

Investigation of the factors that determine the severity of allergic reactions to Hymenoptera venoms

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ABSTRACT

Introduction: Many risk factors that facilitate venom allergy and increase systemic reaction severity have been described in various studies, but the data are limited regarding this issue. We aimed to evaluate the impact of total immunoglobulin E (tIgE), specific IgE, and tryptase levels on the severity of systemic reactions in patients with a history of allergic reactions to Hymenoptera stings.

Method: Eighty-two patients with a history of allergic reaction to Hymenoptera venom admitted to our outpatient clinic between March 2016 and August 2017 were included. Venom-specific IgE (*Apis mellifera* and *Vespula vulgaris*), total IgE, and basal tryptase levels were measured. Skin-prick tests were performed with inhalant allergens. The levels of specific IgE, total IgE, and tryptase were compared between patients with large local reactions and systemic reactions, and the relation of these parameters with the severity of systemic reaction was evaluated.

Results: There were no significant differences in the specific IgE, total IgE, and tryptase values in patients with large local reactions and a history of systemic reactions ($p > 0.05$). The age, basal tryptase, and *V. vulgaris*-specific IgE levels of patients with a grade IV reaction history were higher than those with grades I–III reaction history ($p < 0.05$). An important finding was that high basal tryptase levels were a risk factor for grade IV reactions ($p = 0.047$, $\chi^2 = 4.512$). There was a strong positive correlation between total IgE levels and *V. vulgaris*- and *A. mellifera*-specific IgE values in patients with a grade IV reaction history ($r = 0.94$, $p = 0.005$; and $r = 0.88$, $p = 0.021$, respectively).

Conclusion: Baseline serum tryptase levels were a risk factor for the development of severe systemic reactions in venom allergy. This risk increases with increasing age in these patients. Another notable finding was the correlation between total IgE and venom-specific IgE values in patients with severe systemic reactions.

(Allergy Asthma Proc 40:116–122, 2019; doi: 10.2500/aap.2019.40.4191)

Insect sting anaphylaxis is one of the common immunoglobulin E (IgE) mediated disorders; 94.5% of humans experience Hymenoptera stings at least once throughout their lives.¹ Although typical local reactions mostly occur after Hymenoptera stings, large local reactions occur in 5–15% of cases and systemic reactions result in 3–8.9% of cases; 10% of these may be life-threatening. Even if the first bee sting is tolerated well, repeated stings within 2 months of the first increase the risk of systemic reactions by 58%.² In patients with a history of systemic reaction, the probability of recurrent systemic reaction is ~40–60%. In addition, the risk of anaphylaxis with subsequent stings in those with large local reactions is ~4–10%.¹

Allergic reactions to Hymenoptera stings can be large local or systemic. The causes for these different

reaction patterns are not completely understood.³ Systemic reactions to venom stings may vary broadly, from skin involvement to shock. Several studies have been conducted to identify risk factors for the development of systemic reactions and to predict their severity. Severe systemic reactions are significantly associated with elevated baseline serum tryptase levels, which indicate an elevated whole-body mast cell load.⁴ An atopic constitution may influence symptoms of systemic allergic reaction, there is no evidence of an increased prevalence of large local reactions and systemic reactions in individuals who were atopic.⁵

The influence of total IgE levels on systemic reaction severity has been analyzed in two studies.^{4,6} In a recent study, it was observed that total IgE and honey bee venom-specific IgE levels were significantly lower in patients with grade IV reactions than in lower-severity grades.⁴ Although it is well known that the presence of venom-specific IgE is significantly associated with a history of systemic reaction to Hymenoptera stings, a tendency for a lower venom-specific IgE level in patients with severe systemic reaction has also been described.⁶ Therefore, we aimed to evaluate whether specific IgE, total IgE, and baseline serum tryptase levels were risk factors in patients with a history of Hymenoptera venom allergy. It is our suggestion that if one

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This study was funded by the Scientific Research Projects Office of Necmettin Erbakan University (161218013).

