INSECT VENOM ALLERGY

Dr Bernard Thong

Insect venom allergy is an IgE-mediated reaction to a single sting from a stinging insect. This is in contrast to toxic envenomation, which refers to a reaction due to multiple (usually 4 or more) stings. Adults who have developed an allergic reaction to insect stings have a 30-70% risk of a systemic reaction to a subsequent sting if untreated. There is a 5-10% risk of subsequent systemic reaction in large local reactors.

Properties of insect venom

Insect venom contains vasoactive, haemolytic and neurotoxic substances, all of which contribute to the clinical picture in allergic and toxic reactions. Venom allergens, which are all proteins, most of them enzymes, contain highly potent sensitizing substances which trigger the allergic reaction, eg. phopholipase A2 in the honey bee.

Stinging insects

Stinging insects belong to the order Hymenoptera.

The family, *Vespidae* include the yellow jacket, hornet and wasp. The yellow jackets are ground-dwelling insects which sting with minimum provocation and are often found in the vicinity of food. The hornets are very aggressive. Wasps are often found in honeycomb nests in dark areas.

The family, *Apidae* include the honeybee and bumblebee. The honeybee may be domestic or wild and has a characteristic barbed venom. Recently, bumblebees have been widely used in the agricultural industry in pollinating greenhouse plants. Bumblebee sting allergy is rare but has been reported.

BERNARD THONG, MBBS, MRCP(UK)
Registrar, Department of Rheumatology, Allergy & Immunology, Tan Tock Seng Hospital

Stinging ants

Stinging ants also belong to the order Hymenoptera. The clinically important stinging ant in venom allergy is the fireant. They are often found in mounds and fresh soil in south-eastern United States. The characteristic of the sting is a sterile pustule. More than 80 deaths from anaphylaxis have been reported.

Mosquito bite hypersensitivity

Although local reactions are common, severe reactions including necrotic local reactions associated with haemophagocytic syndrome and NK cell leukemia have been reported in orientals. Serum sickness and anaphylaxis are rare with less than 100 cases reported. Risk factors for severe reactions include immunodeficiency (HIV), young children and visitors to an area with 'new exposure' to indigenous mosquitoes. The natural history of mosquito bite hypersensitivity is that of decreasing reactivity over time.

THE PRIMARY CARE APPROACH TO VENOM ALLERGY

1. HISTORY

a. Identification of the insect: aids to this include
   i. patient's activity eg. cutting a hedge
   ii. location of the patient and type of insect activity in the area
   iii. characteristic of sting eg. stinger (bees), sterile pustule (fireant)
   iv. visual identification of insect.

b. Type of reaction
   i. local reaction – mild and self-limiting
   ii. large local reaction
      - may be an IgE-mediated late phase reaction
      - 5%-10% risk of a systemic reaction.

iii. systemic reaction
– manifest at sites remote from sting
– potentially life-threatening
– immediate type hypersensitivity (up to 4 hours after a sting)
(a) cutaneous (urticaria and angioedema)
(b) bronchospasm, wheezing
(c) nausea, vomiting
(d) anaphylactic shock
– delayed hypersensitivity (> 4 hours after a sting)
(a) serum sickness
(b) vasculitis
(c) neuritis, encephalitis
(d) glomerulonephritis.

c. Concurrent medical illnesses/ medications
i. concurrent illnesses: the elderly, concurrent ischaemic heart disease and cerebrovascular disease may be at risk of myocardial infarction and stroke during anaphylaxis (prolonged hypotension).
ii. concurrent atopy: frequency of sting reactions do not differ but skin test positivity may be higher
iii. concurrent medications
(a) may mask the progression of an allergic reaction eg. anti-histamines, cough suppressants
(b) may prolong anaphylactic shock/ antagonise drugs used in resuscitation eg. anti-hypertensives, b-blockers.

d. Risk factors for venom allergy
i. occupation eg. National servicemen, agricultural, horticultural industry
ii. hobbies eg. outdoor activities
iii. multiple stings
iv. repeated stings in close proximity only weeks apart.

