observations diverge from a previous hypothesis which posed of an augmenting the effect of female sex hormones on the incidence and/or the severity of anaphylactic reactions [11]. The effect of male sex as a risk factor in venom-allergic patients, however, was mainly attributed to a higher degree of exposure to stinging insects [12].

Diseases and treatment

Mastocytosis A close relation between Hymenoptera venom anaphylaxis and mastocytosis or clonal mast cell activation syndromes (cMCAS) seems to occur. The most common trigger of anaphylaxis in patients with mastocytosis is hymenopteran venom with a range from 22 to 53% in adult subjects [13, 14]. In men with indolent systemic mastocytosis without skin lesions (ISMs–), HVA can be the initial presenting symptom in up to around one-half of the cases [14]. Hymenoptera stings do not seem to play a role in eliciting anaphylaxis in children with mastocytosis [15, 16]. On the other hand, the frequency of cMCAS in subjects with Hymenoptera anaphylaxis ranged from 1 to 7.9% [17]. Recent studies show that up to 26% of patients with a life-threatening reaction after a hymenopteran sting might present cMCAS, when using the REMA score [18].

Indolent systemic mastocytosis (ISM) associated with insect-induced anaphylaxis displays unique clin-

Table 1 Classification of risk factors

Patient	Allergen	Reaction
Age	Type of insect	Severity
Gender	Level of exposure	Site of the sting
Diseases	–	Delayed treatment
Treatment		
Immunological response	–	Time interval

ical, biological, and molecular characteristics, as compared with other systemic mastocytosis cases: a marked male predominance, absence of urticaria or angioedema and the presence of cardiovascular symptoms, such as hypotension, leading to loss of consciousness [19]. The absence of urticaria or angioedema in severe reactions to Hymenoptera stings with hypotension might represent the most relevant factor in identifying patients with mastocytosis, regardless of their serum tryptase levels [20].

The safety of skin tests has been confirmed in many studies, which did not report any reactions in patients with mastocytosis and HVA, so these complementary tests should be performed in the context of a complete allergy work-up [13].

Patients with ISM are known to demonstrate lower sIgE and total IgE levels, which is presumably due to the adsorption of sIgE to the surface of the expanded mast cell population resulting in less detectable free IgE [21]. Consequently, it has been suggested that the threshold shall be lowered to 0.10–0.17 kU/l in these patients in order to achieve a better diagnostic accuracy in terms of sensitivity and specificity [22]. Component resolved allergy tests, using recombinant allergens, are a potentially useful tool to demonstrate IgE antibodies in patients with ISM associated with HVA, which could show negative allergy results by routine diagnostics [19, 22].

It is important to remark that the time interval between the sting and sIgE sampling could even constitute a more relevant factor to the level of sIgE in patients with ISM than in patients without mastocytosis, due to only a minority of patients with ISM showing positive sIgE levels after 3 years, while most patients without mastocytosis are still sensitized [23].

Although mastocytosis is a risk factor for both the development of HVA and for more severe SR [23, 24], VIT is usually well tolerated by the majority of patients with underlying systemic mastocytosis [26]. In the largest reported series of patients with HVA and systemic mastocytosis who received VIT, the rate of protection from anaphylaxis after re-sting was 74–86% [25, 26]. Rueff et al. found 11.3% of systemic reactions after a hospital sting challenge test in patients with systemic mastocytosis or basal tryptase ≥ 20 ng/mL [27].

Two patients who suffered from systemic reactions while receiving a standard maintenance dose of 100 mg monthly became fully protected by increasing VIT doses to 200 mg. Experts recommend that they should receive VIT throughout their lives, as they are at greater risk of recurrence once treatment is discontinued [8, 26, 28].

The Spanish network of mastocytosis (REMA): identified 4 clinical elements (male sex, presyncope and/or syncopal episodes, absence of urticaria/angioedema and serum basal tryptase levels >25 ng/mL) as independent predictive factors of cMCAS in patients suffering from insect sting ana-

phylaxis without mastocytosis in the skin [29]. This REMA score was further validated [29]. A value >2 predicts with high efficiency (specificity of 67% and a sensitivity of 92%) the diagnosis of ISM in patients suffering from HVA. The REMA score is a very useful screening tool to select candidates for further bone marrow evaluation.