The authors have no conflicts of interest to declare pertaining to this article
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of these factors is found to be influential in the severity of systemic reaction, it may serve as a guide to physicians in the monitorization of Hymenoptera venom allergy cases and in planning treatment.

METHODS

The study was planned as a prospective cohort study. Eighty-two patients who presented to the Division of Immunology and Allergic Disease outpatient clinic, Meram Faculty of Medicine, Necmettin Erbakan University, between March 1, 2016, and August 1, 2017, with a history of large local and systemic reactions associated with Hymenoptera venom were included in the study. Patients with a history of venom allergy and who were referred to our clinic were asked to complete a venom allergy evaluation form to evaluate the type and severity of the developing reaction. Redness and swelling > 10 cm that lasted for >24 hours was evaluated as a large local reaction. The severity of systemic reactions was evaluated according to the Ring and Messmer classification.⁷ All the subjects gave their written informed consent, and the local ethics committee, Faculty of Medicine, Necmettin Erbakan University, Turkey, approved the protocol (2016/425).

Evaluation of Atopy

We investigated the presence of atopy by using the following indicators: history of atopic diseases and/or positive prick test reactions to common inhalant allergens. Skin-prick tests were performed by using a standard panel, including inhalant allergens: house-dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), grass pollen mix (*Dactylis glomerata*, *Lolium perenne*, *Phleum pratense*, *Poa pratensis*, *Festuca pratensis*), tree mix (*Alnus glutinosa*, *Betula verrucosa*, *Corylus avellana*), *Artemisia vulgaris*, *Chenopodium album*, *Alternaria alternata*, *Blattella germanica*, *Felis domesticus*, *Canis familiaris*, and latex (ALK-Abello, Horsholm, Denmark). A wheal of 3 mm in diameter larger than the negative control was considered a positive result.

Serum Venom-Specific IgE, Total IgE, and Baseline Tryptase Measurement

Sera drawn for the evaluation of venom allergy were stored in a freezer at -80°C under suitable conditions until required for analysis. In the laboratory of our department, total IgE, venom (*Apis mellifera* and *Vespa vulgaris*) specific IgE antibody levels, and baseline tryptase levels were measured by using the CAP fluoroenzyme method (ImmunoCAP Tryptase, Unicap 100; Phadia, Uppsala, Sweden). The patients were divided into three groups according to their total IgE levels: group 1, <50 kU/L (mild level); group 2, 50–250 kU/L (moderate level); and group 3, >250 kU/L (high

level).⁶ In the evaluation of specific-IgE values, the CAP classification (class 0, 1, 2, 3, 4, and ≥ 5) was used. Specific-IgE antibody values of >0.35 kUa/L were considered positive results. The detection limit was <1.0 $\mu\text{g/L}$ for the measurement of tryptase; levels of 11.4 $\mu\text{g/L}$ (95th percentile of the general population) and higher were considered to be elevated.

Statistical Analysis

Statistical analyses were conducted by using the SPSS version 21 statistical software package (SPSS, Inc., Chicago, IL). Whether the variables were distributed normally was evaluated with visual (histogram and probability graphics) and with analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). In this respect, comparisons between groups were made by using the Mann-Whitney U test. Total IgE and specific-IgE values were compared between the patients with large local reactions and those with systemic reactions. In addition, the relationship between the severity of reaction (grades I–III and grade IV) and age, baseline tryptase levels, and atopy was investigated by using the Wilcoxon signed rank test. A $p < 0.05$ was considered statistically significant in all results. In the evaluation of factors that could be a risk factor in the development of grade IV reactions, (total IgE and specific IgE, baseline tryptase, age, and sex), logistic regression analysis was used.

