

Use of sIgE/T-IgE in Predicting Systemic Reactions: Retrospective Analysis of 54 Honeybee Venom Allergy Cases in North China

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Abstract

Background: Venom allergy is significantly underestimated in China. Venom-specific IgE may not provide accurate clinical reactions. Our conducted retrospective analysis observes alternative diagnostic considerations in assessing confirmation and severity of honeybee venom allergy.

Methods: Retrospective review of honeybee venom allergy versus nonallergy patients presented with positive honeybee venom (i1) sIgE results. According to clinically observed reactions caused by a honeybee sting, patients were divided into three groups. Patient residence and exposure types were analyzed. The sIgE/T-IgE among allergy and control groups was compared.

Results: Gender ratio male:female was 32:22; median age was 39 years (31, 50). 48% (26/54) of patients live in urban areas, 52% (28/54) in rural areas. Based on bee sting reactions, patients were divided into common localized reactions (32/54), large localized reactions (7/54), and systemic reactions (15/54). In the systemic reaction group, patients presented as Type II (6/15), Type III (6/15). There is significant difference ($P < 0.001$) between the three groups in regards to exposure types. In the systemic reaction group, 8.7% (13/15) of patients are beekeepers. A significant difference ($P < 0.001$) was observed between allergic and control groups based on sIgE/T-IgE results. As well as significant difference observed between the systemic reaction group to the other two reaction groups in regards to sIgE/T-IgE results. Six systemic reaction patients presented with large localized reactions before onset of system symptoms 1 month to 1 year of being stung.

Conclusions: Occupational exposure is the most common cause in honeybee venom allergy induced systemic reactions. The use of sIgE/T-IgE results is a useful diagnostic parameter in determining honeybee venom allergy.

Key words: Honeybee Venom Allergy; Localized Reaction; Systemic Reaction

INTRODUCTION

The *Hymenoptera* are the third largest orders of insects comprising bees, wasps, and ants, whose sting are among one of the major three causes of anaphylaxis, the other two being food and drug-induced anaphylaxis. Allergic reactions to *Hymenoptera* stings include common localized, large localized, and systemic reactions. European data share prevalence of large localized and systemic reactions to *Hymenoptera* stings in the general population as 20% and 1–5%, respectively.^[1] Systemic reaction incidence to *Hymenoptera* stings in beekeepers is as high as 14–43%,^[2,3] sourcing honeybee venom allergy as dominant. In Europe, over 100 people die from *Hymenoptera* venom-induced anaphylaxis annually.^[4]

Routine venom allergy diagnostics include skin or serum tests detecting venom-specific IgE antibodies,^[5,6] predisposed to a confirmed positive history of allergic reactions. Venom-specific IgE indicates positive in approximately 20% of normal adults, and about 40% in adults with recent bee stings,^[7] however, with low predictive value in assessment of severity.^[8]

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Literature shared positive prediction of sting reactivity through allergy specific activity (the allergen-specific IgE to total IgE ratio; sIgE/T-IgE analysis) involving extensive effector cell activation along with allergen-specific IgE antibody's concentration, affinity (tightness of binding), clonality (epitope specificity) observations.^[9]

We retrospectively analyzed 54 cases to investigate the use of sIgE/T-IgE in predicting honeybee venom allergy systemic reactions in northern Chinese population.

METHODS

Subjects

Retrospectively analyzed fifty-four diagnosed honeybee venom allergy cases treated at the Department of Allergy, Peking Union Medical College Hospital (PUMCH). According to clinical manifestations posthoneybee sting, placed patients with positive honeybee allergy into the allergy group and then subcategorized into three groups: common localized reaction, large localized reaction, and systemic reaction group. Control group comprised patients treated at PUMCH for other allergic disorders presenting with positive serum sIgE to honeybee venom but without a history of honeybee stings.

Diagnosis standard

Clinical history of allergic reactions after honeybee stings, and positive result of skin prick test, or serum specific IgE (sIgE) to honeybee venom present diagnosis.^[10] Since no commercial honeybee venom extracts available for skin tests in China, we measured serum honeybee venom sIgE to evaluate sensitivity instead.

Serum IgE measurement

All serum total IgE and honeybee venom sIgE tests were finished with ImmunoCAP system (Pharmacia, Uppsala, Sweden) in clinical allergy laboratory of PUMCH. This licensed laboratory regularly participates in an external proficiency survey. sIgE levels ≥ 0.35 kUA/L is positive.

