

Insect venom hypersensitivity: experience in a clinical immunology/allergy service in Singapore

BY H Thong, K P Leong, H H Chng

ABSTRACT

Introduction: To study the profile of patients with allergy to the venom of insect stings.

Methods: 31 consecutive cases referred to our clinical immunology/allergy outpatient service from June 1, 1998 to June 30, 2002 were reviewed.

Results: These patients comprised 3.5 percent of 889 cases referred during the study period. Their mean age was 28.8 ± 10.5 (range 19-57) years and the majority were males (90.3 percent). Of these, 20 (64.5 percent) were Chinese, four (12.9 percent) were Malays and seven (22.6 percent) were of other races. 19 patients (61.3 percent) were men from the uniformed services including 12 (63.2 percent) full-time National Servicemen. 71 percent (22 patients) were stung for the first time. Urticaria (22 cases, 71.0 percent), dyspnoea (13, 41.9 percent), angioedema (12, 38.7 percent) and syncope (ten, 32.3 percent) were the most common manifestations of insect allergy. Anaphylaxis occurred in 22 (71.0 percent) cases, constituting 30.1 percent of all cases of anaphylaxis referred to our service during the study period. Although the causative insect was identified as honeybee (12, 38.7 percent), ant (four, 12.9 percent), wasp (three, 9.7 percent), and fire ant (two, 6.5 percent) by the majority of patients, ten (32.2 percent) patients were unable to identify the causative insect. The two patients stung by fire ants were Americans working in Singapore who had been stung while in the United States. Among those with anaphylaxis, honeybee, wasp and fire ant venom, for which specific immunotherapy is available, were identified as the cause in 40.9 percent, 4.5 percent, and 4.5 percent, respectively.

Conclusion: Insect venom hypersensitivity made up 3.5 percent of allergy/immunology referrals and 32.8 percent of cases of anaphylaxis referred to our institution. The majority were military

servicemen who developed allergic reactions during the course of duty. The inability to identify the causative insect in 50 percent with stinging anaphylaxis limits the role of specific immunotherapy in our patients.

Keywords: anaphylaxis, insect venom, radioallergosorbent test, skin tests, specific immunotherapy

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INTRODUCTION

Insect venom hypersensitivity is often an immunoglobulin (Ig) E-mediated allergic reaction to the venom of stinging insects belonging to the order Hymenoptera, which includes bees, wasps and ants. The diagnosis rests on two criteria: a definitive clinical history that temporally associates an allergic reaction with an insect sting, and the detection of venom specific IgE on mast cells in the skin and/or blood of the individual by using a confirmatory skin test or serological assay⁽¹⁾. The most commonly implicated insects are the honeybee (*Apis mellifera*), yellow jacket wasp (*Vespula germanica*) and paper wasp (*Polistes annularis*). Stinging ants which cause anaphylaxis include the red and black fire ants (*Solenopsis invicta* and *Solenopsis richteri*, respectively) in the United States, and *Pachycondyla chinensis* in Korea⁽²⁾. The reaction following an insect sting may range from a mild local reaction, large local reaction to systemic reaction including urticaria, angioedema and life-threatening anaphylaxis. There have been no local studies on the patterns of insect venom allergy in Singapore. The aim of this study was to describe the demographical characteristics, occupational profile, clinical and laboratory features of patients with allergy to the venom of insect stings.

METHODS

31 consecutive patients referred to our clinic over a four-year period from June 1, 1998 to June 30, 2002 were reviewed. Clinical characteristics, occupation,

Department of
Rheumatology,
Allergy and
Immunology
Tan Tock Seng
Hospital
11 Jalan Tan
Tock Seng
Singapore 308433

B Y H Thong,
MBBS, MRCP
Consultant

K P Leong,
MBBS, FRCP
Senior Consultant

H H Chng, MBBS
MMed, FRCP
Senior Consultant
and Head

Correspondence to:

Dr Bernard
Thong Yu Hor
Tel: (65) 6357 7822
Fax: (65) 6357 7837
Email: bernard_thong@
tsh.com.sg