RESULTS

The clinical and laboratory characteristics of the 82 patients included in the study are presented in Table 1. There were no significant differences between patients with large local reactions and those with systemic reactions in terms of venom (*A. mellifera* and *V. vulgaris*) specific IgE, total IgE, and baseline tryptase values ($p = 0.05$, $p = 0.08$, $p = 0.7$, and $p = 0.8$, respectively). Interestingly, there was a significant difference with regard to the frequency of atopic diseases between systemic reactions and large local reactions (10/60 [83.3%], and 9/22 [40.9%], respectively; $p = 0.02$). In terms of the severity of systemic reactions to Hymenoptera venom, 22 patients (36.7%) were grade I, 19 patients (31.7%) were grade II, 13 patients (21.6%) were grade III, and 6 patients (10%) were grade IV. The most frequently reported symptoms were urticaria-angioedema in 61.7%, followed by dyspnea in 33.3%; syncope in 26.7%; hypotension in 21.7%; itching, erythema, and urticaria-like skin rashes in 16.7%; palpitations in 15%; laryngeal edema in 11.7%; nausea and vomiting in 8.3%; incontinence in 5%; and cardiopulmonary arrest in 6.7%.

Baseline tryptase and *V. vulgaris*-specific IgE values were found to be higher in patients with a history of grade IV reactions than in those with a history grades

Table 1 Clinical and laboratory characteristics of patients with systemic and large local reactions

	Systemic Reaction (n = 60)	Large Local Reaction (n = 22)
Age, mean $\pm$ SD, y	40.7 $\pm$ 13.5	39.04 $\pm$ 11.7
Men/women, no.	32/28	8/14
History of atopic diseases, no.	10	9
Asthma	5	1
Allergic rhinitis	2	1
Drug allergy	2	5
Chronic urticaria and/or angioedema	1	2
Skin-prick test positivity with inhalant allergens, no./total no.	4/52	4/14
Species of Hymenoptera, no.		
<i>Apis mellifera</i>	22	2
<i>Vespula vulgaris</i>	19	13
Unknown	19	7
Time between sting and laboratory examination, median (min, max), mo	24 (1, 360)	24 (5, 300)
Specific IgE level of ≥ 0.35 kUa/L, no.		
<i>A. mellifera</i>	18	3
<i>V. vulgaris</i>	26	5
Both	32	5
<i>A. mellifera</i> -specific IgE, no.		
Class 0	42	19
Class 1	5	0
Class 2	10	2
Class 3	2	1
Class 4	1	0
<i>V. vulgaris</i> -specific IgE, no.		
Class 0	34	17
Class 1	8	2
Class 2	11	1
Class 3	6	2
≥ 5	1	0
Total IgE level, median (min, max), kUa/L	26.9 (2, 2420)	19.6 (3.97, 1011)
Tryptase level, median (min, max), μ g/L	2.1 (1, 9.53)	1.9 (1, 8.06)

SD = Standard deviation; min = minimum; max = maximum; IgE = immunoglobulin E.

I-III reactions (Figs. 1 and 2). The *V. vulgaris*-specific IgE to total IgE ratio was significantly higher in patients with a history of grade IV reactions than in patients with a history of grade I-III reactions (mean $\pm$ standard deviation, (9.8 $\pm$ 1.3)% versus (4.6 $\pm$ 1.1)%). There was no difference in the *A. mellifera*-specific IgE to total IgE ratio between the groups.

In addition, the mean age of the patients with grade IV reactions was found to be higher than that of patients with grades I-III systemic reactions (Table 2). Skin-prick test positivity to common inhalant allergens was not different in patients with grade IV reactions than in patients with grades I-III reactions ($p = 0.5$). In addition, we found no significant difference between patients of grade IV and grades I-III in terms of atopic diseases ($p = 0.24$). In patients with a history of grade

