

Epidemiology of Hymenoptera allergy

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Purpose of review

Epidemiology and especially the natural history of Hymenoptera allergy form the background that is essential to improving the clinical management of insect venom allergic patients. This review focuses on the emergence of recent data which could help provide further enlightenment in this field.

Recent findings

The latest data on the extent of the disease, the risk factors for sensitization and for local, systemic and fatal reactions after a hymenoptera sting are reviewed. The emerging problems concerning asymptomatic sensitization, the meaning of constitutively elevated tryptase serum levels and the persisting widespread poor awareness of available therapies in Hymenoptera allergic patients are particularly emphasized.

Summary

The assessment of the risk for systemic reaction in skin-positive subjects with a negative case history, and the suggestion of the baseline serum tryptase level as a risk factor for reaction severity after a sting, are the most important clinical implications of the latest studies. The genetic and environmental factors involved in the persistence of venom specific immunoglobulin E after a sting and the factors which orient towards a systemic or a large local reaction after apparently the same sting remain open questions.

Keywords

epidemiology, hymenoptera allergy, venom hypersensitivity

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Introduction

It is common knowledge that a single Hymenoptera sting can induce an allergic reaction and occasionally fatal anaphylaxis [1,2]. In Europe, the insects responsible belong to the suborder Aculeate, which are essentially made up of the superfamilies of Apoidea (*Apis mellifera*, *Bombus* spp.) and of Vespidae (*Vespula* spp., *Polistes* spp., *Vespa crabro* and *Dolichovespula* spp.). In the United States stinging Hymenoptera also include the fire ant (*Solenopsis invicta*) whose role is becoming of great importance because of its expanding habitat [3]. A sting for sensitive subjects can result in three possible clinical reactions: (1) a large local reaction (local swelling over 10 cm in diameter, which lasts more than 24 h), (2) a systemic reaction, which varies in severity (urticaria, angioedema, bronchospasm, anaphylactic shock) and can lead to death, or (3) a delayed reaction (vasculitis, glomerulonephritis, polyradiculitis). This review focuses on the recent developments in sensitization and large local and systemic reactions to Hymenoptera stings; delayed reactions are extremely rare and do not fall within the scope of this paper.

Insect sting prevalence

Very few data reporting the prevalence of Hymenoptera stings in the general population are available. A study carried out in Italy on 701 conscripts revealed that 56.6% of the interviewees remember being stung by a Hymenoptera insect at least once in their lives [4]. In the general adult population in France and Turkey the percentages are 61–75% and 94.5% respectively [5,6]. Therefore, in countries with a predominantly moderate climate, where the stinging insects are present in the environment for a larger part of the year, over half the population receives a sting at least once in their first 20 years of life and virtually the whole adult population has been stung at least once. In the United States, even more worrying data were obtained in areas endemically infested by fire ants, where 55% of sting victims reported being stung three weeks after their arrival in such areas [3].

Sensitization

The prevalence of sensitization (indicated by a positive skin test or the detection of specific immunoglobulin E in patients with no previous case history) is estimated at between 9.3% and 28.7% in the adult population. Several epidemiological observations indicate that this figure is related to the degree of exposure to stings; in Sweden, where the population is less exposed to Hymenoptera, a lower degree of sensitization is docu-

mented with respect to southern European countries [1,2,7,8].

In specific populations, such as beekeepers, who are exposed to numerous and short-interval stings, the risk of sensitization increases [1,2,9]. The higher prevalence of sensitization in men can likely be accounted for by longer outdoor working hours or recreational activities, which increase the risk of exposure [1,2]. Also, the higher prevalence of sensitization to *Vespula* spp., compared with *Polistes* spp. and *A. mellifera*, in the general population is another factor affected by exposure. Indeed, the *Vespula* spp. manifest aggressive behaviour and a marked tendency to share man's environment, because they are attracted by human foods and garbage. *Polistes* spp. and *A. mellifera*, on the other hand, have different eating habits which interfere very little with man's lifestyle. Moreover, their behaviour is much less aggressive unless they or their nest are disturbed.

A recent paper reporting the low prevalence (3.7%) of sensitization in children seem to contrast with the link between exposure and sensitization [10]. It is commonly held that children are stung more frequently than adults because they spend more time outdoors and are less wary than adults of insects; this figure could, therefore, suggest that nowadays children spend more time indoors. Otherwise, since only 7% of these children with a positive case history had positive skin tests to venoms, a sharp decrease of immunoglobulin E after the sting in childhood or the poor sensitivity of the method used (prick test) could affect the results.