It is necessary to have further data on another concomitant diseases and their role as risk factors, such as asthma and cardiovascular comorbidities [30].

Treatment Medication: although there is one study which reported angiotensin-converting enzyme inhibitors (ACEI) to confer a higher risk for more severe SSR, there is a growing base of evidence that indicates that ACEI do not increase the risk for severe SSR in untreated patients [31].

Immunological response

Higher specific/total immunoglobulin E (IgE) ratios: Those patients are at higher risk of developing systemic reactions [11]. Specific/total IgE ratios have been established for the assessment of allergic disease due to food, inhalative allergens, and drugs, and have been proposed to be taken into account for the diagnosis of bee venom allergy [32–35].

It has been hypothesized that patients with a higher ratio are more likely to suffer from clinically relevant allergy [32]. In the same line, Arzt et al. showed higher specific/total IgE ratios in patients with clinically relevant vespa venom allergy, compared to participants with asymptomatic sensitization to vespa venom and rVes v 5. Baseline levels of total IgE, sIgE, and specific immunoglobulin G4 (sIgG4) were assessed immediately after the field sting in allergic patients and prior to sting challenges in asymptotically sensitized patients and VIT-treated patients. Then, serological tests were repeated 4 weeks later. Specific and total IgE, rApi m 1, and rVes v 5 antibody levels as well as sIgG4 levels in the patients' sera were measured. Only in VIT-treated patients were the sIgE and sIgG4 levels very stable after bee and vespid sting challenges [35].

Arzt et al. demonstrated low specific/total IgE ratios for bee venom and vespid venom as well as the respective marker allergens in individuals without a history of sting-induced anaphylaxis.

Moreover, sensitization to hymenopteran venom is common, but systemic sting reactions are rare as stated by Sturm et al. [35, 36]. In this elegant study, 131 challenges with bees and wasps were performed in 94 subjects with a previous apparently irrelevant sensitization. The clinical outcome was recorded, and results of specific IgE determinations, skin tests, and basophil activation tests were correlated to the sting reaction. The authors conclude that although sensitization to Hymenoptera venoms was common, the risk of SSRs in sensitized subjects was low. The sIgE level increase after the sting was not an indi-

cator for conversion into symptomatic sensitization. Currently available tests were not able to distinguish between asymptomatic sensitization, large local reactions (LLR), and SSR [36].

Allergen-related risk factors

Type of insect involved: vespid > bee stings

Identification of the insect responsible for the sting reaction can be very useful in establishing the diagnosis, prescribing treatment, and educating patients in avoidance measures. Different insects have different nesting and behavioral characteristics that can be distinct and specific [37].

In addition, identification of the culprit insect is important because it implies different risk factors during the natural history of the disease. In older studies using hospital sting challenges performed in venom allergic patients who had not received VIT, bee venom allergic subjects were at a greater risk of systemic reactions after re-sting than those with vespid venom allergy [38, 39]. Therefore, it has been thought that bee venom allergy is generally more dangerous than vespid venom allergy. However, a European prospective multicenter study observed that vespid venom allergy was an independent predictor of a higher risk at the index field sting [12]. For this reason, the well-known association between bee allergy and more severe systemic reactions could be untrue for field stings. It is possible that less honeybee venom is delivered at a field sting as most sting victims attempt to rapidly remove the stinger, thereby reducing the amount of bee venom delivered [38, 39].

Degree of exposure in beekeepers

Beekeepers represent a unique population of those affected by honeybee allergy. Because of their frequent exposure and higher sting rate, they are thought to be at higher risk for honeybee allergy, which should warrant special attention. There is a significantly higher incidence of systemic reactions among beekeepers than that observed in the general population. Beekeepers receiving more than 200 stings yearly could be protected, although 50 stings per year may also provide benefit [38, 39].

