

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



Anna M. Feldweg, MD

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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.

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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

Allergy/Immunology, Brigham and Women's Hospital, Chestnut Hill, Mass
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Corresponding author: Anna M. Feldweg, MD, Allergy/Immunology, Brigham and Women's Hospital, 850 Boylston St, Ste 540, Chestnut Hill, MA 02467. E-mail: Afeldweg@partners.org.

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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

TABLE I. Augmenting factors for FDEIA

Augmenting factors for FDEIA	
Common	
Exercise (in all cases, by definition)	
NSAIDs	
Alcohol	
Less common	
Increased body temperature (high heat and humidity)	
Infections	
Physical stress, sleep deprivation	
Pollen season in pollen-allergic patients	
Premenstrual or menstrual phase of cycle (women)	
Narcotics, opioids	

allergen in this disorder,³⁷ as well as in wheat allergy causing anaphylaxis independent of exercise.³⁸ Omega-5 gliadin is water insoluble but ethanol soluble. Other wheat allergens have also been implicated in WDEIA, although less commonly.^{15,18,39,40} A detailed review of wheat allergens in WDEIA has been published.⁴¹

In 2014, Brockow et al²⁹ demonstrated that exercise was not absolutely necessary to induce symptoms in all patients with WDEIA, something that had been noted in a previous case report.³¹ The study described 16 patients with WDEIA and sensitization to omega-5 gliadin. These individuals were challenged with gluten-enriched bread + exercise to confirm the diagnosis, and then challenged sequentially with increasing amounts of bread, alone or combined with aspirin, alcohol, and exercise. Four subjects developed symptoms with 10 to 80 g of gluten-enriched bread alone, without exercise. Another 10 subjects required premedication with 500 to 1000 mg of aspirin, 10 to 30 mL of 95% alcohol, plus gluten-enriched bread to develop symptoms without exercise. In the remaining 2 subjects, all these measures, plus exercise, were required to elicit symptoms. These findings demonstrated that exercise is simply another augmenting factor for the clinical expression of an underlying food allergy, albeit the most important one for these individuals in their normal lives. The authors suggested the term “augmentation factor-triggered food allergy” instead of FDEIA. Another interesting finding in this study was that gastric and intestinal permeability in these patients, as measured by absorption of nondigestible sugars, did not appear to differ from that in normal controls, either as baseline or during exercise, arguing against the theory that patients with FDEIA are food-allergic individuals with abnormal gastrointestinal permeability. These findings should be repeated by other groups and with other food allergens, if possible. It remains to be determined why exercise is such a potent augmenting factor in certain food-sensitized individuals, and whether there are additional augmenting factors that have not yet been recognized, which could be involved during patients’ real-life reactions, as most reactions occur in the absence of NSAIDs or alcohol.

A variant of WDEIA has been described in patients (mostly Japanese women) who appeared to have been sensitized through cutaneous exposure to hydrolyzed wheat protein, a water-soluble foaming agent in personal products (eg, facial soap).^{39,40} Omega-5 gliadin is not the main allergen in this syndrome, and some

patients present with urticaria or anaphylaxis, rather than WDEIA. Avoidance of hydrolyzed wheat protein-containing products may lead to resolution of the allergy with time, which is different from traditional WDEIA, as the latter tends to be persistent.^{42,43} The relevance of these findings to other populations has not been reported.

DIAGNOSIS

The diagnosis of FDEIA is made clinically in most cases largely on the basis of historical details of events surrounding the episodes. Food + exercise challenge confirms the diagnosis, but carries risk and is not always necessary.

The following criteria are suggested:

- Signs and symptoms consistent with anaphylaxis that occurred during (or within an hour of) exercise but only when exercise was preceded by food ingestion.
- No other diagnosis that explains the clinical presentation.

If a specific food is implicated, there should be

- evidence of specific IgE to the implicated food, either by skin testing or by food-specific IgE immunoassays and
- no symptoms on ingestion of that food in the absence of exertion and no symptoms if exercise occurs without ingestion of that food, although there may be rare exceptions (patients may report isolated incidences when symptoms occurred at rest in the presence of other augmenting factors, such as illness).

There are no physical findings that are unique to patients with FDEIA. Most patients develop urticaria during episodes, with wheals that are larger than the pinpoint lesions of cholinergic urticaria. A complete skin examination should be performed to exclude maculopapular cutaneous mastocytosis (urticaria pigmentosa), the characteristic skin finding in mastocytosis. Mastocytosis can present with flushing and other characteristic symptoms of exertion, as well as in response to various other triggers. A serum tryptase level should be measured in all patients and should be normal in individuals with FDEIA when the patients are in their usual state of health. Elevated values at baseline should prompt an evaluation for a mast cell disorder.