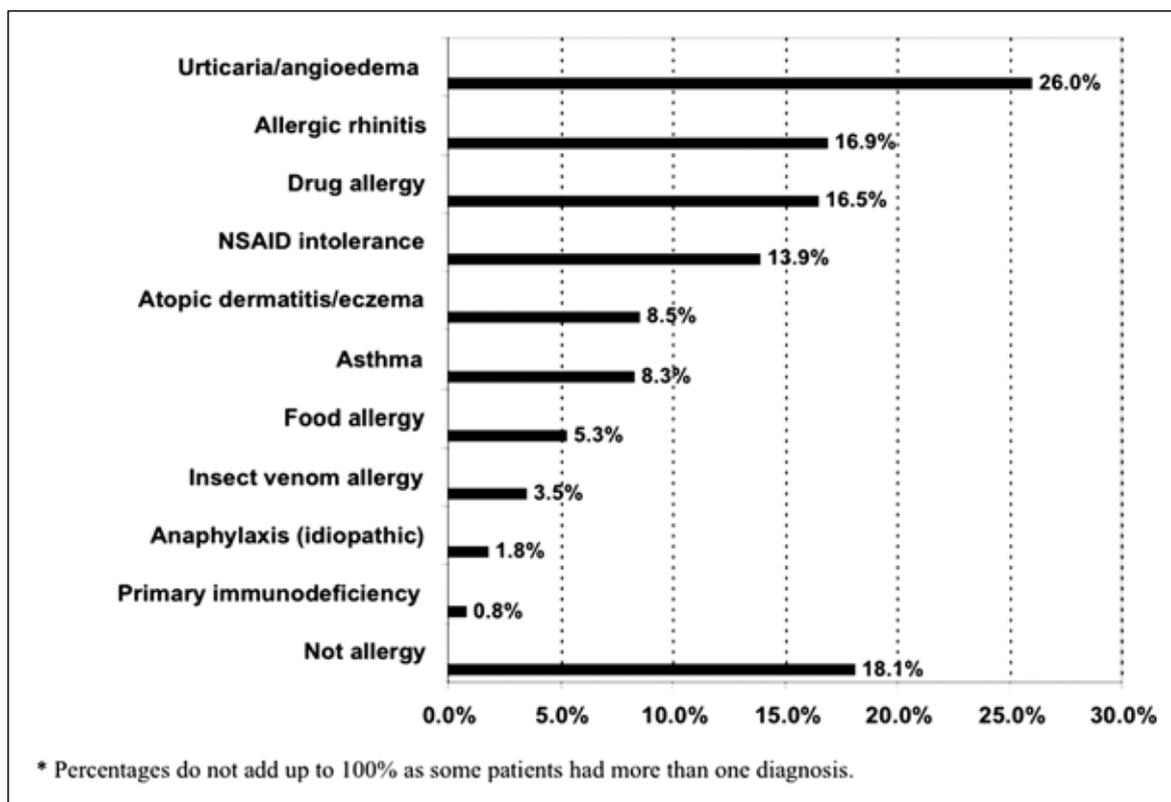


Fig. 1 Pattern of referrals to the clinical immunology/allergy clinic (n=889).

the manifestations and severity of the allergic reactions, and the type of stinging insect were recorded. Venom-specific IgE to honeybee and wasp were measured using the CAP system fluorescein enzyme immunoassay (FEIA, Pharmacia®, Uppsala, Sweden), a sensitive, quantitative, capsulated, hydrophilic carrier polymer method. A positive test was defined as CAP specific IgE ≥ 0.7 kU/L. Recombinant venom extracts for skin testing were not available locally for honey bee and wasp. However, the results of skin prick and intradermal tests of two patients from the United States to fire ant venom were available.

RESULTS

31 consecutive patients were seen during the study period. This comprised 3.5% of 889 cases referred to our clinical immunology/allergy outpatient service (Fig. 1). The mean age of the patients was 28.8 ± 10.5 (range 19-57) years. The majority were males (28 cases, 90.3%). There were 20 (64.5%) Chinese, four (12.9%) Malays, and seven (22.6%) of other racial denominations. 19 patients (61.3%) were men from the uniformed services including 12 (63.2%) full-time National Servicemen.

