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Exercise–induced Anaphylaxis: the Role of Cofactors

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ABSTRACT

Introduction: Anaphylaxis is a dramatic clinical emergency. It is a very severe, life-threatening generalized or systemic hypersensitivity reaction. Based on immunologic mechanism the anaphylaxis is divided in IgE, IgG, complement, or immune complexes-mediated *vs* non allergic anaphylaxis. There are a lot of etiologic factors of anaphylaxis, but the three principal immunologic triggers are drugs, insect stings, and foods. Regarding the clinical severity there are several proposed grading systems. The diagnosis of anaphylaxis is mainly clinical. **Discussion:** The anaphylaxis markers measured in clinical laboratories are total tryptase and histamine. There are some conditions that modulate the onset of anaphylaxis, acting as co- or augmentation factors, which significantly lower the allergen dose necessary for triggering anaphylaxis. The well-documented cofactors of anaphylaxis are physical exercise, alcohol consumption, some foods, co-administration of nonsteroidal anti-inflammatory drugs (NSAID), and concomitant infectious diseases. Development of anaphylaxis depends on the sensitization pattern, the proportion of the involved immunoglobulin classes, characteristics of the allergen, the proportion of the involved immunoglobulin classes, the avidity and affinity of immunoglobulins to bind an allergen, the route of allergen application, and, last but not least, the presence of cofactors of anaphylaxis. **Conclusion:** Anaphylaxis remains a continuous challenge for the diagnosis and treatment. The adequate management of anaphylaxis requires rapid diagnosis, implementation of primary and secondary prevention measures, and immediate administration of subcutaneous epinephrine.

Key words: anaphylaxis, cofactors, exercise-induced anaphylaxis, food-dependent exercise-induced anaphylaxis, epinephrine.

1. INTRODUCTION

Anaphylaxis is an acute hypersensitivity reaction with fatal or potentially fatal outcomes. The diagnosis is established based on the clinical history and physical examination. It includes symptoms of airway obstruction, generalized cutaneous reactions such as itching, flushing, urticaria, angioedema, gastrointestinal cramps or diarrhea and cardiovascular symptoms including hypotension (1-6). All these symptoms are attributed to mast cell mediators' release, especially histamine and lipid mediators such as leukotriene and platelet activating factor on shock tissue (2). Anaphylaxis is a bi-phasic immediate hypersensitivity reaction, elicited within minutes after antigen exposure, followed by a latter phase reaction. Mast cell mediator release can be triggered by immune mediated (both IgE and non-IgE-mediated factors) and non-immune mediated reactions. In IgE mediated immune reactions, the most common triggers are: drugs (typically penicillin or other beta-lactam antibiotics), foods, most commonly nuts, peanuts, fish and shellfish, or hymenoptera stings (3-6). Non-IgE-mediated triggers (immune and non-immune) imply complement activation. These elicitors may be plasma proteins or compounds that act directly on the mast cell membrane, such as vancomycine, quinolone antibiotics, or radiographic contrast media (7). The pathophysiology of some triggering factors, such as aspirin, remains unclear. Anaphylaxis treatment is a multidimensional attitude. It implies patients' education, trigger avoidance, desensitization, preventing pharmacologic therapy when known trigger agents need to be re-administered, early sign recognition and prompt emergency therapy administration (8, 9).

2. EXERCISE INDUCED ANAPHYLAXIS SYNDROME

Exercise-induced anaphylaxis (EIA) is a rare disorder occurring after physical activity. The most common symptoms are: pruritus, hives, flushing, wheezing, and GI involvement, including nausea, abdominal cramping, and diarrhea. The symptoms may progress to a more severe grade, if physical activity persists, including angioedema, laryngeal edema, hypotension, and cardiovascular collapse. Clinical history and physical examination are crucial for diagnosis of EIA. Patients diagnosed with EIA manifest anaphylactic symptoms associated only with exercise such as hives and/or angioedema or cardiovascular collapse, with or without other anaphylactic symptoms such as gastrointestinal disorders (10, 11). If symptoms occur outside of exercise course, it is more likely that the right diagnosis is cholinergic urticaria. Since the early 1980's, interest has grown in patients with anaphylaxis triggered by exercise. Exercise-induced anaphylaxis (food dependent and nonfood dependent) is a clinical syndrome in which anaphylaxis is related to the exercise. Patients with EIA represent about 5% to 15% of all anaphylactic cases reported (11). Exercise of moderate intensity

is sometimes enough to trigger symptoms of EIA. Episodes of EIA are not fully predictable since the exercise threshold for eliciting anaphylaxis is individual and sometimes it is different even for the same patient (12, 13). Sheffer and Austen described 4 phases of the anaphylaxis attack in a case series of 16 patients aged 12-54 years with exercise-induced anaphylaxis: prodromal phase, early phase, fully established phase, and late phase. Prodromal symptoms included a feeling of fatigue, generalized warmth and pruritus, and cutaneous erythema. The early phase implied generalized urticaria (10, 12). In fully established attacks, symptoms described were choking, respiratory stridor, GI colic, nausea, and vomiting. The late phase included frontal headaches that persisted for 24-72 hours in the subpopulation of patients with food -dependent exercise–induced anaphylaxis (FDEIA) (10, 14).