Skin testing or *in vitro* testing

In patients with FDEIA, skin testing and/or *in vitro* testing for food-specific IgE is essential to the evaluation because sensitization to the precipitating food(s) is demonstrable, with rare exceptions.⁴⁴ If with a commercial extract or standard food-specific IgE immunoassays yield negative results, which is not uncommon, SPT with the fresh food should be performed.

In patients with suspected WDEIA, SPT with purified gluten (commercially available as vital wheat gluten or high-gluten flour), mixed into saline to form a paste, had a sensitivity of 100% in one study.²⁹ An ImmunoCAP assay for IgE to recombinant omega-5 gliadin (Thermo Scientific, Waltham, Mass) is commercially available. The sensitivity of this assay was found to be 80% in a study of 50 Japanese patients with positive wheat/exercise challenges⁴⁵ and 100% in the study of 16 patients mentioned previously.²⁹

Skin testing or *in vitro* testing for IgE sensitization to environmental allergens is sometimes useful if the patient is more susceptible to attacks during certain pollen seasons or in a patient

TABLE II. Clinical recommendations for patients with FDEIA

Recommendation	Specific points for discussion and planning
Have epinephrine autoinjector and mobile phone available in all exercise settings.	Who will carry the autoinjector and where will it be: Patient, teacher, coach, companion? That person must be trained in how and when to administer and be able to recognize early signs and symptoms. Runners can be reluctant to carry autoinjectors and mobile phones, which they may find bulky. Autoinjectors should not be left in lockers or cars away from the patient. Provide patient and others with Anaphylaxis Action Plan.
Stop exertion immediately if any symptoms occur (never “push through”).	Are there situations in which the patient will be reluctant/unable to stop? In adolescents involved in team sports, there may be reluctance to stop for fear of disappointing others or interrupting a game. This needs to be discussed and a plan made with the coach. In patients in high-activity jobs, work conditions may need to be altered. In military personnel or pilots, the causative food may need to be avoided altogether.
Avoid the causative food for 4-6 h before exercise, at least initially. Time may be reduced going forward, although most patients must avoid the food for a minimum of 2 h.	Patients in school or whose mealtimes and activity are structured should plan to have “safe” foods available for snacking. Planning lists of safe foods with parents/caregivers is particularly helpful for children and adolescents.
Avoid possible augmenting factors and pay close attention to circumstances surrounding symptoms to detect other factors that might be important.	Provide patient with a list of possible augmenting factors and review this periodically, especially if new symptoms occur. When new symptoms occur, instruct patient to contact clinic and review circumstances surrounding symptoms while details are fresh in the patient’s memory.
Exercise with other informed individuals, at least initially until it is clear to the patient and the clinician that the situations that induce symptoms can be avoided successfully.	Exercise with a companion, in a gym, or under the supervision of a coach or trainer who has been taught to recognize early signs and administer epinephrine appropriately.
As with prevention of anaphylaxis of any etiology, adult patients should be informed about the risks of certain long-term medications, such as beta-blockers and angiotensin-converting enzyme inhibitors, and discuss with allergist if another clinician prescribes.	Provide education to patient and in communications with other clinicians. Review patient’s medication list regularly to make sure the medications have not been added.

with concomitant allergic respiratory disease. However, it is not a routine component of the evaluation.

CHALLENGE PROCEDURES

A positive food + exercise challenge confirms the diagnosis, but a negative challenge does not reliably exclude the diagnosis because symptoms can be difficult to induce in a laboratory setting and the procedure is not standardized.^{1,20,29,33,46,47} If pursued, challenges should be performed with informed consent and by allergy specialists with the expertise, staff, and equipment available to recognize and treat anaphylaxis, because severe symptoms can occur.²⁹

A 1998 review of 234 reported cases of FDEIA found that food + exercise challenges successfully induced symptoms in approximately two-third of cases.⁴⁶ There is great variability among patients in terms of the amount of food, vigor and duration of exercise, and requirement for additional augmenting factors necessary to reproduce symptoms. Since then, several challenge procedures have been published for adults^{29,41,48} and children,¹⁸ which have in common the withholding of any antihistamines, premedication with acetylsalicylic acid, relatively large amounts of the suspect food, and strenuous exercise.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of FDEIA includes exercise-induced anaphylaxis independent of food, idiopathic anaphylaxis, cholinergic urticaria with systemic symptoms,⁴⁹ mastocytosis, exercise-associated gastroesophageal reflux (milder symptoms), and postural orthostatic tachycardia syndrome.⁵⁰

MANAGEMENT

The management of FDEIA is centered on avoidance of the culprit food before exercise and identification of other augmenting factors that are important for that individual.