71 percent (22 patients) developed the allergic reaction after being stung for the first time. Urticaria (22 cases, 71.0%), dyspnoea (13, 41.9%), angioedema

(12, 38.7%) and syncope (ten, 32.3%) were the most common manifestations of insect venom allergy. Anaphylaxis, defined as a severe life-threatening systemic IgE-mediated hypersensitivity reaction, occurred in 22 (71.0%) cases, among which recurrent episodes occurred in eight (38.4%) patients before patients first sought treatment. Insect venom anaphylaxis constituted 32.8% of all cases of anaphylaxis referred to our service during the same period, with other causes being food allergy (44.8%) and idiopathic (22.4%). The remaining nine patients developed large local reactions, urticaria and/or angioedema without any other major organ involvement.

The implicated insect was identified from the patient's description and photographs of stinging insects from an on-line atlas available in the allergy clinic. Although the implicated insect was identified as honeybee (12, 38.7%), ant (four, 12.9%), wasp (three, 9.7%), and fire ant (two, 6.5%) by the majority of patients, 32.2% of patients were unable to identify the causal insect. The two patients stung by fire ants were Americans working in Singapore, who had been stung while in the United States. Among those with anaphylaxis, honeybee, wasp and fire ant venom, for which venom specific immunotherapy (SIT) is available, were identified as the cause in 40.9%, 4.5%, 4.5% of cases, respectively.

Table I. Correlation between visual identification of the putative insect and outcomes of venom-specific IgE measurements.

Insect	No. of patients who identified putative insect visually	No. tested for venom specific IgE	No. positive for honeybee specific IgE (%)	No. positive for wasp specific IgE (%)
Honeybee	12	12	5 (41.7)	4 (33.3)
Wasp	3	2	0 (0)	0 (0)
Unknown	10	7	2 (28.6)	2 (28.6)

Only six (19.4%) patients had a personal history of atopy: two had asthma, three had allergic rhinitis and one had both. Four (12.9%) patients had a family history of atopy while three had a family history of insect venom allergy. Venom-specific IgE was positive for honey bee in seven of 14 cases (50.0%) tested and for wasp in eight of 14 cases (57.1%) tested. Among the patients with anaphylaxis, venom-specific IgE was positive for honeybee in four of ten cases (40.0%) tested and for wasp in five of ten cases (50.0%) tested. Correlation between visual identification of the insect and outcomes of venom specific IgE measurements are summarised in Table I.

The two patients from the United States with fire ant venom allergy had positive skin prick tests (SPT) with a mean wheal diameter 3mm more than the negative control, using 1mcg/ml fireant venom extracts *S. invicta* and *S. richteri*. All patients were given self-injectable adrenaline (Epipen®) for emergency use, and educated on methods of sting avoidance. One patient who was started on SIT from overseas for fire ant anaphylaxis continued her SIT. None of the patients who had a consistent history of insect venom anaphylaxis and positive venom-specific IgE opted for SIT. All military servicemen were exempted from field training by their commanders.

DISCUSSION

The prevalence of insect (hymenoptera) venom systemic sting reaction varies with the geographical locality, seasonal peaks in summertime, data collecting techniques, and the degree of sting exposure. Prevalence rates from Europe are reported to range from 0.15-3.3%, whereas prevalence rates from emergency department studies in the United States and Australia have been reported as 15% and 17.5%, respectively⁽³⁾. There have been no prevalence studies that we are aware of from South-east Asia where one would expect year-round risk of exposure to insect stings in view of the tropical climate. Although hymenoptera hypersensitivity comprised 3.5% of referrals and 32.8% of anaphylaxis evaluated by our service, the prevalence is probably higher as local or mild cutaneous reactions are probably

managed by primary care physicians. Most insect stings are associated with local reactions, including pain, swelling and redness, which are self-limiting. However, systemic reactions can lead to potentially life-threatening manifestations in 0.4% to 0.8% of children⁽⁴⁾ and 3% of adults⁽⁵⁾. Large local reactors have a 5%-10% risk of subsequently developing a systemic reaction if re-stung.