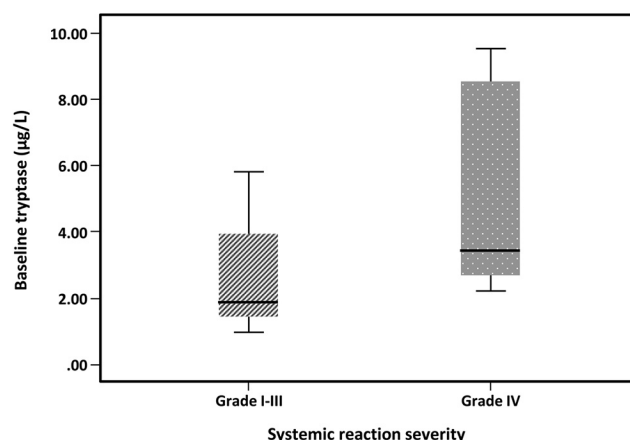


Figure 1. Baseline tryptase levels according to the severity of reaction.

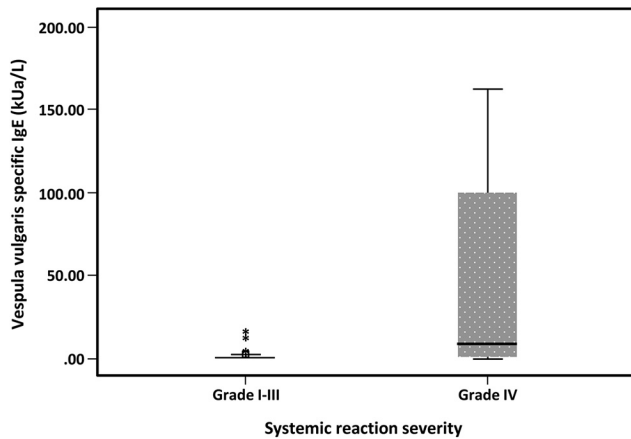


Figure 2. *Vespa vulgaris*-specific immunoglobulin E (IgE) levels according to the severity of reaction.

IV reactions, a strong positive correlation was found between total IgE values and *A. mellifera*- and *V. vulgaris*-specific IgE values ($r = 0.94$, $p = 0.005$; and $r = 0.88$, $p = 0.021$, respectively).

Tryptase and Reaction Severity

In the logistic regression model, it was established that high baseline tryptase levels were a risk factor for grade IV reactions ($p = 0.047$, $\chi^2 = 4.512$) (Table 3).

Age and Reaction Severity

Age was not found to be a risk factor for grade IV reactions; however, in the Wilcoxon signed rank test, age was found to be higher in patients with a history of a grade IV reaction than in those with a history of a grade I-III reaction ($p = 0.02$) (Tables 2 and 3).

The Effect of Total IgE and Specific-IgE Values on Reaction Severity

There was no relationship between mild-moderate and high-level total IgE values and grade IV reactions ($p = 0.1$). In addition, classified or unclassified venom-specific IgE values were found to have no significant effect on the development of grade IV reactions ($p = 0.4$, $p = 0.2$, $p = 0.5$, $p = 0.09$) (Table 4).

DISCUSSION

Allergic reactions to Hymenoptera venom are among the most common causes of anaphylaxis of individuals who present to emergency services worldwide. The annual incidence of venom-associated immunologic reactions around the world is between 0.3 and 7.5%. Each year, 100 million cases of Hymenoptera venom reactions are reported, with severity ranging from local reactions to death.^{7,8}

In the development of life-threatening reactions, the identification of patients at risk has clinical importance. Various risk factors have been described for severe

anaphylaxis in the literature. To date, three major risk factors have been defined: (1) patients with mastocytosis with or without high tryptase levels, (2) patients with high tryptase levels without mastocytosis, and (3) elderly patients. In this context, the individual mast cell load may have an important role. Mast cells are key in the development of early type allergic reactions. It has been reported that both the activity and number of mast cells have a positive correlation with the severity of allergic reactions.^{9,10} The mast cell load of the body may be reflected by baseline serum tryptase concentrations and has been used by various investigators to characterize Hymenoptera venom allergy.¹¹⁻¹⁵ It has been observed that patients with high baseline tryptase levels experience more severe allergic reactions than those with normal levels.^{13,14}

Interestingly, in recent studies, it has been shown that, even in patients without mastocytosis, increased tryptase levels may be a risk factor for allergic reactions. In the study of Haeberli *et al.*,¹¹ it was reported that baseline serum tryptase levels were high in 7.3% of patients with venom allergy. Similar results were obtained in the study of Kucharewicz *et al.*,¹⁵ who established that baseline tryptase levels were high in 11% of patients allergic to bees or wasps. Moreover, a significant correlation was found between baseline serum tryptase levels and the severity of reaction in both studies.

