

Food-Dependent, Exercise-Induced Anaphylaxis: Diagnosis and Management in the Outpatient Setting



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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

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List of Design Committee Members: Anna M. Feldweg, MD

Learning objectives:

1. To understand new developments in the role of augmenting factors in food-dependent exercise-induced anaphylaxis (FDEIA).
2. To understand the clinical presentation and diagnosis of FDEIA.
3. To recognize management options for FDEIA.

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Food-dependent, exercise-induced anaphylaxis is a disorder in which anaphylaxis develops most predictably during exercise, when exercise takes place within a few hours of ingesting a specific food. IgE to that food should be demonstrable. It is the combination of the food and exercise that precipitates attacks, whereas the food and exercise are each tolerated independently. Recently, it was demonstrated that exercise is not essential for the development of symptoms, and that if enough of the culprit food is ingested, often with additional augmentation factors, such as alcohol or acetylsalicylic acid, symptoms can be induced at rest in the challenge setting. Thus, food-dependent, exercise-induced anaphylaxis appears to be more correctly characterized as a food allergy syndrome in which symptoms develop only in the presence of various augmentation factors, with exercise being the primary one. However, additional factors are not usually

present when the patient exercises normally, so ongoing investigation is needed into the physiologic and cellular changes that occur during exercise to facilitate food-induced anaphylaxis. © 2016 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2017;5:283-8)

Key words: Anaphylaxis; Exercise; Food allergy; Food-dependent, exercise-induced anaphylaxis; Wheat-dependent, exercise-induced anaphylaxis; Omega-5-gliadin; Augmentation factors

CASE REPORT

A 46-year-old woman with mild allergic rhinitis presented with 3 past episodes of symptoms. In the first, she developed scattered urticaria without other symptoms while exercising on an elliptical trainer. She stopped and the urticaria resolved without treatment. Nearly a year later, she developed urticaria while working out at the gym, this time with some lightheadedness. She again rested and symptoms resolved without treatment. However, a few months later in the summer, she had a severe episode. She was walking her dog briskly one morning and became suddenly hot, flushed, and fatigued. Large urticaria appeared on her arms, and she became very lightheaded and then lost consciousness. After some time, she awoke to her dog standing over her. She was bleeding from a head laceration and her tongue was swollen. She called 911 on her cell phone and

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Abbreviations used

FDEIA- Food-dependent, exercise-induced anaphylaxis
NSAID- Nonsteroidal anti-inflammatory drug
SPT- Skin prick testing
WDEIA- Wheat-dependent, exercise-induced anaphylaxis

was taken to the emergency department, treated, and released. That morning, about 1 hour before walking the dog, she'd had coffee with milk and a buttered "everything" bagel (onion, sesame seeds, caraway, and poppy seeds). She took no medications and was in her usual state of good health that day. She did not have a regular exercise regimen, but was active, walking the dog daily and going to the gym occasionally. She had eaten the same type of bagel since the episode. She had not exercised vigorously since but was walking the dog daily. She rarely drank alcohol and did not take nonsteroidal anti-inflammatory drugs (NSAIDs).

Skin prick testing (SPT) to 40 commercial food extracts, including wheat, rye, barley, milk, sesame, and onion, showed positive results only to shrimp, crab, and lobster, all of which she'd eaten in the past without symptoms, including shrimp since her severe episode. IgE immunoassays to the components of her breakfast, including the seeds on the bagel, revealed positive results to wheat (3.19 kU/L), rye (6.24 kU/L), and barley (0.5 kU/L). She was diagnosed with food-dependent, exercise-induced anaphylaxis (FDEIA), educated about the disorder, advised to avoid these grains for 4 hours before exercise, and trained in how and when to use an epinephrine autoinjector.