Classification of honeybee venom allergic reactions

Honeybee venom allergic reactions classified into common localized skin reactions, large localized reactions, and systemic reactions. Common localized skin reaction is defined as redness or swelling around the sting site. Large localized reaction is swelling exceeding a diameter of 10 cm lasting longer than 24 h.^[11] With systemic reactions, the skin, gastrointestinal, respiratory, and cardiovascular systems may be involved. Systemic reaction severity is classified into four grades based on the Ring and Messmer standard [Table 1].^[11,12]

Study design

Demographic characteristics of enrolled patients were reviewed, recording information regarding age, gender, clinical manifestations, serum total IgE, sIgE level and other coexisting allergic disorders, such as allergic rhinitis, allergic asthma, atopic dermatitis, food allergy, and drug allergy. Details of allergic reactions to honeybee venom, including local reaction size, duration, and involvement

Table 1: Severity grading of systemic anaphylactic reactions

Grade	Skin	Abdomen	Respiratory tract	Cardiovascular symptoms
I	Itching Flush Urticaria Angioedema	-	-	-
II	Itching Flush Urticaria Angioedema	Nausea Cramps	Rhinorrhea Hoarseness Dyspnea	Tachycardia (increase ≥ 20 /min) Hypotension (decrease ≥ 20 mmHg systole) Arrhythmia
III	Itching Flush Urticaria Angioedema	Vomiting Defecation	Laryngeal edema Bronchospasm Cyanosis	Shock
IV	Itching Flush Urticaria Angioedema	Vomiting Defecation	Respiratory arrest	Cardiac arrest

of other systems were investigated. If other systems were involved, relevant symptoms, treatment, and outcome of patients were recorded. The correlation between severity of allergic reactions and possible influencing factors include residence region, profession, venom exposure types, and patient IgE specific activity (sIgE/T-IgE) were analyzed. Venom exposure types were classified into (1) natural exposure (hiking), (2) occupational exposure (beekeeper), and (3) iatrogenic exposure (honeybee apitherapy).

Statistical analysis

All the analyses were performed using SPSS version 22.0 (SPSS; Chicago, Illinois, USA). Descriptive data for categorical and numerical variables were expressed as frequencies and means with standard deviations for normally distributed variables or as medians with interquartile ranges in parentheses for the nonnormally distributed variables. Group comparisons were established using rank-sum test for ranked data and Fisher's exact test for categorical variables. Bonferroni method was used to do multiple comparisons among groups (differences were considered statistically significant at $P < 0.05$. While Bonferroni method was used and the number of comparisons was N , differences were considered statistically significant at $P < 0.05/N$).

RESULTS

From 2011 to 2015, 54 patients were enrolled in the allergy group [Table 2]. 67% (36/54) of patients came from North China, including Beijing, Tianjin, Hebei, Shanxi and Inner Mongolia.

Based on the severity of allergic reactions after honeybee stings, patients were divided into three groups: common localized reactions (32/54), large localized reactions (7/54), and systemic reactions (15/54).

In the systemic reactions group, 6/15 were classified as Grade II and 6/15 were Grade III according to Ring and Messmer standard [Table 3].^[11] Six cases only showed large localized reactions when they were stung before, but they developed systemic reactions when they were re-stung after 1 month to 1 year.

Honeybee venom exposure types

Allergy group presented with three channels of honeybee venom exposure: natural exposure, occupational exposure, and iatrogenic exposure [Table 4]. According to Fisher's exact test, there is a significant difference between exposure types ($P < 0.0001$). Using Bonferroni method for multiple comparisons, there was no difference between common localized and large localized reaction group ($P = 0.5900$). However, there was significant difference between the common

Table 2: Fifty-four patients were enrolled in the allergy group

Property	Value
Male:female	32:22
Median age, years, median (Q1, Q3)	39 (31, 50)
Residence, % (n/N)	
Urban	48 (26/54)
Suburb	52 (28/54)
Coexisting allergies, % (n/N)	
Allergic rhinitis	52 (28/54)
Allergic asthma	35 (19/54)
Food allergy	13 (7/54)
Drug allergy	2 (1/54)
Atopic dermatitis	2 (1/54)

Table 3: Frequency and classification of systemic reactions (n = 15) according to Ring and Messmer

Classification	Symptoms	Frequency (n)
Grade I	Generalized skin symptoms (e.g., flush, generalized urticaria, angioedema)	2
Grade II	Mild-to-moderate pulmonary, cardiovascular, and/or gastrointestinal symptoms	6
Grade III	Anaphylactic shock, loss of consciousness	6
Grade IV	Cardiac arrest, apnea	1

Table 4: Correlation between severity of allergic reactions and honeybee venom exposure types (n)

Group	Natural exposure	Occupational exposure	Iatrogenic exposure
Common localized reactions	26	4	2
Large localized reactions	5	1	1
Systemic reactions	2	13*	0

*Beekeepers indicate a high systemic reactions due to frequent direct occupational exposure. Due to this, they are highly trained and familiar with treatments to common localized/large localized reactions hence often do not seek immediate medical attention.

localized and systemic reaction group ($P < 0.0001$), and between large localized and systemic reaction group ($P = 0.0021$). Natural exposure was the most common cause in common/large localized reaction groups, and occupational exposure was more common in systemic reaction group.