However, there are some limitations to the above-mentioned studies, such as being conducted at a single center and with few patients. In the multicenter study by Rueff *et al.*,⁹ it was demonstrated that, in life-threatening Hymenoptera venom allergies, the baseline serum tryptase level was an independent risk factor. In addition, it was found that even slight increases in baseline tryptase levels considerably increased the severity of systemic reactions.¹⁶ In another study, conducted with an elderly population, high tryptase levels were found to be a risk factor for the development of severe anaphylaxis, and it was concluded that they could be useful in guiding venom immunotherapy.³

In patients with high tryptase levels and without mastocytosis, it was seen that more severe and frequently cardiovascular anaphylaxis developed.¹⁷ Therefore, both America and Europe consensus recommends that, in all patients with a history of systemic reaction to Hymenoptera venom, baseline tryptase levels should be measured.^{8,18} Similarly, in the present study, it was established that high baseline tryptase levels were a risk factor for grade IV reactions; tryptase levels were higher in patients with grade IV reactions than in patients with grades I-III reactions.

It can be seen in the literature that various risk factors facilitate venom allergy and increase the development of systemic reactions.⁵ A history of systemic reactions, a short time period between two stings,

Table 2 The analysis of the relation between severity of reaction and age, baseline tryptase value, and total and venom-specific IgE values*

Grade IV vs Grades I–III	Age	Baseline Tryptase Value	Total IgE Value	<i>Apis mellifera</i> –specific IgE Value	<i>Vespula vulgaris</i> –specific IgE Value
<i>p</i>	0.02#	0.03#	0.3	0.8	0.01#

IgE = Immunoglobulin E.

* Wilcoxon signed rank test.

$p < 0.05$.

Table 3 Logistic regression analysis of the relationship between the severity of systemic reactions and age, sex, and baseline tryptase, total IgE, and venom-specific IgE values

Variable	DF	<i>p</i>	χ^2
Age	1	0.247	1.215
Sex	1	0.179	0.005
Tryptase value	1	0.047*	4.512
Total IgE value	1	0.840	0.999
<i>Apis mellifera</i> –specific IgE value	1	0.490	2.109
<i>Vespula vulgaris</i> –specific IgE value	1	0.228	1.610

IgE = Immunoglobulin E; DF = degree of freedom.

* $p < 0.05$.

Table 4 Logistic regression analysis of the relationship between severity of reactions and age, sex, and baseline tryptase, grouped total IgE, and classified venom-specific IgE values

Variable	DF	<i>p</i>	χ^2
Age	1	0.177	1.101
Sex	1	0.249	0.029
Tryptase value	1	0.067	2.867
<i>Apis mellifera</i> –specific IgE value*	1	0.528	1.832
<i>Vespula vulgaris</i> –specific IgE value*	1	0.090	4.053
Grouped total IgE value#	1	0.196	3.784

IgE = Immunoglobulin E; DF = degree of freedom.

* Specific IgE CAP classification (class 0, 1, 2, 3, 4, and ≥ 5).

Group 1: <50 kU/L; group 2: 50–250 kU/L; group 3: >250 kU/L.

beekeeping, being elderly, and cardiovascular diseases are among these risk factors.¹⁸ The presence of atopy might also influence systemic allergic symptoms.^{19,20} Currently, there is no evidence that the presence of atopy increases the risk of systemic reactions.²¹ An atopic constitution is found with similar frequency in patients with Hymenoptera venom allergies and in the general population.²² We found no significant difference between patients with mild-moderate reactions and those with a history of severe systemic reactions in terms of atopy. Interestingly, there was a significant difference with regard to the frequency of atopic dis-

eases in the history of systemic reactions compared with a history of large local reactions.