However, an elevated risk for systemic reactions was found in beekeepers with initial stings within the first few years of beekeeping, fewer than 10 annual bee stings, history of atopic disease, and symptoms of upper respiratory tract allergy during work with beehives [38–40].

Reaction-related risk factors

Severity of initial systemic reaction

It is agreed that an initial SSR is more prone to produce a higher risk for future SSR [1, 10]. In patients with a history of systemic reactions to stings, the frequency of systemic reactions to subsequent stings is

correlated with the severity of the previous reactions. In a study using challenge stings, systemic reactions occurred in more than 40% of those with previous severe reactions, but SSR were recorded in only 23% of those with previous moderate systemic reactions and was observed in 17% in of those with mild (cutaneous) systemic reactions [41]. A surprising proportion (up to 30% in several large studies) of people with a history of systemic reaction to a sting have negative venom skin test results. However, many of these individuals have positive serum IgE test results, leaving approximately 15% of history-positive patients with no detectable venom-specific IgE. In sting challenge studies, only approximately 6% of such individuals have a systemic reaction to a challenge sting [41].

Delayed administration of epinephrine

The probability of anaphylactic reactions is increased with delayed administration of epinephrine regardless of the elicitor [42].

Time interval between sting and adverse reaction

A time interval of less than 5 min between sting and adverse reaction is predictive of severe anaphylaxis [43].

Site of the sting

Arzt et al. could not confirm that stings on the head or neck more frequently result in severe SSRs. This was also reported by an Australian study [44, 45].

Risk factors associated with venom immunotherapy

Although the natural history of the disease describes the course without any treatment, it is worth mentioning the different risks associated with immunotherapy, taking into account the efficacy of this type of immunotherapy. In fact, there is agreement in all guidelines about the efficacy of this treatment in patients with systemic allergic reactions.

Type of venom in immunotherapy

There are different risks associated with treatment with bee VIT with respect to vespid VIT. This may be explained by the fact that bee venom consists of more allergen components than vespid venom and also a broader IgE sensitization pattern is observed in bee venom allergy.

The most important risk factor for the occurrence of systemic adverse events is treatment with honeybee venom. It has been consistently reported that there is a 3.1- to 6-fold higher risk for systemic adverse events due to treatment with honeybee venom [1]. In a multicenter European study, one of the most important factors significantly associated with severe reactions during the build-up phase of VIT was bee venom allergy [12].

The reasons why honeybee venom immunotherapy induces systemic reactions more frequently than vespid venom immunotherapy have yet to be fully understood. However, a different sensitization profile in bee allergy patients could be an influence in small sample studies [46].

The effectiveness of honeybee and vespid VIT is different and ranges from 77 to 84% for honeybee venom compared with 91 to 96% for vespid venom [1]. Therefore, the protection rate for bee venom is lower than for vespid venom. The reason for this discrepancy is not yet fully understood. It has been speculated that the amount of venom delivered by a honeybee sting is much larger and more consistent. Recent studies of molecular allergy have shown that relevant allergens to bee venom may be poorly represented in some extracts used for specific immunotherapy [47–49].

Another observed fact is that the patients who were treated with honeybee venom had a higher risk for relapse compared with those who were treated with vespid venom [1]. The risk of systemic reactions after discontinuation of venom immunotherapy for bee was 16% vs 8% of patients treated with wasp venom [50].

Systemic adverse events during VIT

Different publications have reported a remarkable risk of showing a subsequent SSR in 16.4–46% of patients instead of 5.4–8% who did not suffer a systemic reaction [51].

Premedication in VIT

Additionally, there is little data about the natural history and prognosis of patients treated with premedication before VIT. After 180 administered doses, 173 (96.12%) were tolerated without major incidence, 3 (1.67%) induced large local reactions (LLR), 2 mild unspecific reactions (1.11%) and 2 elicited systemic reactions (1.11%). In those 2 patients who suffered systemic reactions, VIT could be continued normally using premedication with antihistamines [52].

There is scarce data about the suitability of premedication before and during VIT (Table 2) and, if available, it is not clearly stated in the available literature whether those patients combined different premedication regimens, except in one publication [52–59].