One of the most intriguing open questions concerns the natural history of asymptomatic sensitization, as the risk factors for the first severe reaction or death after an insect sting in subjects, who are usually unaware of their condition, are still unknown [2,11]. The synthesis of specific immunoglobulin E subsequent to a sting is usually transitory. In the first month after a sting over 30% of adults show allergic sensitization. Skin tests become negative in 30% of patients after 2 years and in virtually 50% after three years. A decrease rate of approximately 10% in skin sensitivity occurs in sensitized adults [11]. Indeed, the risk of a systemic reaction increases by 58%, compared with controls, if the first sting-induced reaction has been preceded by a well-tolerated sting within the 2 previous months [12]. Since the frequency of stings is usually low, the majority of patients lose their sensitivity. It has, however, been noted that in a significant percentage (17%) of skin positive subjects with a negative case history, the possibility of a systemic reaction still exists even up to 10 years after the evidence of a positive skin test [11].

The frequency of stings could be one of the key factors; a very short sting interval (or multiple stings) can induce a systemic reaction, thus changing the natural history of the disease from asymptomatic sensitization to Hymenoptera allergy. Otherwise, the absence of further stings for many years cures the condition in the majority of sensitized subjects. Persistent asymptomatic sensitization without an intervening sting probably involves genetic factors, but the cause of prolonged persistence of specific immunoglobulin E after a sting is an unresolved question [13].

Epidemiological studies assessing sensitization to Hymenoptera and atopy, which is the best known genetic factor in allergic patients, provide little insight. Prevalently negative data were obtained on the correlation between rhinitis or allergic asthma and sensitization to Hymenoptera in patients who received only occasional stings, even though a lower threshold response to venom skin tests and a higher level of venom specific immunoglobulin E in atopic than in non-atopic venom allergic patients has been documented. [1,2,7,14]. In atopic individuals an increased risk for the presence of venom specific immunoglobulin E has been reported and a genetic predisposition that enhances the production or the persistence of venom specific immunoglobulin E has been suggested [7,14]. Alternatively, recent results could partially explain the link between atopy and venom immunoglobulin E: carbohydrate determinants present in venoms and inhalant allergens could cause cross-reactivity. This finding has a negligible clinical relevance but could interfere with the results of epidemiological studies when only in-vitro methods are used [15••].

A further aspect was highlighted by one epidemiological study: the difference between the physiopathology in the production of specific immunoglobulin E among inhalant- and venom-allergic patients. In inhalant-allergic subjects specific immunoglobulin E tends to decrease with age while the opposite happens in venom allergic patients. Therefore, age rather than atopy represents a positive risk factor for developing venom sensitisation [7].

In conclusion, the balance between environmental factors (the frequency of stinging), age and genetic factors (the persistence of immunoglobulin E) is responsible for the low prevalence of systemic allergic reactions to stings in the general population (about 3%), despite a high prevalence of sensitization (about 25%).

Large local reactions

The prevalence of large local reactions varies widely in the populations studied and ranges from 2.4% [4],

through 4.6% [8], 18.6% [16] and 26.4% [17] up to 76.6% [6]. In children the prevalence is 19.6% [10] and in beekeepers 38.8% [18]. The causes of such a wide variation are not known; it has been suggested that methodological aspects in the definition of the reaction or the exposure to insects could be involved [8]. Population studies performed in similar environments would seem to underline the above doubts as they reveal a notable difference between similar levels of exposure (16.4% of asymptomatic sensitization in Spain and 28.7% in Greece) and a large difference in the prevalence of large local reactions respectively (26.4% and 4.6%) [8,17].

Various studies have demonstrated that patients with large local reactions tend to have the same type of reaction when re-stung. The risk of developing a systemic reaction on being re-stung is low and varies between 5 and 10% in adults and is 2% in children [19,20]. Paradoxically, in adults the risk of a systemic reaction appears to be lower than that estimated (17%) in asymptomatic sensitized individuals [11]. A recent study performed in Spain confirmed the low risk of systemic reactions in patients with previous large local reactions [17].

Even though epidemiological studies indicate a clear difference in the natural history between large local and systemic reactions the standard methods of diagnosis (the skin test and serum immunoglobulin E level) are not able to discriminate between them. Just how the same stimulus (the venom injection) provokes such different clinical responses will require further investigation. Some initial suggestions are available from studies on immunotherapy [21].

Systemic reactions

The prevalence of systemic reactions after an insect sting is low but the fear of a more severe reaction or a premature death at re-sting can induce a very negative effect on emotional status and social activities of these patients. On the other hand, the availability of very effective immunotherapy returns the vast majority of them to a normal life.