Risk factors for the occurrence of the first systemic reaction and recurrence of systemic reactions include adult age and male sex⁽⁶⁾. Predisposing risk factors for severe sting reactions include mastocytosis, atopy⁽⁷⁾, and a previous severe reaction⁽⁸⁾. Neither the size of the skin test nor the level of venom-specific IgE predicts the severity of a subsequent reaction. Although fatalities from insect stings are probably low and have been reported to range from 0.03 to 0.48 fatalities per million inhabitants per year⁽³⁾, this is probably underestimated. The risk factors for fatal stings include a positive history of sting allergy, male sex, age over 40 years (probably because of comorbid cardiovascular disease), sting site (head or neck) and bee sting⁽⁶⁾.

Most of the patients in our series were young men from the uniformed services. This pattern is likely to be peculiar to Singapore as all male Singapore citizens are required to serve full-time National Service (NS) when they reach 18 years of age. This period may be served in the armed forces, police or civil defence force. Hence, training in the outdoors, in particular jungles and forests, poses an occupational risk to these servicemen. There have been no studies showing a predominance of insect venom hypersensitivity in military/uniformed servicemen although 56% of conscripts from western studies have recalled being stung at least once in their lives⁽⁹⁾.

The diagnosis of hymenoptera venom hypersensitivity is based on a definitive clinical history that temporally associates an allergic reaction with an insect sting and the detection of venom specific IgE in the skin and/or blood of the individual by using a confirmatory skin test or serological assay. Correct identification of the implicated insect helps in subsequent avoidance measures, and the use of antihistamines and

Epipen® (self-administered epinephrine) is crucial in the management of acute systemic reactions. SIT is the definitive treatment for the prevention of future systemic reactions.

However, limitations in the diagnostic tests for venom allergy have resulted in difficulties with clinical interpretation and assessment for suitability of SIT. Up to 30% of adults with clinically determined severe systemic reactions have been shown to be skin test negative. Recent recommendations suggest concomitant in-vitro testing for venom-specific IgE⁽¹⁰⁾ as some patients may have negative intradermal skin tests at 1mcg/ml venom and yet have detectable venom-specific IgE in their blood. Possible reasons for these include better diagnostic sensitivity of some specific IgE assays compared to commercial skin testing reagents, and antibodies to cross-reacting carbohydrate determinants from oligosaccharide side chains of unrelated plant and insect glycoproteins which may result in “falsely elevated” venom-specific IgE results⁽¹¹⁾. Conversely, some patients with a consistent clinical history of venom allergy may have negative venom-specific IgE in their blood and negative skin tests. Possible reasons for these include an allergic reaction resulting from other aetiologies, incorrect identification of the putative insect, occult mastocytosis, or other non-IgE mediated mechanisms for the systemic reaction.

In our centre, serological assays for venom specific IgE have been used in the diagnosis of insect venom allergy rather than skin testing because the latter is not commercially available locally. The CAP FEIA system is a widely used, commercially available, second generation serological assay approved by the US Food and Drug Administration. It has been documented to perform well in detecting honeybee venom specific IgE antibody when moderate levels (>5ng/ml) are present in the serum (sensitivity and specificity of 96%-98%)⁽¹²⁾. In our series, there appeared to be little correlation between in-vitro testing and the visual identification by the patient, possibly because of incorrect visual identification of the putative insect.

Although sting challenges would be able to determine the clinical sensitivity of these patients with inconsistent blood/skin test results, such challenges are not feasible for clinical use, for ethical and logistic reasons and due to variable reproducibility⁽¹³⁾. Novel in-vitro basophil flow cytometry (CD63, CD203c) based assays, and in-vitro basophil histamine and sulfidoleukotriene release assays may have clinical utility in such cases although they presently remain as supplementary, secondary diagnostic tests⁽¹²⁾.

Allergen SIT is a form of desensitisation recognised by the World Health Organisation for the treatment of insect venom anaphylaxis, allergic rhinitis and asthma⁽¹⁴⁾. It involves administering gradually increasing quantities of an allergen extract to an allergic subject to ameliorate the symptoms associated with subsequent exposure to the causative allergen. This form of therapy induces tolerance via T cell anergy, and switching the immune system from TH2 (allergic-inflammation) to TH1 (non-allergic inflammation) mediated cytokine responses⁽¹⁵⁾. SIT for honey bee, wasp, fire ant, and recently other non-fire ant species particularly in Australia⁽¹⁶⁾, have been found to be effective. In insect venom anaphylaxis, SIT reduces the risk of a subsequent systemic sting reaction to less than 3% (i.e. confers 97% protection) compared to the risk of a systemic reaction in untreated patients, which may be as high as 60%. Patients on SIT also generally experience milder systemic reactions, if any, after a sting^(17,18).