2. PHYSICAL EXAMINATION

a. Airway
– tachypnoea, stridor, rhonchi
b. Breathing
– tachypnoea, stridor, rhonchi
c. Circulation: signs of anaphylactic shock
– hypotension, tachycardia, flushing, generalised erythema
d. Cutaneous – urticaria, angioedema
e. Site of sting – sterile pustule, stinger.

3. INVESTIGATIONS

Principle: These must be used together with the history of the reaction.

a. In-vitro testing
– RAST (radioallergosorbent test) for honey bee, hornet, common wasp specific-IgE
– Correlate with skin testing in 85%-95% of cases
– Advantages: where there are medical contraindications to skin testing:
i. inability to discontinue medications that interfere with skin testing eg. antihistamines
ii. severe uncontrolled atopic dermatitis or generalized skin disorder
iii. severe dermatographism
iv. history of life-threatening anaphylaxis to particular antigens when alternative in-vitro tests may be safer.
– Limitations:
i. less sensitive compared to skin testing
ii. positive in only 80% of those with positive skin test.

– Test result: reported as Class 0-VI (negative to positive) for venom-specific IgE.

b. Skin testing
– Stinging insect venom/ whole body extract.
– Indication: Anyone over 16 years old with a history of a systemic reaction where immunotherapy is being considered.
– Caveats
  i. Venom testing should be deferred for 3 weeks or more after the sting
  ii. Children 16 years old and under with a history of a systemic reaction limited to the skin do not require skin testing or immunotherapy.
– Advantages
  i. most specific
  ii. convenient
  iii. least expensive.
– Limitations
  see medical contraindications to skin testing above.
– Positive test: 3 mm wheal/5 mm erythema in the presence of a positive histamine control and a negative saline control, implies presence of venom specific IgE.

4. MANAGEMENT

a. Immediate management
  i. Resuscitation
    (a) Airway
    (b) Breathing
    (c) Circulation
    (d) Drugs (S/C EPINEPHRINE, I/V BENADRYL OR PROMETHAZINE)
  ii. Symptomatic treatment eg. cold compress, local anaesthetic cream, oral antihistamine/ analgesics
  iii. Remove stinger (honeybee) by flicking/ scraping with fingernail
  iv. Antibiotics generally not required.

b. Further management
  i. General education on avoidance
  (a) Personal
    - clothes – long pants, long-sleeved shirts, socks, shoes, hats, gloves when outside
    - avoid brightly-coloured clothing or strong-scented lotions
    - walk outside with shoes
    - use of insecticides/ repellents.
  (b) Home and the environment
    - evaluation of home/ extermination of nests
    - caution near bushes, eaves, attics, sources of food.
  ii. Symptomatic treatment: oral antihistamines prn for 3-5 days.
  iii. Review in 2-3 days for resolution of symptoms/ signs.
  iv. Inform patient to return for early review (clinic or emergency department) if
    (a) urticaria progressively increases over the next 8-12 hours
    (b) angioedema or
    (c) signs of anaphylaxis develop.
  v. Prognosis: fate of individuals with a history of venom allergy on subsequent stings unpredictable and variable. Only 30% - 60% adults with sting allergy have systemic reaction during sting challenge. Children with cutaneous reaction have 10%

subsequent incidence of systemic reaction and 0.4% incidence of respiratory or circulatory symptoms.

c. Disposition
   i. Inpatient treatment: refer to hospital emergency department immediately if there are systemic symptoms/ anaphylaxis for:
      (a) further resuscitation and/or observation
      (b) evaluation by an allergist:
      - systemic reaction to an insect sting
      - anaphylaxis with insect sting as a possible cause
      - education of avoidance/ emergency treatment
      - venom immunotherapy (VIT)
      - co-existing condition that may complicate treatment of anaphylaxis eg. b-blockers, hypertension, cardiac arrhythmias
      - patient requests for a consultation.
   ii. Outpatient treatment (by the family physician)
      (a) local reactions (including large local reactions)
      (b) review in 2-3 days for resolution of rash.
   iii. Outpatient referral (to an allergist)
      In the event that a previous reaction(s) need to be evaluated eg. National servicemen.