Prevalence

The prevalence of Hymenoptera sting systemic reactions in the general population has been the subject of various studies which estimate the phenomenon to be between 0.15% and 3.3% [1,2,16]. European data gathered in the 1990s confirm the extent of the disease (Table 1). The degree of variability of these figures can essentially be accounted for by two influencing factors, namely the data collection technique and the degree of exposure to stings.

As regards sting exposure, the difference in prevalence in the general population between northern and southern European countries correlates well with the presence of insects in the environment (Table 1) [6–8]. Moreover, the high prevalence of systemic reactions among beekeepers, which falls between 14% and 42%, clearly confirms the important influence of this factor [9,18]. It has been shown, however, that there is an inverse relationship between the number of stings received in 1 year and the prevalence of systemic reactions. This would seem to indicate that spontaneous desensitization is triggered above a certain number of stings per year [9]. The high prevalence of reactions among members of beekeepers' families or non-professional beekeepers, who receive a number of stings greater than the number received by the general population, but less than that of a professional beekeeper, is consistent with this finding [2].

As for the data collection technique, the most used tool is the questionnaire. This approach does present certain significant limits, which were well documented in an epidemiological cross-sectional study performed in France by means of a case history questionnaire administered to different groups of people [5]. Even though the questions were identical, extensive variability, ranging from 0.6 to 3.3%, in the prevalence of systemic reactions was documented [5]. This phenomenon is associated with how the term 'systemic reaction' is interpreted. Greater control over the results of the questionnaire, including the supervision of a medical expert and skin and serological tests to confirm case histories, reduces the prevalence of reactions and gives a picture of the data that is closer to the reality [5].

Table 1. Epidemiological studies in Europe in the 1990s

Study	Country	Prevalence of systemic reactions	Target of the study	Method
1992 Charpin [5]	France	0.6–3.3%	General population	Questionnaire
1995 Björnsson [7]	Sweden	1.5%	General population	Questionnaire and skin test or RAST
1996 Schäfer [14]	Germany	3.3%	Rural area population	Questionnaire and skin test or RAST
1997 Kalyoncu [6]	Turkey	7.5%	Cellulose paper factory	Questionnaire and skin test or RAST
1997 Grigoreas [8]	Greece	3.1%	Hellenic air force	Questionnaire and skin test or RAST
1997 Incorvaia [4]	Italy	2.7%	Conscripts	Questionnaire
1998 Novembre [10]	Italy	0.34%	Children	Questionnaire and skin test or RAST
1999 Fernandez [17]	Spain	2.3%	Rural area population	Questionnaire and skin test or RAST

RAST, radio-allergo-sorbent test

Another way of assessing the extent of the disease is to examine casualty department records. The methodology of such an approach has likewise come under criticism because only the most severe reactions are treated at the casualty department. Moreover, there is no one single International Classification of Diseases-9 code for the diagnosis of insect sting anaphylaxis and, therefore, the risk of underreporting or misdiagnosis is present [22,23•].

A recent retrospective casualty department study in the United States estimated an incidence rate of anaphylactic shock of 21 per 100 000 inhabitants per year [24]. The study revealed that insect-sting-induced anaphylaxis is responsible for 15% of the total number of cases reported and reflects a typical seasonal trend which peaks in summertime, when the presence of insects in the environment is higher [24]. Similar percentages of prevalence of insect sting anaphylaxis in casualty department studies was reported in England (16%) and in Australia (17.5%) [25,26]. A much lower level was documented in Italy (5.8%) but the study was performed in a hospital in the centre of Milan, where the likelihood of being stung is slight. Once again this reinforces the close relationship between exposure and reactions [27].

Risk factors

In the general population, adult age, male sex (male:female ratio, 2:1) and the type of stinging insect (honeybee stings are more dangerous than vespid stings) are well known risk factors for both the occurrence of the first systemic reaction and the recurrence of systemic reactions [1,2]. A specific risk factor for the occurrence of the first reaction is a well-tolerated sting in the previous 2 months [12], while the interval between stings does not seem to be relevant in the recurrence of systemic reactions [2]. A large number of simultaneous stings (>50) may sensitize and then be followed by single-sting anaphylaxis; the majority of people, however, who develop a first-sting reaction have no identifiable risk factors for their allergy.

The most important risk factor for the recurrence of systemic reactions is the severity of the previous one. The disease tends towards a spontaneous self-limitation and the tendency to relapse varies from 21 to 73% but the more severe the symptoms of first reaction the more likely the reaction is to recur [28,29].

