Hymenoptera Venom Anaphylaxis

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INTRODUCTION

Hymenoptera stings cause more deaths than other insects all over the world [1]. The Hymenoptera team includes Apoidea (bees), Vespoidea (wasps, hornets, and yellow jackets), and Formicidae (ants) [2]. The venom of these insects is mixture of low molecular weight substances like biogenic amines, lipids and carbohydrates, cationic peptides and high molecular weight substances like enzymes (phospholipases, hyaluronidases), peptides (mellitin, apamin, mastoparans, bombolitins) called allergens. Generally, low molecular weight substances are responsible for local reactions, while systemic reactions are linked to allergic proteins [3]. Various types of reactions may develop after stinging by Hymenoptera insects [4]. These are non-allergic and allergic reactions.

Non-allergic reactions

1. Local Reaction: Small area of swelling, redness and pain that lasts less than 24 hours.

2. Systemic Toxic reaction: In multiple stings, the toxin can cause fatal disease. The most frequently serious conditions triggered in this way are rhabdomyolysis, hemolysis, hepatic and renal dysfunctions.

3. Unusual Reactions: Cardiac ischaemia, encephalomyelitis, serum sickness, thrombocytopenic purpura, vasculitis [5].

Allergic reactions

1. Large Local Reaction: More than 10 cm and persisting longer than 24 hours [6].

2. Systemic reaction: Can be divided into two groups. These reactions include multiple organ system involvement (Anaphylactic reaction) and skin-limited reactions (Generalized cutaneous reaction) [7,8].

EPIDEMIOLOGY

Among adults the prevalence of systemic reaction after bee sting was reported between 0.5% and 3.3% in the United States and between 0.3 % and 7.5% in Europe [9,10]. In children, the study reported by Novembre et al., showed that the prevalence of systemic reaction with bee sting was 0.34 % and was lower when compared with the reported prevalence (0.8-5.0%) for the general population [11]. The prevalence of systemic reaction with bee sting in adults has been evaluated in a number of studies reported in Turkey. In a study by Kalyoncu et al., the incidence of serious systemic reaction was found 2.2% [12]. Gelinik et al., claimed in their study that the prevalence of hymenoptera sting reactions in their geographical region was comparable with other European studies [13].

PATHOPHYSIOLOGY

Systemic anaphylactic reactions with bee sting are mostly
immunoglobulin E (IgE) mediated [9]. At least one previous sting is necessary to sensitize a person to venom. When sensitivity occurs, stings can lead to mast cell and basophil degranulation, resulting in the release of histamine and other inflammatory mediators responsible for the symptoms and symptoms of anaphylactic and some major local reactions [14].

**TYPES OF REACTIONS**

Allergic reactions to hymenoptera stings are divided into two groups such as local reactions and systemic reactions.

**Large local reactions**

Large local reactions to hymenoptera venoms are characterized with edema, erythema and itching, with a diameter more than 10 cm and resolving 3 to 10 days [6].

In a study by Golden et al. the risk of systemic reaction in patients experiencing large local reaction is reported as 7% [15].

In a recent study Pucci S et al., suggested that patients with repeated large local reactions to stings had no risk of systemic reaction but a single large local reaction does not exclude such risk [16].

Systemic reactions include multiple organ system involvement (Anaphylactic reaction) and skin-limited reactions (Generalized cutaneous reaction).

Anaphylactic reaction effects more than one organ system. Some of the most serious reactions occur in the absence of any skin findings. Skin reactions (urticaria and angioedema) are seen frequently but respiratory or circulatory symptoms may also be prominent. Some of the serious reactions may occur in the absence of skin reactions [12].

Skin-limited reactions (Generalized cutaneous reactions) include widespread urticaria, flushing and pruritus which are not contiguous with the sting site [6].

Systemic reactions are classified according to their severity. Mueller and Ring-Meisser classifications are most frequently used (Tables 1, 2) [17].

In children and adults anaphylaxis clinic can be distinguished when they occur due to bee stings while they do not differ when they are caused by various reasons. Children generally have only cutaneous symptoms. Anaphylaxis, facial or generalized angioedema are rare in children [18].

**RISK FACTORS**

**Systemic reaction history**

Systemic Reaction can become progressively more severe with each sting in some cases. If the time between stings is short interval; subsequent stings increases the risk of systemic reaction. With increasing interval between stings the risk of reaction generally decreases [14].

**Large local reaction**

The study by Pucci and colleagues have confirmed that recurrent large local reactions resulting from bee stings carry the risk of a systemic reaction, but only one large local reaction [16].

**Age**

In children, systemic reactions are usually confined to cutaneous findings with urticaria and angioedema, whereas airway obstruction or hypotension is more common in adults [18].

In addition, severe systemic reactions more develop in elderly patients and mortality rates are higher than children and young adults [19].

**Passing time after the last reaction**

After stings the risk of the reaction is initially over 50%. It declines by about 35% after three to five years and 25% after 10 years or more. However, in some cases the risk of anaphylaxis remains the same throughout the intervening period [20].

**Family history**

The occurrence of systemic reactions to insect infestations does not correlate with family history except in a few cases. It has been suggested that the result of bee sting in patients with mastocytosis may result in particularly serious and even fatal systemic reactions [21].

In venom-allergic patients, even without mastocytosis, elevation in basal serum tryptase levels was associated with severe anaphylactic reactions [22].