Specific facts of Hymenoptera hypersensitivity in children

With regard to hypersensitivity in children, there is a sole prospective longitudinal observational study in the literature, nested in the BASELINE Birth Cohort Study ($n=2137$) aiming to explore the natural history of hymenopteran stings in children and adolescents. Sting-related questions were asked at 6 and 12 months and 2 and 5 years. Skin prick testing (SPT) was per-

Table 2 Types of premedications used in VIT

Premedication	Number of patients	Reference
Montelukast 10 mg	15 adults	[53]
Antihistamine (not specified)	2 adults	[52]
Terfenadine	20 adults	[54]
3-day course of oral 20 mg prednisone twice daily, 150 mg ranitidine, and 10 mg loratadine started 2 days before VIT	42 adults	[55]
Omalizumab	1 adult	[56]
	3 children	[57]
	1 adult	[58]
	10 adults	[59]

formed at two time-points, i.e., 2 and 5 years. sIgE testing was performed on selected cases at 2 years. A total of 77 children (6.8%) were stung by the age of 2. Of these, 25 (32.5%) reported adverse reactions (four systemic). Eleven (0.9%) had positive SPT at 2 years (eight bee, two wasp, one both). Four stung children had positive SPT. Two (one stung, one never stung) had positive sIgE to a venom component at 2 years. A total of 268 children (21.9%) were stung by 5 years, 144 (52.1%) reporting local reactions and none systemic. Four children (0.4%) had positive SPT at 5 years: one bee and three wasps. Of the 11 SPT-positive children at 2 years, none were still positive at 5 years. The results warranted the prior hypothesis that hymenopteran venom allergy is less common in this cohort than in adults. Moreover, systemic reactions were not medically documented in this population, in keeping with previous literature [60].

Notwithstanding, HVA in children may impact not only on the patient's health-related quality of life, but also the quality of life (QoL) of the patient's relatives, mainly their parents and caregivers. A cross-sectional study, which comprised the analysis of data from 101 parents of children and adolescents aged 9–17 with a history of SR after IS, referred to tertiary level consultations in 2010–2013. The authors used the Parents of Children with Hymenoptera Venom Allergy Quality of Life Scale (PoCHVAQoLS). The authors conclude that the longest VIT duration in children and adolescents with HVA is related to the decreased anxiety of their parents. In mothers, greater support is related to a greater level of limitations and discomfort [61].

Lange et al. aimed to determine the rate of sting recurrence and natural history of HVA in children not treated with VIT. A total of 219 children diagnosed as having HVA who were not treated with VIT were identified in 3 pediatric allergology centers. The authors performed a telephone survey with 130 patients responding [9].

During the median follow-up period of 72 months, 8 children developed severe systemic reactions (SSRs; 18%) of those who were re-stung. The subsequent reaction was significantly milder ($P<0.001$), especially in the case of patients re-stung by the same insect

($P < 0.001$). None of the children previously diagnosed with large local reactions and negative test results for venom sIgE developed SSRs after being re-stung by the culprit insect ($P = 0.03$). In children with SSRs, median time from diagnosis to re-sting was 2 times longer than that in those with large local reactions and normal reactions ($P = 0.007$). Therefore, the authors concluded that most children with HVA not treated with VIT reported milder reactions after a re-sting [9].

Conclusions

Several risk factors have been proposed, analyzed and stated as showing a greater extent of subsequent higher risk in future stings. Children usually have a better prognosis after being stung by insects but there is a need for further epidemiologic studies, which may create the exact picture of future reactions both in children and adults.

HVA is less common in children than in adults. Children diagnosed with HVA not treated with VIT show milder reactions after a re-sting. There is scarce data with regard the natural history of HVA both in adults and in children. Several risk factors may influence the natural history of HVA, namely patient-related, allergen-related and reaction-related. Other factors are inherent to the use of VIT. Moreover, pre-medication may improve the tolerance of VIT, but only scarce reports dealing with protocols of premedication in VIT are available, so its suitability may be considered with caution.

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