

Exercise-induced urticaria, cholinergic urticaria, and Kounis syndrome

Sir,

Physical exercise may provoke the onset of clinical symptoms that are usually associated with an allergic reaction. Distinct forms of recognized physical allergies are exercise-induced anaphylaxis (EIA), food-dependent EIA cholinergic urticaria, exercise-induced bronchospasm, and rhinitis.^[1]

In a report,^[2] the authors described a 26-year-old male with 3-year history of exercise-induced rash accompanied by flushing, feeling unwell and warm, eyelid angioedema, pruritus, and headache. His symptoms were relieved with discontinuation of exercise.

No history of any specific food, drink, or medication intake before exercise was apparent, but the patient described nonspecific allergic rhinitis episodes to dust. He subsequently underwent extensive investigation including skin prick tests to numerous food items including meat and vegetables as well as specific immunoglobulin E (IgE) for wheat, most of which proved to be negative. The only positive skin prick tests were for mites and grasses. His symptoms subsided with antihistamine and antileukotriene therapy with montelukast that enabled him to start exercising again without symptoms.

EIA is an unpredictable and potentially fatal syndrome affecting pediatric individuals also^[3] with a prevalence of 0.048% and can seriously damage the patient's quality of life. This condition may occur independently or may require the ingestion of a food allergen either pre- or post-exercise. Atopic individuals are specifically prone to this condition.^[4]

Therefore, this report raises several important questions concerning the etiology, pathophysiology, associations and treatment of EIA.

The authors have correctly speculated on mediators from degranulation of mast cells, lowering of degranulation threshold and increased sympathetic activity, but additional causes should be taken into consideration as has been emphasized in a recent position paper.^[5]

The consumption of substances such as alcohol or aspirin that damage the gastric mucosa may significantly increase the risk of food allergic patients developing anaphylaxis. On the other hand, the inhibitory effect of exercise on gastric acid secretion decreases the digestion of oral allergens and preserves the structural integrity that leads to continued systemic absorption of the allergens whether it be profilins, lipid transfer proteins, or other antigenic determinants.^[6]

Increased IgE cross-linking may be the result in tissue transglutaminase enzyme alterations causing peptide aggregation during exercise. Sudden redistribution of blood during exercise transports allergens away from the gut to the skin and/or skeletal muscle, where phenotypically different mast cells reside.

During exercise, a fall in pH takes place creating an acidic state that may promote mast cell degranulation. *In vitro* studies have shown that during exercise, plasma osmolarity is raised and this can increase basophil activation and histamine release.

In the described patient, there was no history of any specific food or medication intake before exercise, but there are several kinds of commonly used foods drugs and environmental exposures [Table 1] that should be always tested for. For example, tomato salad is a commonly used food which can induce exercise anaphylaxis and should be always tested. Although tomatoes have become one of the most consumed vegetables worldwide, unfortunately, tomatoes are accompanied by an increasing risk of tomato allergy via five proteins with putative clinical relevance as tomato allergens.^[7]

Another effort-induced anaphylactic condition is the so-called cholinergic urticaria known as stress urticaria, allergy to effort and aquagenic urticaria.^[8] Cholinergic urticaria is a type of physical urticaria characterized by a number of short-lasting, highly pruritic weals. This kind of urticaria has been attributed to water in sweat (aquagenic), during exercise, which reacts with sebum forming a compound acting as an allergen that induces the release of histamine. This condition can be accompanied by systemic

Table 1: Causes associated with food dependent exercise-induced anaphylaxis

Conditions	Fruits
Atopy	Apples
Inheritance	Grapes
Mastocytosis	Lemon
Menstrual cycle	Lime
Environmental factors	Mango
Cold	Oranges
Dust mite	Fish
Humidity	Cuttlefish
Insect sting	Fish
Pollen warm	Shellfish
Food	Shrimp
Alcohol	Nuts
Barley	Chestnuts
Beans	Hazelnuts
Beef	Peanuts
Buckwheat	Pistachios
Cheese	Vegetables
Chicken	Cabbage
Chickpeas	Celery
Cow's milk	Garlic
Corn	Leek
Eggs	Mints
Lentils	Onions
Maize	Tomatoes
Mushrooms	Drugs
Mustard	Aspirin
Paprika	Dental amalgam
Pork	NSAIDs
Peas	Sex hormones
Rice	
Snails	
Soy	
Turkey wheat	

manifestations such as abdominal pain, nausea, vomiting and diarrhea.^[8] The humanized monoclonal IgG anti-IgE antibody omalizumab that binds specifically to circulating IgE molecules and interrupting the allergic cascade has been used to treat cholinergic urticaria.^[9]

Recent reports have associated food-dependent EIA with acute coronary syndrome and especially with the Kounis hypersensitivity-associated coronary syndrome.^[10,11] This syndrome is associated with anaphylactic or anaphylactoid reactions and is increasingly encountered in clinical practice. It can manifest as allergic angina, allergic myocardial infarction or stent thrombosis with thrombus infiltrated by eosinophils and mast cells.

As far as the treatment is concerned, physicians should be aware and mindful of the anaphylactic cardiovascular events

during exercise, and treatment should include supine position, oxygen and antiallergic medications such as antihistamines, steroids, sodium cromoglycate, leukotriene modifiers, humanized monoclonal antibodies, and intravenous fluids. A personalized, written anaphylaxis emergency action plan should be readily available. Patients and caregivers must always keep self-injectable epinephrine available and should be educated about its indications and contraindications.^[1]

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Conflicts of Interest

There are no conflicts of interest.

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