Three years later, she reported symptoms following the ingestion of very small amounts of wheat and moderate or mild exertion. She had been meticulous about avoiding wheat/rye/barley before exertion initially after diagnosis, but had realized over time that she was able to "cheat" with small handfuls of wheat-based snacks and not develop symptoms with exertion. Lately, however, this appeared to be changing. She noticed that the symptoms occurred almost exclusively in the late summer and fall, on hot, very humid days. She was also having more severe symptoms of allergic rhinitis with time. SPT to an environmental panel showed strong positive results to dust mite (explaining the previous positive results to crustaceans), *Alternaria* mold, and multiple weed pollens. Results were negative to tree and grass pollens. IgE to omega-5-gliadin, which had become commercially available, was positive at 15.9 kU/L. Repeat IgE was obtained to wheat (5.85 kU/L), rye (7.98 kU/L), and barley (0.57 kU/L). A nasal steroid spray and an oral antihistamine were initiated for her allergic rhinitis, and she was advised to be more careful in avoiding wheat, rye, and barley before exercise during weed pollen season and on hot, humid days.

SIGNS AND SYMPTOMS AND COMMON FOODS

Symptoms of FDEIA may begin at any stage of exercise and occasionally occur just after exercise.¹ The culprit food is usually ingested within the 4 hours preceding exercise, or rarely just after exercise.¹ The frequency with which symptoms occur varies among patients with FDEIA and can be very unpredictable, even for a given patient. Early signs and symptoms typically include sudden fatigue, diffuse warmth, flushing, itching, and/or urticaria.^{2,3} If the patient stops and rests, symptoms usually resolve,

but continued exertion can result in angioedema, gastrointestinal symptoms, laryngeal edema, bronchospasm, hypotension, or collapse.

Vigorous forms of exercise, such as jogging or aerobics, are most often implicated, although lower levels of exertion (eg, brisk walking or yard work) are capable of triggering attacks in some patients.⁴ In older adults, symptoms may develop with minimal exertion (eg, crossing the street and ironing).^{5,6}

The foods most commonly implicated in FDEIA are wheat, other grains, and nuts in Western populations and wheat and shellfish in Asian populations; however, a wide array of culprit foods has been reported.^{1,7-15} Most patients develop symptoms only after eating a specific food, although a few have attacks if any food (usually solids rather than liquids) has been ingested.¹⁶ Patients have been described in whom symptoms occurred only if 2 foods were eaten together before exercise.^{17,18} The processing of the food may also be critical in some cases, such as a patient who developed FDEIA with tofu but could tolerate soy milk.¹⁹

EPIDEMIOLOGY

FDEIA is uncommon but reported around the world. A Japanese group determined a prevalence of approximately 0.02% among junior high school students.^{20,21} The disorder most commonly affects young adults, but patients of all ages are reported.

THE CENTRAL ROLE OF AUGMENTING FACTORS IN PATHOGENESIS

The most consistent augmenting factor in this food allergy syndrome is exercise. According to leading theories, exercise precipitates food-induced anaphylaxis in sensitized patients either by increasing the absorption of allergen^{22,23} or by lowering the activation threshold of sensitized mast cells and/or basophils.²⁴ However, these theories have not been conclusively demonstrated to date. There is indirect evidence that these mechanisms are at play, because other factors that increase gastric permeability (NSAIDs and alcohol) improve the likelihood that a food + exercise challenge will elicit symptoms.^{22,23,25,26} NSAIDs can also lead to enhanced mast cell degranulation through effects on arachidonic acid metabolism and other mechanisms.^{27,28} Still, research to determine the physiologic and cellular changes that occur during exercise is needed because most patients with FDEIA have symptoms in the absence of any additional augmenting factors.

As with anaphylaxis from other causes, various other factors are important for individual patients. As just mentioned, these may include NSAIDs,^{22,29-33} alcohol,^{4,29} infections,³⁴ increased body temperature (ambient high heat and humidity),⁴ seasonal pollen exposure in pollen-sensitized patients,⁴ premenstrual or ovulatory phases of the menstrual cycle in women,^{11,30} and other less common factors^{35,36} (Table I). A recent review summarized current theories on how various augmenting factors may facilitate allergic reactions and anaphylaxis.³⁵

WHEAT-DEPENDENT EXERCISE-INDUCED ANAPHYLAXIS

Wheat is the most commonly reported allergen in FDEIA overall, and wheat-dependent exercise-induced anaphylaxis (WDEIA) is the best-studied form of FDEIA. Omega-5 gliadin, a protein component of gluten, is an important

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