3. FOOD-DEPENDENT EXERCISE-INDUCED ANAPHYLAXIS

Food-dependent exercise-induced anaphylaxis (FDEIA) is a special form of food allergy and a subtype of exercise-induced anaphylaxis (EIA) characterized by the onset of symptoms of anaphylaxis during or following physical exertion. This condition is less commonly known compared to other severe allergic reactions (9, 15). It's well known that food-intake alone does not induce any symptoms (16). FDEIA anaphylaxis occurs only when triggering factors such as exercise or aspirin-intake are added after ingestion of the causative food (15, 17). The symptoms of EIA can be observed at any moment during or after physical activity. However, approximately, 90% of patients develop symptoms within 30 min after exercise cessation (18). In cases of FDEIA, ingestion of allergenic food usually precedes exercise by several minutes or even hours, but anaphylaxis may occur if the patient ingests allergenic food soon after the completion of exercise (19, 20). FDEIA should be differentiated from Cholinergic Urticaria (CU) and EIA. FDEIA requires the combination of allergenic food and physical exercise whereas EIA is caused by exercise alone (21-24). CU is induced by exercise, stress, and heat (16). Vascular collapse and laryngeal edema is not observed in CU (25). The most frequent allergenic foods in European population responsible for FDEIA are: tomatoes, cereals, and peanuts whereas wheat and particularly the omega-5 gliadin allergen is found as the main trigger in Japanese population (18, 26).

4. CLINICAL ASSESSMENT AND PATHOPHYSIOLOGY OF EIA AND FDEIA

Provocation test is not encouraged as a routine test for confirming the diagnosis of EIA. Only a skilled physician in the diagnosis and treatment of anaphylaxis should perform such a test when patient's history is not very clear. The provocation test should be done under close medical supervision in properly equipped visiting room for prompt assistance in case of potentially life-threatening reactions onset (27, 28). Assessment for other triggers is the next step after EIA diagnosis is established (29). In vivo and in vitro food allergy tests might be of a great help in clinical evaluation. A negative skin test to a particular food might rule out the possibility of that food as culprit of EIA. Positive skin test on the other part, with the suspected food as per the patient's history, ingested within 24 hours before the EIA onset, may be the causative allergenic food (25).

The pathophysiology of EIA and FDEIA is not fully understood but increased plasma histamine has been documented during EIA and FDEIA episodes. Hypotheses still under research imply alterations in plasma osmolality and pH, tissue enzyme activity, blood flow redistribution, altered gastrointestinal permeability and facilitated epitope recognition/allergen binding (19, 21, 23). As both the food and the exercise are independently tolerated, this suggests a pliable state of immunological tolerance. More than 80% of the patients with wheat-induced FDEIA have IgE reacting to omega-5 gliadin and the rest, to high molecular weight glutenin (HMW-glutenin). Wheat-dependent exercise-induced anaphylaxis (WDEIA) is a specific form of wheat allergy, typically induced by exercise after ingestion of wheat products. Wheat ω-5 gliadin is a major allergen associated with conventional WDEIA (30, 31, 32). Detection of serum immunoglobulin E (IgE) specific to recombinant ω-5 gliadin is a reliable method for its diagnosis (31- 35). It has been hypothesized that exercise-induced alterations in tissue transglutaminase (tTG) enzyme may result in peptide aggregation that leads to increased IgE cross-linking. Inflammatory mediators and specifically interleukin-6, increases tTG expression (37). The main sources of interleukin-6 are monocyte/macrophages, fibroblasts and endothelial cells. Exercise activity enhances interleukin-6 production within contracting skeletal muscles and the central nervous system (CNS) as well as peri-tendinous tissue (38).

Blood redistribution occurs via sympathetic control from the kidneys, liver, stomach and intestines to the skeletal muscle, heart and skin during an exercise course. It occurs also with moderate exercise that redistributes a higher percentage of cardiac output to the muscle and skin compared to other areas of the body. Exercise-induced redistribution of blood flow away from the viscera to skeletal muscle and skin lately, is one of the hypothesis regarding the triggering factor for FDEIA. This hypotheses states that absorbed-food allergenic peptides are tolerated by gut-specific mast cells thereby not inducing noticeable symptoms when the individual is at rest (33). With exercise, the recently ingested allergen is transported via the blood redistribution phenomenon to phenotypically different mast cells of the skin/and or skeletal muscle compartments hence, increasing the potential for exercise-induced anaphylaxis. Thus, exercise increases the bioavailability and influences the distribution of certain allergens and it lowers the mast cells and basophils activation threshold (37).

Tight junctions increased permeability in the gastrointestinal epithelium because of thermal injury, alcohol ingestion and non-steroidal anti-inflammatory agents is another pathophysiological mechanism under study. Recent studies demonstrate that aspirin can induce gastric epithelial barrier dysfunction by altering tight junctions' modulation, leading to increased gliadin absorption in both healthy and FDEIA patients following an aspirin and wheat challenge (without exercise involvement). It is found that the combination of exercise and aspirin may significantly increase the risk of developing anaphylaxis in the 'otherwise tolerant' food allergic patients (39, 40).