Serum sIgE (i1) results

Serum honeybee venom sIgE level in four groups: common localized reactions 1.62 (1.15, 3.87), large localized reactions 2.56 (1.85, 10.74), systemic reactions 13.56 (4.04, 41.95), and control 1.57 (1.07, 4.22). Serum honeybee venom sIgE level ranged from 0.71 kUA/L to 15.2 kUA/L in control group. Statistically significant difference was found among the four groups ($\chi^2 = 16.926$, $P = 0.001$) [Figure 1].

Statistical difference was observed between systemic reactions group and common localized reactions group ($Z = 3.515$, $P < 0.001$) or between systemic reactions group and control group ($Z = 3.646$, $P < 0.001$), but not found between systemic reactions group and large localized reactions group ($Z = 1.657$, $P = 0.098$), between large localized reactions group and common localized reactions group ($Z = 1.354$, $P = 0.176$), between large localized reactions group and control group ($Z = 1.527$, $P = 0.127$), or between common localized reactions group and control group ($Z = 0.346$, $P = 0.730$).

SigE/T-IgE

The IgE specific activity (sIgE/T-IgE) was 0.55% (0.19%, 1.67%) in the common localized reaction group, 1.42% (0.65%, 5.54%) in the large localized reaction group, 15.39% (5.87%, 23.81%) in the systemic reaction group, and 0.16% (0.09%, 0.49%) in the control group. There was significant difference among the IgE specific activity of the four groups ($\chi^2 = 37.491$, $P < 0.001$) [Figure 2].

After multiple comparisons, results showed that the IgE specific activity was significantly higher in the systemic

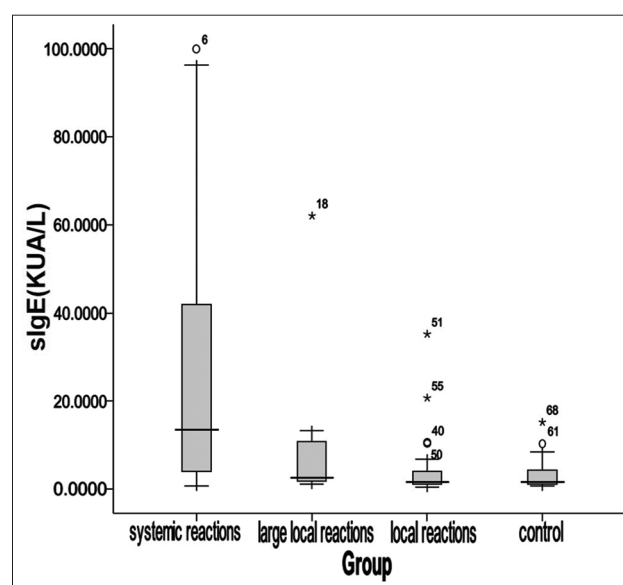


Figure 1: Comparison of sIgE among different allergy and control groups.

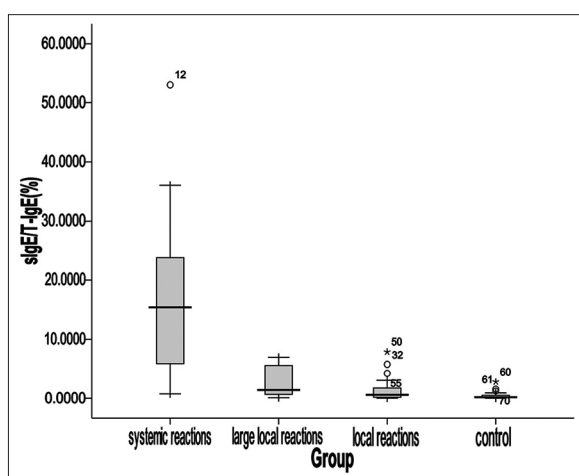


Figure 2: Comparison of the IgE specific activities among different allergy and control groups.

reaction group than the IgE specific activities in common localized reaction group ($Z = 4.907$, $P < 0.001$), large localized reaction group ($Z = 2.643$, $P = 0.0082$), and control group ($Z = 5.099$, $P < 0.001$). Statistically significant difference was also found between common localized reaction group and control group ($Z = 2.702$, $P = 0.007$), but not between large localized reactions group and common localized reactions group ($Z = 1.317$, $P = 0.188$), or between large localized reactions group and control group ($Z = 2.439$, $P = 0.015$).