Atopy is frequently associated with an increase in total serum IgE levels. An elevated total serum IgE level is not an appropriate marker of atopy because it can be demonstrated in numerous nonatopic conditions.²³ The total IgE level is not used at present as an additional parameter in the diagnosis of venom allergy.⁶ Further, it is not higher in patients with venom allergy than in the general population. In a retrospective study by Przybilla *et al.*,²³ it was reported that patients with a total IgE level of ≥ 100 kU/L experienced less-severe systemic reactions than

those with a total IgE level of ≤ 100 kU/L, but the groups with a high total IgE level were younger and it was concluded that the results might also have been influenced by age.²³

In a study conducted in Austria, it was found that patients with venom allergy and a total IgE level of ≥ 250 kU/L experienced less-severe reactions, whereas those with a total IgE level of ≤ 50 kU/L experienced more-severe systemic reactions.⁶ In our study, no effect of total IgE levels or mild-moderate and high total IgE levels on severity of systemic reaction could be demonstrated. However, a strong positive correlation was found between total IgE values and *A. mellifera*- and *V. vulgaris*-specific IgE values in patients with a history of grade IV reactions. This can be explained as follows: in patients with known IgE-mediated diseases, the total IgE level is constituted, to a considerable extent, by allergen-specific IgE antibodies.²³ A total IgE value is a nonspecific marker, and studies with larger patient groups are required to determine whether it is a risk factor in venom allergy.

There are not enough studies in the literature on the relationship between venom-specific IgE values and the severity of systemic reactions. Patients with lower venom-specific IgE levels were reported to experience more-severe reactions.⁴ This result indicated that, although the presence of venom-specific IgE is associated with a history of systemic reactions, it is not related to reaction severity. However, in our study, *V. vulgaris*-specific IgE values were found to be higher in patients with severe systemic reactions and were determined to be risk factors in its development. Otherwise, the *V. vulgaris*-specific IgE to total IgE ratio was significantly higher in patients with a history of grade IV reactions than in patients with a history of grades I–III reactions.

Allergic reactions, which range from skin involvement only to life-threatening reactions, occur after Hymenoptera stings. However, the causes of the varying reaction patterns are not fully understood. Skin reactions characterized by urticaria, angio-oedema, and generalized pruritus occur more frequently than in patients with normal baseline tryptase levels than in those with elevated tryptase.¹⁷ Large local reactions have long attracted the attention of physicians because they are reported to be probable risk factors in subsequent Hymenoptera stings. The reason why large local reactions develop in some patients and systemic reactions develop in others has yet to be clearly explained.

Similarly, in the present study, our findings did not suffice to answer this question. Interestingly, we found that age, baseline tryptase levels, the rate of atopy, and total IgE and venom-specific IgE levels revealed no differences between patients with systemic reactions and those with large local reactions. There are few data on the epidemiologic and clinical aspects of this issue. In a case series that included 3500 patients, mean age

and the rate of atopy was found to be significantly higher in patients with systemic reactions than in those with large local reactions, and the proportion of patients who were monosensitized was found to be higher in the groups with local reactions. In those with grade IV reactions, the number of patients with total IgE levels of ≥ 250 kUa/L was found to be lower than in the grades I–II and local reaction groups.⁵

CONCLUSION

In Hymenoptera venom allergy, high baseline serum tryptase levels were a risk factor for the development of severe systemic reactions. In these patients, risk increased in parallel to advancing age. In addition, there was a correlation between total IgE and venom-specific IgE values in patients with severe systemic reactions. The determination of risk factors in the development of systemic reactions to venom allergens is important in that it may guide the selection of patients for venom immunotherapy.

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