5. UNDERSTANDING THE ROLE OF COFACTORS

The risk to develop anaphylaxis depends on numerous and various factors such as the sensitization pattern, the proportion of the involved immunoglobulin classes, the avidity and affinity

of immunoglobulins to bind an allergen, characteristics of the allergen, the route of allergen application, and, last but not least, the presence of cofactors of anaphylaxis. Risk assessment and early intervention in anaphylaxis is a priority. Understanding how all these factors interact with each-other might be of a great help in this matter (41, 42). Important progress for risk assessment in anaphylaxis is based on component-resolved stratified diagnostics (CRSD). That allows determine a patient's sensitization pattern on a molecular basis, correlate clinical responses to defined sensitization patterns, and better identify cross-reactive allergens. It is widely accepted that the clinical manifestations of systemic type I allergic reactions are a complex orchestrated process involving different organs and systems. Theoretically many components can be involved in anaphylaxis onset via a complex formula. The key elements of this formula would be the type of allergens an individual is sensitive to, the level of sensitization, the quality of binding allergens, relative proportions of antigen-specific immunoglobulin subtypes, the route of allergen application, and, the presence and measureable quantity of cofactors (43,44,45, 46).

It is well known that cofactors are allergen-independent factors modulating the clinical development of the allergic reaction. They are classified in three subgroups:

- Patient intrinsic factors that may increase the symptoms of type I allergy without modulating the immunological reaction itself. These could imply diseases that in most cases act in an organ-affected specific pattern.
- Patient extrinsic factors that may have non-immunological modulating effects on type I allergy, implying mostly drugs.
- Factors that may directly modulate the type I immune reaction (44, 46).

Although anaphylaxis seems to be triggered by an allergen in most cases, the role of co- or augmentation factors, for the elicitation of anaphylaxis is increasingly accepted. Registries of anaphylaxis document the role of cofactors in about 30% of anaphylactic reactions (48, 49). The role of additional factors/cofactor-dependent anaphylaxis was described for the first time in 1979 by Maulitz et al. They reported the case of a patient with 'exercise-induced anaphylaxis to shellfish'. In a mean time, physical exercise is the best studied cofactor of anaphylaxis and 'food-dependent exercise-induced anaphylaxis' (FDEIA) is accepted as a defined clinical entity. Other well-documented cofactors of anaphylaxis are non-steroid anti-inflammatory drugs (NSAID) like acetylsalicylic acid (ASA) in 6.1–9% of severe anaphylactic reactions (40, 50), alcohol consumption in 15.2%, and infectious diseases (1.3–11% in children and 2.5–3% in adults). The infectious diseases are cofactors of high risk for anaphylaxis onset, as long as they can't be avoided nor foreseen. Different reports state that co- or augmentation factors significantly lower the allergen dose necessary for triggering anaphylaxis(43-46). Drugs on the other part might directly lead to mast cells and basophils degranulation, augmenting IgE mediated reactions to systemic levels leading to anaphylactic shock. Important drugs are radio contrast media (iodinated contrast media, most frequently iomeprol and iopromide), miorelaxants (most frequently suxamethonium), opioids, and certain antibiotics like DNA gyrase inhibitors (49). Another potential mechanism of anaphylaxis cofactors are drugs like H2-receptor antagonists and the so-called proton pump inhibitors (PPI) that due to their primary effect on blocking or inducing long-lasting suppression of the gastric acids may lead to allergen persistence (37, 40).

The intestinal allergen absorption is increased in the presence of cofactors like alcohol or exercise. Alcohol consumption is a facilitating factor of food allergies and it may also trigger FDEIA. It increases the permeability of tight junctions in gut epithelium, leading to increased protein absorption in the intestine and that is the underlying mechanism for anaphylaxis related to alcohol consumption. The rapid allergen uptake results in higher peak concentrations allowing even low amounts of allergen to reach or exceed the anaphylaxis onset threshold (51).

Early phases of infectious diseases and clinically mild infections have been reported as considerable anaphylaxis cofactors in various case reports and anaphylaxis registries Anaphylaxis registries, together with case report is very important and the best evidence showing their role as cofactors of anaphylaxis (48, 49).

6. CONCLUSION

Anaphylaxis is an acute hypersensitivity reaction with fatal or potentially fatal outcomes. Recognition of the triggers and cofactors, and the stratification of anaphylaxis risk assessment from the clinicians could prevent and/or properly assist patients in our daily work with an individual plan. Cofactors of great importance such as exercise, alcohol, ASA, other drugs and infectious diseases should always be kept in mind when dealing with anaphylaxis. Further study is needed to shed more light on possible mechanisms how cofactors enhance an IgE mediated reactions to anaphylaxis. The patients' education on allergen and cofactors avoidance, early recognition of symptoms of an anaphylactic shock and prompt epinephrine administration is of vital importance. The first line treatment is epinephrine and the second line treatment includes antihistamines and steroids (47, 50, 51).

CONFLICT OF INTEREST: NONE DECLARED

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