5. VENOM IMMUNOTHERAPY

a. What is venom immunotherapy (VIT)?
Administering increasing doses of venom that stimulates the body's own immune system to become resistant (tolerant) to an allergic reaction.

b. What are the indications?
Insect venom anaphylaxis with positive skin tests.

The decision to administer VIT must be individualized ie. medical, financial, logistic factors.

It is not indicated in cases of:
i. local, toxic or delayed reactions
ii. children with urticaria, angioedema, flushing, pruritus

It is controversial in cases of severe systemic reactions, skin test negative at 1.0 mcg/mL but in-vitro test for venom-specific IgE positive.

c. What is the mechanism of action?
The allergen (venom) triggers the immune system to produce a variety of cytokines called interleukins (IL) and specific IgG4 (blocking antibodies). There are 2 patterns of cytokine production: TH1 and TH2 which are produced by TH1 and TH2 CD4+ T cells respectively. TH2 cells are allergic disease "promoters" whereas TH1 cells are allergic disease "inhibitors".

In VIT, it is now believed that IL-10 induces T cell anergy, which reduces the production of venom specific TH2 cytokine responses. VIT also causes an increase in specific IgG4 (blocking Ab) which further downregulates the venom-specific IgE. The cytokine microenvironment in anergic T cells influences the success or failure of VIT. IL-2, IL-12, IL-15 (TH1 pattern of cytokine production) results in immunity against an

allergic reaction and hence effective VIT. Conversely, IL-4 production (TH2 pattern) results in the persistence of allergy.

d. What are the aims of VIT?
This reduces the risk of a systemic sting reaction in adults from 30%-70% to less than 2%. It prevents life-threatening reactions 97% of the time and alleviates anxiety related to insect stings.

e. What are the risks?
Anaphylaxis 0.17% per year. Systemic reactions occur in 5% - 15% of patients in the induction phase and less in the maintenance phase.

f. How is it done?
In general, injections should be given with each extract to which the patient has a positive skin test. Occasionally, when a single insect is implicated and significant immunologic cross-reactivity exists, it is reasonable to give injections with a single extract.

This consists of an induction phase where weekly then bi-weekly s/c injections of the venom (usually mixed vespid venoms rather than pure venom as protection is better) are given slowly in escalating doses over 6-20 weeks, starting at 0.1 - 0.5 mcg. The aim is to achieve a maintenance dose of 100 mcg. After this has been achieved, a maintenance phase follows where 4-weekly injections are given during the 1st year, then 6-8 weekly for the next 3-5 years.

There are various regimes including classical (standard) protocols (20 weeks to reach maintenance), rush (9 weeks to reach maintenance) and ultrarush (few days to reach maintenance) protocols. The basis of rush protocols is to reduce the incidence and severity of adverse reactions by giving fewer injections and increasing the dose over a shorter period.

g. How long should VIT be continued for?
The average duration is for 3-5 years. After 5 years, VIT is generally successful regardless of history, skin test or RAST test results. Most post-VIT reactions then are also milder than pre-treatment and there is no rebound venom sensitivity even when re-stung.

At the end of VIT, there is a 10% chance of reaction to a future sting even if skin tests and sting challenge are negative, compared to a 2% risk of reaction if kept on maintenance VIT.

Those at higher risk of reaction at the end of VIT include those with a severe reaction (especially near-fatal), honeybee allergy and systemic reaction during treatment (to sting or VIT).

REFERENCES

1. Naguwa SM, Gershwim ME (Ed). Hanley and Belfus. Allergy and immunology secrets.
2. Portnoy JM, Moffitt JE, Golden DB, Bernstein IL, et al. Stinging insect hypersensitivity: a practice parameter. J Allergy Clin Immunol 1999; 103(5) Pt 1: 963-80. (http://www.jcaai.org/Param).