The degree of skin reaction and the level of venom specific immunoglobulin E are neither predictive of the re-sting reaction nor of its severity. Moreover, a recent report estimated that vespid allergic patients with a positive case history but a negative skin test have a 22% reaction rate [30•].

Adults are more likely to have re-sting reactions than children. An increased risk for middle age is partially related to comorbidity, especially the presence of cardiovascular diseases and related treatment with beta-blockers or angiotensin-converting enzyme inhibitors [2].

It is well known that mastocytosis, even in non-allergic patients, may predispose subjects to a severe reaction after an insect sting [31]. A recent paper underlines the fact that the baseline high tryptase level, irrespective of a clear clinical manifestation of mastocytosis, represents a new risk factor for an anaphylactic reaction after a sting in allergic patients [32••]. Nine patients out of 12 (75%) with an elevated basal tryptase level experienced a severe reaction subsequent to an insect sting compared with 28 out of 102 (28%) patients with normal tryptase levels. In those 12 patients urticaria pigmentosa was shown only in two and inconspicuous cutaneous lesions of telangiectasia macularis eruptiva perstans in nine [32••].

Atopy is a risk factor for severe reactions in beekeepers [2,18]; in fact the risk of a systemic reaction after bee sting is four times greater in atopic than in non-atopic beekeepers [18]. Moreover, while working at hives, atopic beekeepers develop respiratory allergies to inhalant bee body debris and possibly to venom more easily [18].

Mortality

The incidence of insect sting mortality is low (Table 2), but certainly underestimated [2,6]. At the beginning of the 1980s, a study reported the presence of specific immunoglobulin E to venoms in 23% of the post-mortem sera samples taken from victims between 15 and 65 years of age, who died suddenly and inexplicably between the end of May and the beginning of November [33].

The risk factors for fatal stings include a positive history of Hymenoptera allergy, male sex (men are three times more at risk than women), age over 40 years (probably because of comorbidity with cardiovascular diseases), the sting site (head or neck) and bee sting [1,2]. It must be

Table 2. Fatalities following Hymenoptera sting

Country	Fatalities/1 000 000 inhabitants/year
USA	0.16
Australia	0.10
Denmark	0.25
France	0.48
Germany	0.18
Italy	0.03
England	0.09
Switzerland	0.45

pointed out, however, that around 40% of the victims had no positive case history for previous reactions [2,11]. This may be partly explained by the lack of reliable information provided by the victims' relatives but other factors, connected to the last tolerated sting and the persistence of asymptomatic sensitization, might also be involved [11,12]. Increasing evidence points to the possible role of urticaria pigmentosa and subclinical mastocytosis as another risk factor [32,34].

In conclusion, the insect sting mortality rate is low compared with other causes. At least half of these deaths in patients with a positive case history, however, could have been avoided through specific immunotherapy.

General awareness of available treatment

The rate of avoidable deaths is regarded as a marker of the effectiveness of the health service. Indeed, the series of epidemiological studies conducted throughout Europe in the 1990s revealed the startling lack of awareness of the potential opportunities of specific immunotherapy. Not one of the patients who took part in the surveys, in very different countries (Sweden, Germany, France, Spain, Greece and Turkey) [2,6,7,8,14,17] received the proper treatment, confirming the persisting gap between available therapy and medical practice already emphasized in previous papers [2]. Nor does the pharmacological treatment of anaphylaxis appear to adhere to the provided guidelines [35]. One study carried out in Britain documented that adrenaline was not administered to 29 out of 32 fatal insect sting induced anaphylaxis patients, while in the remaining patients it was given only after respiratory or circulatory arrest [36]. A report from Australia confirms the poor management of venom allergic patients. Five out of seven victims of vespid sting fatalities were perfectly aware of their condition, but they were never treated with immunotherapy nor did they carry an adrenalin kit with them [37]. In conclusion the epidemiological studies document the wide persistence of a cultural risk factor which should have been virtually eradicated many years ago.

Conclusion

Epidemiological studies allow us to constantly broaden our knowledge of Hymenoptera allergy. In particular, over the last year the value of elevated baseline tryptase level for anaphylactic reactions has been highlighted. Future studies should focus on the natural history of the disease to provide a fuller understanding of the risk factors and the correct targeting of available therapies. Moreover, and no less important, studies continue to show the persistent lack of awareness of available therapies, thus indicating the urgent need to educate the general population and doctors on the management of venom allergic patients.

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