EIGHT EXERCISE

DIAGNOSIS OF HYMENOPTERA VENOM ALLERGY

Hymenoptera venom allergy is an immunoglobulin E (IgE)- mediated hypersensitivity to the venom of insects in the insect order Hymenoptera. This allergic reaction may be caused by stings from a number of species in this insect order, occurring only in persons who have previously been sensitized to Hymenoptera venom.

In the central and northern Europe vespid (mainly Vespula spp.) and honeybee stings are the most prevalent, whereas in the Mediterranean area stings from Polistes and Vespula are more frequent than honeybee stings; bumblebee stings are rare throughout Europe and more of an occupational hazard. The amount of venom which is released during a sting varies from species to species and even within the same species: bee stings release an average of 50 μg up to 140 μg of venom protein per sting; however, venom sacs may contain up to more than 300 μg of venom. Bumblebee stings release 10–31 μg of venom. In contrast Vespinae, which are capable of repeated stings, generally inject less venom per sting: Vespula stings release 1.7–3.1 μg of venom, Dolichovespula stings 2.4–5.0 μg and Polistes stings from 4.2 to 17 μg of protein. The amount of venom injected by a single European hornet sting is not known. The dry weight of venom per sac was found to be 260 μg.

Several major allergens, usually glycoproteins with a molecular weight of 10–50 kDa, have been identified in venoms of bees, vespids and ants. Venom hypersensitivity may be mediated by immunologic mechanisms (IgE-mediated or non-IgE-mediated venom allergy) but also by nonimmunologic mechanisms.

Reactions to Hymenoptera stings are classified into normal local reactions, large local reactions, systemic toxic reactions, systemic anaphylactic reactions, and unusual reactions. The most frequent clinical patterns are large local and systemic anaphylactic reactions. **Large local reaction** is defined as a swelling exceeding a **diameter of 10 cm which lasts longer than 24 h;** blisters may rarely be present. The underlying mechanisms of large local reactions are unknown. **Systemic anaphylactic reactions** are most often IgE-mediated. Rarely, they may be due to short-term sensitizing IgG antibodies or complement activation by IgG–venom complexes. For most venom-allergic patients an anaphylactic reaction after a sting is very traumatic event, resulting in an altered health-related quality of life. It has been demonstrated that patients with anaphylactic responses following yellow jacket stings experienced impairment in their quality of life especially because of the emotional distress associated with having to be constantly on the alert while leading their everyday ‘normal’ lives. Risk factors influencing the outcome of an anaphylactic reaction include the time interval between stings, the number of stings, the severity of the preceding reaction, age, cardiovascular diseases and drug intake, insect type, elevated serum tryptase, and mastocytosis. Severe reactions or a status after resuscitation may leave patients with a permanent disorder: hypoxic brain damage with permanent neurologic deficits, and myocardial infarction. Fatal reactions after insect stings may occur. Autopsies after fatal sting reactions revealed significant cardiopulmonary comorbidity in 50%.

Risk factors of Hymenoptera venom allergy

A distinction has to be drawn between risk factors, which are associated with a higher risk of stings and those increasing the risk to develop a severe sting reaction. Zone, climate, temperature, insect behavior, certain occupations or activities will influence the risk of

receiving a sting. Beehives or vespid nests located in the near vicinity of dwellings, work places and also outdoor sport, have to be taken into account as risk factors.

Risk factors influencing the outcome of an anaphylactic reaction

1. **Time interval between stings, number of stings.** A short interval between stings increases the risk of a systemic reaction to the later one.
2. **Venom sensitization.** In adult subjects without a history of a previous systemic anaphylactic sting reaction and a positive skin test the risk of a later anaphylactic sting reaction is 17%*vs* 0% in skin test-negative individuals.
3. **Severity of the preceding reaction.** After a large local sting reaction, between 5% and 15% will develop a systemic reaction when next stung. In those with mild systemic reactions the risk of subsequent systemic reactions is 18% in childre and 14–20% in adults with mild to 79% in adults with severe reactions.
4. **Age.** In children about 60% of systemic sting reactions are mild, whereas in adults respiratory or cardiovascular symptoms occur in about 70%. Elderly patients more often develop particularly severe sting reactions, and the fatality rate is higher than in children and young adults. Children also have a better prognosis than adults with respect to the risk of systemic reactions to re-stings. Both sting challenges and studies of the natural course of insect venom allergy show lower risks in children than adults.
5. **Cardiovascular diseases, β-blockers** Studies on larger groups of patients identified cardiovascular diseases or treatment with β-blocking drugs to be associated with particularly severe sting reactions. β-blockers do not however, seem to increase the overall risk of a systemic reaction.
6. **Insect** Bee venom-allergic patients are at a greater risk of a systemic reaction on next sting than those with vespid venom allergy.

Diagnosis

History

Skin tests

Diagnostic tests should be carried out in all patients with a history of a systemic sting reaction to detect sensitization. It is recommended to perform skin tests at least 2 weeks after the reaction to a sting to avoid the possibility of false-negative results during the refractory period. Because the duration of refractoriness may be longer, they should, if negative in the presence of a definitive history of a systemic sting reaction, be repeated after 1–2 months. Skin tests are performed by skin prick or intradermal testing. Stepwise incremental venom skin tests are recommended. If the patient has a conclusive reaction at a set concentration the test can be stopped. For skin prick test venom concentrations of 0.01–100 μg/ml are usually used. Intradermally a 0.02 ml venom concentration ranging from 0.001 to 1 μg/ml is injected into the volar surface of the forearm.

In vitro tests

Allergen-specific IgE *In vitro* radioallergosorbent test (RAST). In the first few days after a sting the IgE specific to the injected venom may be low or may not even be demonstrable. Venom-specific IgE usually increases within days or weeks after a sting. In patients with no detectable specific IgE to the presumptive relevant venom, the tests should be repeated after a few weeks.

Venom immunotherapy induces an initial rise of venom-specific IgE antibodies followed by a decline after a few months, with a large individual variation. There is no clear correlation between the concentration of venom-specific IgE and the reactivity status of the individual patient.

Allergen-specific IgG The level of specific IgG primarily reflects exposure. Venom-specific IgG increases after a sting and does not correlate with the presence or absence of an allergic sting reaction. Specific IgG initially decreases more rapidly than specific IgE. In beekeepers bee venom-specific IgG correlates to the number of annual stings and to the number of years spent in bee-keeping.

Baseline serum tryptase

Other in vitro tests. When venom skin tests and the measurement of venom-specific IgE antibodies in serum by RAST or an equivalent method yield negative results in patients with a history of a systemic anaphylactic sting reaction, additional *in vitro* tests may be used to demonstrate immunologic sensitization (like immunoblotting, the basophil histamine release test, basophil activation test and leukotrine release test).

Sting challenge tests

As already evident from the fact that some patients tolerate venom immunotherapy (VIT) very well, but still have systemic reactions to a sting from the same insect, challenge tests with subcutaneously or intracutaneously administered venom are not reliable. Therefore, if challenge tests are to be performed in Hymenoptera venom-allergic patients these should be performed using live insects. Sting challenges are recommended in patients on maintenance VIT to identify those who are not yet protected. The effectiveness of VIT should be assessed by a sting challenge particularly in those patients who are at increased risk of re-stings due to high exposure or due to their proneness to very severe anaphylaxis. This could be of important practical use, as full protection may be achieved by an increase of the venom maintenance dose.