Patients must show evidence of IgE sensitisation to the venom, preferably through the demonstration of positive skin prick and/or intradermal skin tests or venom specific IgE in the blood, before they can be considered for SIT. Currently, four quite different treatment schedules with variations in the duration and frequency of injections during the initial induction or “build-up” phase are used in specialised centres. The main regimens are termed conventional (induction phase comprising weekly incremental doses for outpatients over 12-14 weeks), rush (induction phase over 4-7 days for inpatients), ultrarush (the maintenance dose is reached within 1-2 days), or cluster (a modified rush approach, which involves giving several injections at 15- to 30-minute intervals during the first visits and reaching a maintenance dose in about 6 weeks)⁽¹⁹⁾. In rush protocols, patients receive higher doses of venom in a shorter time period and thus reach the maintenance dose of 100 mcg of venom extract faster than in conventional schedules. This might be of great importance when patients present too soon before the onset of the flying season of insects, in highly sensitised patients at high risk of life-threatening stings. Injections during the maintenance phase are then given once every four weeks during the first year, then every 6-8 weeks during subsequent years. The duration of therapy is for 3-5 years, by which time, the patient should be able to tolerate subsequent stings with no or minimal systemic reactions.

From the limited data of patients followed-up beyond seven years while off immunotherapy, the incidence of systemic reactions to a sting appears

to remain as high as 10% after 5-13 years of stopping treatment, regardless of the repeat skin test result, as venom-specific IgE and skin tests become negative in only 25% after five years of SIT⁽²⁰⁾. It has recently been shown that SIT in children leads to a significantly lower risk of systemic reaction to stings even ten to 20 years after treatment is stopped, and this prolonged benefit is greater than the benefit seen in adults⁽²¹⁾.

However, systemic reactions during the initial phase of treatment have been reported to occur in up to 17.8% – 67.3% of cases, the large disparity due to varying definitions of these adverse reactions. This is especially so in patients with asthma, on beta-blockers or angiotensin converting enzyme (ACE) inhibitors. Further limitations include commitment in time needed (frequent visits during the induction phase) and expense.

Approximately 3% of individuals may not respond to SIT. The risk of relapse after completion of SIT is higher in honey bee allergic patients and those who developed a systemic reaction to a sting or injection during SIT. Some of these problems, including costs, decreasing compliance from both patients and clinicians and inconveniences from conventional schedules, may be overcome using more rapid schedules although safety data have been inconsistent⁽²²⁾.

Presently, SIT is not offered routinely to all our patients with insect venom anaphylaxis. Firstly, only 45.4% of patients developed anaphylaxis following honeybee and wasp stings, the only two commercially-available recombinant venoms in this region. Secondly, the seemingly low prevalence of insect venom hypersensitivity in the Far East and Asia Pacific has made the import of these products expensive. However, SIT may be considered on a case-by-case basis especially if there is an occupational risk, avoidance is difficult or health-related quality of life is considerably impaired⁽²³⁾. Military servicemen with insect venom anaphylaxis, who may otherwise be fit to continue military duties, may benefit from SIT, thus allowing them to continue in their military vocations^(24,25). However, the benefits of SIT have to be balanced with the inconvenience posed to servicemen on active duty, which has been found to be a major reason for non-compliance in a previous study of SIT in military servicemen⁽²⁶⁾.

In conclusion, insect venom hypersensitivity comprised 3.5% of referrals and 32.8% of anaphylaxis evaluated by our service. The majority of patients were military servicemen who developed allergic reactions during the course of service. The inability to identify the causative insect in 50% of cases with sting

anaphylaxis limits the role of SIT. Given the expense of SIT locally, we propose that SIT be offered on a case-by-case basis especially if avoidance is difficult.

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