

Elevated baseline mast cell tryptase: a marker of severe insect venom anaphylaxis

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Anaphylaxis represents the most severe form of immediate-type allergic reactions [1,2]. Its prevalence is increasing, particularly in children and young adults. Whilst food allergy is the most common cause of anaphylaxis in children, allergy to insect venom and medications predominates in adults. The critical role of mast cell mediators in the pathophysiology of anaphylaxis is well established. Recently, complement and platelet-activating factor have been highlighted as key molecules in anaphylaxis. The management of anaphylaxis relies, where possible, on prevention of exposure to the offending allergen, as well as early treatment with intramuscular epinephrine. In patients with insect venom allergy, subcutaneous immunotherapy is a highly effective treatment which significantly reduces the risk of subsequent anaphylaxis. The current issue provides summaries on new insights and developments in the diagnosis and management of anaphylaxis, with particular emphasis on hymenoptera and ant venom anaphylaxis. A common theme that goes through these articles is the recent recognition of the clinical significance of elevated baseline tryptase levels in patients with severe anaphylaxis [3]. This observation is likely to change our clinical practice and may help clinicians identify patients at increased risk of fatal anaphylaxis or nonresponse to insect venom immunotherapy.

Exercise-induced anaphylaxis (EIA) is a rare and often puzzling condition. Its underlying mechanisms (EIA) are still poorly understood. Certain medications, such as angiotensin-converting enzyme inhibitors, may increase the risk of EIA. Wheat is the main food that may cause the food-dependent form of EIA. Robson-Ansley and Du Toit [4] present the current literature on mechanisms in EIA and review pathophysiological models in the context of exercise physiology. Published hypotheses have so far mainly focused on exercise-induced alterations in plasma osmolality and pH, activation of tissue transglutaminase, increases in interleukin-6 levels, redistribution of blood flow and altered

gastrointestinal permeability. Robson-Ansley and Du Toit [4] challenge some of the current hypotheses as these have not always taken into account the physiological changes observed during various levels of exercise. The authors speculate that significant changes in local blood flow occur in muscle tissue, even after mild to moderate exercise. This may increase muscle-derived mast cell activation, resulting in the release of vasoactive compounds and subsequent anaphylaxis. However, the exact mechanisms of EIA remain elusive and require further study.

Several of the articles in the anaphylaxis section focus on recent developments in insect venom anaphylaxis. To set the scene, Demain *et al.* [5] provide an overview of the diagnosis, prevention and treatment of anaphylaxis in patients with insect venom allergy. There are significant regional differences in the rates of allergic reactions to hymenoptera (e.g. honey bee, wasp, yellow jacket or hornet), ants and other insects. Although the prevalence of anaphylaxis has increased over the past decades, the true extent of the increase may be underestimated due to undertreatment and a lack of recognition of insect venom anaphylaxis. This may, in part, be due to limitations regarding the sensitivity of diagnostic tests. Some patients, despite having a convincing clinical reaction after an insect sting, may fail to fulfill the diagnostic criteria for venom allergy. Abnormalities in basophil activation or mast cell disorders with an elevated baseline tryptase level may cause exaggerated clinical reactivity in these patients despite low levels of circulating venom-specific IgE. A high degree of clinical suspicion is therefore required.

In recent years, there have been several advances in the in-vitro and in-vivo diagnosis of hymenoptera venom allergy. Hamilton [6] provides a detailed overview of the steps involved in the diagnostic evaluation of patients with suspected hymenoptera venom allergy. Intradermal testing with dialyzed venom extracts has been shown to have the best diagnostic properties. However, more reliable diagnostic markers are needed. Component-resolved allergen testing and microarray assays are currently being developed and are likely to further improve the diagnostic accuracy of IgE-based in-vitro assays. These may also be able to distinguish between true cosensitization, as opposed to cross-reactivity, to honeybee and yellow jacket venoms.

