

AAAAI 2014 Seminar: Exercise-induced anaphylaxis and food-dependent exercise-induced anaphylaxis

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Exercise-induced anaphylaxis (EIA) is a heterogeneous form of anaphylaxis in which exercise is the immediate trigger for the development of symptoms (Lieberman 2010). Clinical manifestation includes skin symptoms such as flushing, pruritus, urticaria, warmth, and extreme fatigue, which may progress to angioedema, and respiratory symptoms or collapse (Castells 2003). Symptoms usually begin to resolve as soon as the patient stops the activity. Symptoms are typically induced by aerobic forms of exercise, and rarely by weight training or isometric exercises. The level of exertion is typically moderate to high, but some patients (especially older adults) can have mild symptoms with light activity, such as walking (Perez-Rangel 2013).

Some patients only experience symptoms when other contributing factors are simultaneously present. These factors include ingestion of specific foods, as in food-dependent, exercise-induced anaphylaxis (FDEIA), non-steroidal anti-inflammatory drugs (NSAIDs), narcotics, heat and humidity, high pollen counts, premenstrual status, stress, infections, or sleep deprivation. Food-dependent EIA seems to be more common than pure EIA, based on the number of reported cases of each type in the literature. Common food triggers include grains such as wheat and shellfish, although many other foods have been implicated such as fruits, vegetables, nuts, seeds, milk, meats, foods contaminated with aeroallergens (dust mites, penicillium mold), and wine (Morito 2010, Du Toit 2007). In FDEIA both exercise and the food are separately tolerated.

The pathophysiologic events during exercise that precipitate symptoms are unknown, although there are several theories. These include alterations in plasma osmolality and pH, tissue enzyme activity, blood flow redistribution, autonomic instability, altered gastrointestinal permeability and facilitated epitope recognition (reviewed recently by Robson-Ansley 2010):

- Exercise may modify enzyme and cytokine expression, resulting in altered processing and enhanced immunogenicity of food allergens. About 80% of Japanese patients with wheat-dependent EIA are sensitized to omega-5-gliadin [and the rest to high molecular weight glutenin (Morito 2010)], which is modified by tissue transglutaminase (tTG), resulting in the formation of large peptide complexes with increased IgE crosslinking capacity (Palosuo 2003). IL-6 increases expression of tTG and is actively produced by contracting skeletal muscles and peritendinous tissue during exercise. Although marathon-level exercise has been shown to increase IL-6 levels hundred-fold, less strenuous exercise may be unlikely to be associated with significant elevations in circulating IL-6.
- Exercise (and NSAIDs) can induce increases in gut permeability and can result in increased food allergen absorption or perhaps other physiologic changes. Although vigorous exercise was shown to increase small intestine permeability, this has not been reported with exercise of mild to moderate intensity. Negative food /exercise challenges are sometimes positive if repeated after the ingestion of 500 mg aspirin (Matsuo, 2008).
- Exercise may redistribute blood flow away from viscera to muscle and skin containing phenotypically different mast cells and thereby increase the potential for EIA (Robson-Ansley 2010).

The diagnosis is usually based on history, including evaluation for the contributing factors and sensitization to food allergens, and exclusion of other disorders. If skin testing is negative or not possible, IgE immunoassays for suspect foods should be performed. To detect possible wheat allergy, the use of fresh food (such as a paste of wheat flour) in skin testing or measurement of IgE to omega-5-gliadin appears to be more sensitive than using commercial extracts for skin testing or wheat-specific IgE (Hofmann, 2012). Serum tryptase may be elevated immediately after symptoms, although it should be normal at baseline. Although an exercise challenge testing with and without a trigger food is indicated to unequivocally establish the diagnosis of EIA, it is not always positive, may require fairly intense exercise or premedication with aspirin to reproduce symptoms, and poses some risk to the patient (Du Toit 2007, Matsuo, 2008).

The most direct approach to management is avoidance of exercise if exercise is the only trigger for EIA. However, it is difficult for children to avoid physical activity, and the many health benefits of regular exercise make this a less

than satisfactory approach in adults. Patients must understand the importance of stopping all exertion at the first sign of symptoms (ie, "Never push through"). A personalized emergency plan and epinephrine autoinjector should be provided to the patient. An autoinjector should be with the patient or immediately accessible whenever exercise occurs (ie, not locked in a locker). Patients should exercise with a partner who can recognize and treat symptoms, or educate teachers, coaches or gym supervisors about the disorder and its treatment. The doctor can help with this process. Prophylactic H1 antihistamines are not effective in the majority of patients, although a few patients appear to benefit. If food is a contributing factor, avoidance of the culprit food 3 hours pre- and 1 hour post-exercise is recommended. Occasional patients must avoid the food for longer periods before exercise (eg, 4 to 6 hours). In young children, in whom physical activity cannot be easily separated from meals, it may be safer and more practical to completely avoid the food in question. Oral cromolyn sodium (200 mg in adults, 100 mg in children) taken 20 minutes before eating (if eating is to be followed by exercise), reduces or prevents symptoms in some patients, although not all. Patients with severe symptoms can take cromolyn before every meal. Omalizumab can be offered if the patient also has asthma and dietary/activity restrictions are difficult to adhere to (Bray, 2012). Patients should also avoid NSAIDs and alcohol prior to exercise.

The prognosis is generally favorable and fatalities are rare. Most patients experience fewer and less severe attacks over time (Lieberman 2010). It is not known whether this is due to the natural history of the condition itself or due to modulated lifestyle.

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