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**Table 1:** Classification of systemic reactions according to Mueller after bee sting.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Generalize Urticaria, itching, anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Any of the above + at least two and over Symptoms: Angioedema, chest compression, nausea, vomiting, diarrhea, abdominal pain, dizziness</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Any of the above + at least two and over Symptoms: shortness of breath, wheezing, stridor, dysarthria, phobia, confusion</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Any of the above + at least two and over Symptoms: hypotension, collapse, unconsciousness, incontinence, cyanosis</td>
</tr>
</tbody>
</table>

**Table 2:** Classification of Ring-Meisser for systemic reactions resulting after bee sting.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Generalized skin symptoms (redness, generalized urticaria, angioedema)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Moderate pulmonary, cardiovascular and / or gastrointestinal symptoms</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Anaphylactic shock, Unconsciousness</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Cardiac arrest, apnea</td>
</tr>
</tbody>
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DIAGNOSIS

The diagnosis of Hymenoptera allergy is based on anamnesis and supported by testing for the presence of venom-specific IgE antibodies.

Anamnesis

When the history is taken, the following questions need to be answered

1. When did the sting event happen?
2. The characteristics of previous bee stings.
3. Bee gender: An important distinguishing feature to determine the bee pattern is the color of the bee and the presence of needles in the inserted spot. Honey bees often leave their needles, but wild bees do not leave their needles.
4. Developing reactions large local reaction or systemic reaction?
5. How many stings were exposed? The toxic reactions may develop in multiple stings [17].

Patients with had a history of systemic reactions should be evaluated with testing for the presence of venom-specific IgE antibodies [23].

Skin testing

It is advisable to wait at least four to six weeks before the skin test as possible, if the reaction history is near. In most cases skin testing is the first method to show venom-specific IgE because it is more sensitive. 70-90% of patients who describe venom allergy have positive skin test. If clinical history is proven by positive skin test in vitro testing is not necessary [24].

In vitro testing

In vitro testing is less sensitive and more expensive than skin testing. It is necessary in some cases as follows:

1. If patient with positive clinical history has negative skin testing
2. Patients not eligible for skin test (dermographism, urticaria, active skin disease)
3. Patients who cannot discontinue interfering medications (antidepressant drug)

IgE immunoassays: Immucap is identified as a reliable commercial assay [25].

Skin test and in vitro test combination can detect approximately 95% of patients who have a systemic reaction [26].

Component-resolved diagnostic

Double sensitization to hymenoptera venom often occurs in skin prick test. Carbohydrate determinant of venom can be cross-reactive. Component-resolved diagnostic provide improved discrimination between primary sensitization and cross-reactivity in hymenoptera venom allergy [27].

If the both skin testing and in vitro testing are negative the investigational testing may be considering Basophil activation tests.

The diagnosis of Hymenoptera venom allergy is based on history, skin tests and demonstration of hymenoptera venom-specific IgE-antibodies [28]. Basophil activation is associated with the expression of CD63 and may be valuable for diagnosing immediate type allergic reactions. In a study Erdmann SM, et al., were compared skin tests and specific IgE measurements with CD63-based basophil activation test for wasp venom allergy and they were suggested CD63-based basophil activation test is a useful tool for diagnostic tests such as specific IgE [29]. Furthermore, Basophil sensitivity can be used to monitor allergen specific immunotherapy and anti-IgE treatment response [33,31]. Rodríguez Trabado A, et al., suggested that BAT is an optimal non-invasive test for close monitoring of VIT [32].

Tryptase

Serum tryptase should be measured for the detection of an underlying mast cell disorder. Some specialists recommend measuring basal tryptase levels in all patients requiring venom immunotherapy. In addition, in some studies, patients with hypotensive syncope after bee sting have been found to have a monoclonal mast cell activation syndrome when the tryptase is normal and the skin is not detected [22,33]. If both the skin tests and the in vitro test are negative, if the serum tryptase is normal and there is still a systemic reaction history, the patient should be retested for venom-specific IgE after 3-6 months [14].

TREATMENT

Local reactions to hymenoptera stings are treated with oral antihistamines and topical corticosteroids. A short course of oral corticosteroids may be needed for large local reactions.

Immediate treatment

Patients with airway obstruction or hypotension should be treated with adrenaline intramuscularly. Adrenaline is the first drug for treatment of anaphylaxis. However fluid replacement is required with adrenaline. High flow oxygen and beta-agonist therapy should be given for bronchospasm treatment [34].

Long term treatment

Adrenaline auto-injector: Patients with a systemic reaction to bee sting should be prescribed the adrenaline auto- injector and the patient and family should be trained in their use [35].

Venom immunotherapy: In adults, venom immunotherapy (VIT) is performed if the systemic reaction is positive and venom-specific IgE antibodies are defined (skin test or immunoassay). In the study reported by Golden DB et al., the protection of VIT from systemic reactions was found to be 75-98% [9]. This protection is higher in vespid allergy than honey bee allergy. VIT should generally be continued for at least 3-5 years after starts [26,36]. There are no specific tests to determine which patients will relapse after VIT, but some patients have a higher risk than others. Factors such as the patient’s lifestyle, occupation, coexisting diseases, medications, and severity of stinging reactions should be taken into consideration during the VIT period [37]. Patients with a severe history of anaphylaxis (severe airway obstruction,
shock or loss of consciousness) may still be at risk for a systemic reaction even after 5 years of treatment [30,31,38].

**Venom immunotherapy + Omalizumab:** Anaphylaxis may occur rarely during specific venom immunotherapy (VIT). This ratio is significantly higher for honey bee VIT than vespid VIT [39]. Omalizumab is a recombinant humanized immunoglobulin G1 monoclonal antibody that has provided a treatment option for allergic asthma and chronic idiopathic urticaria diseases [40]. Pretreatment with omalizumab has been implicated in the prevention of anaphylaxis during the VIT administration, as shown in various published reports. This efficacy is associated with a marked lowering of free IgE levels and downregulation of IgE receptors on mast cells, basophils and eosinophils [41-43].

**REFERENCES**