Bee venom allergy accounts for a significant proportion of severe anaphylactic reactions in children, adolescents and adults. If recognized and managed appropriately, fatal reactions can usually be averted. Over the past decades, immunotherapy has been established as a highly effective immunomodulatory treatment in patients with insect venom allergy and anaphylaxis [6–8]. Immunotherapy to bee venom is now considered the treatment of choice for patients with a history of hymenoptera venom anaphylaxis. Immunological studies have demonstrated evidence of stimulation of regulatory T-lymphocyte responses and a reduction in circulating venom-specific IgE levels. Biló *et al.* [7] reviewed the different venom preparations that are available for subcutaneous venom immunotherapy. Purified aqueous and aluminium hydroxide-adsorbed depot venom preparations have been used, although not all of these are universally available. Purified venom appears to offer a similar clinical efficacy compared to nonpurified preparations but is associated with a lower rate of adverse reactions. Purified venom preparations are therefore thought to be preferable for venom immunotherapy. However, well conducted comparative studies between purified and nonpurified venom preparations are to date not available.

Only a few studies have assessed the long-term outcome after immunotherapy to bee venom. Golden [8] provides a detailed overview of the efficacy of bee venom immunotherapy. Prospective studies have shown that the majority of patients with bee venom anaphylaxis will be protected against severe allergic reactions after about 3–5 years of subcutaneous venom immunotherapy. Given the safety and efficacy of immunotherapy, Golden proposed a widening of the indications for immunotherapy, including large localized reactions in individuals with frequent bee stings. Elevated serum tryptase concentrations may predict nonresponse to venom immunotherapy. These patients are considered to be at high risk of potentially fatal anaphylaxis and may therefore require immunotherapy indefinitely.

Apart from hymenoptera, ants are a common cause for allergic reactions and may cause anaphylaxis. The article by Hoffman [9] summarizes the characteristics of ant venoms. Ant species are biodiverse, and thousands of species have been described. With international trade, ant species are spreading globally. In general, ant venoms are still poorly characterized. Only the venoms of fire ants and Jack jumper ants have been extensively studied. At this stage the diagnostic evaluation of patients with allergic reactions to stinging ants is still hampered by a lack of accurate in-vitro assays. However, with increased knowledge of the proteomics of ant venoms, component-resolved diagnostics may soon become available. Access to immunotherapy to ant venoms is still limited. Some ant

venom immunotherapy extracts have been developed for clinical trials but these preparations are generally not commercially available [10].

The role of mast cell disorders in patients with severe allergic reactions or anaphylaxis has recently been highlighted [1]. An elevated baseline serum beta tryptase level ($>5\mu\text{g/l}$) has been found to be associated with more severe allergic reactions to insect venoms or anaphylaxis. Higher baseline tryptase concentrations ($>11.4\mu\text{g/l}$) may indicate mastocytosis and warrant further evaluation, including bone marrow biopsy. Müller *et al.* [11] provide a detailed overview of the current diagnostic criteria for mastocytosis and related mast cell disorders. The authors discuss the link between elevated tryptase levels and the risk of severe anaphylaxis and propose that serum tryptase measurements be included in the baseline work-up of patients with severe allergic reactions or anaphylaxis to insect venoms.

Intramuscular epinephrine remains the main life-saving medication used in the acute treatment of anaphylaxis [1]. Simons and Simons [12] provide a detailed overview of the pharmacology of epinephrine, as well of its indications and limitations in the use of the treatment of anaphylaxis. Although its main effects are widely recognized, epinephrine also has a range of unwanted qualities that may expose the patient to adverse reactions or toxicity. Epinephrine auto-injectors should be made available to patients with a history of anaphylaxis, including respiratory or cardiovascular compromise during an acute allergic reaction. Patients deemed at significant risk of anaphylaxis should also be prescribed an epinephrine auto-injector, although clinical practices vary between health systems. As mentioned above, the measurement of baseline serum tryptase levels may be helpful in identifying high-risk patients. Importantly, all patients issued with an epinephrine auto-injector need to be provided with education on the correct use of the device, as well as a written anaphylaxis treatment plan.

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