DISCUSSION

According to literature, there are more than 2000 beekeeping enterprises, thousands of beekeepers and over 8 million honeybee colonies in China. Within recent 10 years, the development of tourism created millions of travel enthusiasts in China. Both beekeepers and travel enthusiasts are at high risk to honeybee stings and are susceptible to venom allergy. This study indicates that 87% (13/15) of patients with systemic reactions were beekeepers, suggesting that occupational exposure was the most common cause of systemic reactions to honeybee venom in China. Beekeepers are more likely to be stung resulting with more serious reactions requiring close attention. Our study indicated that nearly half of honeybee venom allergy patients lived in cities far from rural area, however, were exposed to honeybees during travel to rural surroundings for work or tourism. Hence, concluding outdoor tourism might be an important cause of venom allergy.

The use of honeybee venom in chronic inflammatory disease treatment, especially arthritis was reported. Kim *et al.*^[12] shared bee venom therapy in treatment of complex regional pain syndrome. Our study 6% (3/54) allergy subjects were iatrogenic exposure, indicating cautious consideration of apitherapy.

Diagnosis of honeybee venom allergy depends on clinical history, venom extract skin test, and/or venom sIgE test.

Without a history of the previous allergic reaction after being stung, positive skin test, and/or venom-specific IgE are not enough to give the diagnosis. Sun *et al.*^[13] measured serum sIgE to 16 kinds of allergens in 320 children with respiratory disorders in Guangzhou and found 0.94% children had positive sIgE to honeybee venom. In this study, the highest sIgE in control group is 15.2 kUA/L, but this patient had no history of honeybee sting. Some studies^[14,15] investigated the ones who had positive venom sIgE but without honeybee sting history and found that the ones having positive venom sIgE usually had high total IgE. This kind of asymptomatic sensitization to venom may be caused by cross-reacting carbohydrate determinants, which exist in many plant allergens.

To discriminate real venom allergy from cross-reactions, Hamilton *et al.*^[16] recommended differentiation using IgE specific activity (specific IgE to total IgE ratio). If sIgE/T-IgE ratio increases, sIgE density increases closer to the residues closer to each other on the surface of effector cells. After allergen re-exposure, the probability of inflammatory factors released from activated effector cells will increase. Johansson *et al.*^[17] reported for IgE-specific activities greater than 4%, currently recommended Xolair[®] dosage has limited effect on allergen sensitivity. Hamilton *et al.*^[16] found the ratio of sIgE/T-IgE exceeded 4% in 54% of *Hymenoptera* venom allergy patients. This study suggests IgE specific activity was 15.39% (5.87%, 23.81%) in the systemic reaction group, which was significantly higher than IgE specific activities in large localized reaction group 1.42% (0.65%, 5.54%), common localized reaction group 0.55% (0.19%, 1.67%) and control group 0.16% (0.09%, 0.49%). Our results indicate the severity of allergic reactions in venom allergy patients directly correlates to IgE specific activities, and this ratio may provide accurate information for diagnosis than serum sIgE.

In all kinds of allergic reactions, systemic reactions are most severe. Patients with a history of anaphylaxis may result in anaphylactic shock when re-exposed. Long-term care includes patient education (allergen avoidance, course of action on re-sting) and an emergency kit prescription. The emergency kit includes epinephrine (intramuscular auto-injection; EpiPen), and patients should be instructed to carry it at all times. Venom immunotherapy has been established as specific treatment for *Hymenoptera* venom allergy patients in developed countries. According to data, specific immunotherapy maintenance dose of 100 μ g prevented a systemic reaction in 75–95% of patients who were stung again. Higher maintenance dose provides better effect.^[1] Whether patients with large localized reactions need venom immunotherapy are controversial, but Severino *et al.*^[18] pointed 5–10% patients with a history of large localized sting reaction develop systemic symptoms when re-stung. This study also indicates that after large localized sting reactions, six patients developed systemic reactions 1–12 months later when re-stung. Patients with large localized reactions also require close follow-up and equipped with an emergency kit.

This study initially concludes the clinical characteristics of honeybee venom allergy patients in North China, and influencing factors of severe allergic reactions, providing helpful information for diagnosis and treatment of honeybee venom allergy in Chinese patients. However, limitations exist due to the small sample size and single testing method. In the future, we may enlarge sample size and develop new diagnostic tools, to facilitate appropriate diagnosis and treatment.

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Conflicts of interest

There are no conflicts of interest.

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