As with all forms of anaphylaxis, patient education is an ongoing process that should take place at regular follow-up visits and after any recurrent symptoms. An Anaphylaxis Emergency Action Plan can be provided, listing the most common symptoms and signs of anaphylaxis and providing instructions for prompt epinephrine injection.

Precautions with exercise

Patients usually have a strong desire to continue to exercise, and every attempt should be made to construct a management plan that allows them to do so. However, modifications in the patient’s choice of activities may be required, and several precautions surrounding exercise are advised (Table II).

Food avoidance

Individuals with FDEIA should avoid the culprit foods for 4 to 6 hours before exercise initially. Exercising in the mornings before eating anything is one way to comply with this restriction, although some patients find this difficult. Over time, individuals often come to learn that less time (ie, 2-3 hours) is adequate, but caution is prudent at first.

Avoiding the combination of certain foods and exercise can also prove difficult for children, who are active throughout the day, adolescent athletes who need to eat before practices, people in physically strenuous jobs, people sensitized to common foods (eg, wheat), and people whose symptoms are elicited by minimal

exertion. Approaches that can work better in these situations include generating a list of “safe” foods that a parent or the patient can make sure to have available, or completely removing the causative food from the diet.

PROPHYLACTIC PHARMACOTHERAPY

There are no randomized trials of medications to prevent episodes of FDEIA, and recommendations are based on small series, case reports, and clinical experience. Prophylactic medications are not needed in cases in which behavior can be modified and triggering foods and augmenting factors identified and avoided. However, this is not feasible in all cases. In addition, pharmacotherapy is used to control concomitant allergic disease, such as allergic rhinitis.

Cromolyn sodium

Several published case reports suggest that full-dose cromolyn sodium taken orally before food ingestion can be useful for preventing symptoms of FDEIA.^{17,51-53} However, without controlled studies, it is unclear whether it is helpful for all patients and to what extent. Therefore, it should not replace food avoidance, but can be considered as an additional protective measure when avoidance proves difficult.

Cromolyn sodium comes in an oral formulation in the United States, in ampules of 100 mg/5 mL. The dose for adults is 200 mg, orally, taken 20 minutes before meals (ie, up to 3 times daily). The usual dose used in children is 100 mg taken in the same manner. Case reports describe school children with FDEIA who were advised not to exercise for 4 hours after food ingestion, but were not able to comply with this. Oral cromolyn taken 20 minutes before lunch appeared to prevent the children from developing symptoms if they exercised in the afternoon. The children developed symptoms only on days they forgot to take the cromolyn.⁵² In reports of adult patients with wheat-dependent FDEIA, premedication with cromolyn prevented absorption of wheat allergen into the blood in one⁵³ and prevented a rise in plasma histamine in the other.⁵¹ However, in another adult with wheat-dependent FDEIA, a lower dose (100 mg) taken 1 hour before food/exercise challenge prevented neither symptoms nor absorption of gliadin into the blood.⁵⁴

H1 antihistamines

A few cases in which premedication with first-generation H1 antihistamines prevented FDEIA have been reported,^{4,55,56} but this intervention has not been systematically studied, and there are concerns about masking early symptoms. Clinical experience suggests that newer antihistamines are not consistently effective and cannot be relied upon to prevent future episodes. However, if needed to control concomitant allergic disease, such as severe allergic rhinitis, standard doses of newer antihistamines do not appear to interfere with recognition of early symptoms.

Other agents

Omalizumab⁵⁷ and misoprostol (a synthetic analogue of the gastroprotective prostaglandin, prostaglandin E1)^{54,58} have been helpful in case reports. Oral glucocorticoids and leukotriene-modifying agents have not been studied.

PROGNOSIS

A small number of case reports describe fatalities attributed to FDEIA.⁵⁹⁻⁶² FDEIA appears to be a persistent disorder, with

the exception of some patients sensitized to allergens in hydrolyzed wheat protein.^{42,43} Most patients do well, reporting fewer attacks over time.^{4,8} Improvement may be attributable to recognition of early symptoms, modifications in exercise habits, and improved avoidance of triggering food and augmenting factors.

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