CASE REPORT

Food-dependent exercise-induced anaphylaxis

Robert H Wauters,¹ Taylor A Banks,² Evelyn M Lomasney²¹Internal Medicine, Walter Reed National Military Medical Center, Bethesda, Maryland, USA²Allergy/ Immunology, Walter Reed National Military Medical Center, Bethesda, Maryland, USA**Correspondence to**

Dr Robert H Wauters, robert.h.wauters.mil@mail.mil

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SUMMARY

Food-dependent exercise-induced anaphylaxis (FDEIAN), first reported in 1979, is a condition defined by the consumption of a trigger food with temporally related exercise that results in an immediate hypersensitivity (type 1) reaction in the setting of the trigger food being tolerated independent of exercise and exercise being tolerated in the absence of trigger food consumption. The most common trigger food in the west is wheat and shellfish in Asia. The exact mechanism of FDEIAN is unknown, though several hypotheses exist. Cofactors such as non-steroidal anti-inflammatory drug use, alcohol consumption and others have been associated with reported cases.

BACKGROUND

Food-dependent exercise-induced anaphylaxis (FDEIAN) is a potentially life-threatening and rare subtype of anaphylaxis that occurs only when exertion takes place with temporal relation to trigger food consumption (table 1), usually wheat. In this manuscript we offer an atypical case of food dependent exercise induced anaphylaxis to illustrate the clinical considerations in this disease processes. The manuscript highlights the clinical characteristics, pathophysiology, diagnosis and management of FDEIAN. Diagnostic pitfalls and review of several reported pharmacological prophylactic measures are addressed. This work will be a valuable addition to the existing medical literature by updating the practising allergist-immunologist and fellow-in-training alike on the most up-to-date knowledge available on this rare disease and can also serve as a concise review reference.

CASE PRESENTATION

A 32-year-old female US Army soldier presents to allergy clinic endorsing a recent anaphylactic reaction. She states that while vigorously dancing at a wedding, she developed urticaria on her shoulder that rapidly spread to her chest, arms, neck and face. Her symptoms quickly progressed to throat pruritus, angioedema of the tongue and dyspnoea. Prior to dancing, the patient consumed steak, vegetables, crab cakes, a glass of red wine and one cocktail. Emergency medical services treated her with intramuscular epinephrine, diphenhydramine and corticosteroids during transport to the hospital. Her symptoms resolved in 4 hours without additional treatment. During allergy consultation, detailed history revealed that since this episode she had avoided crab but had tolerated all other foods, including beef, fish, a variety of vegetables and

exercise without recurrent symptoms. She denied any use of non-steroidal anti-inflammatory drugs (NSAIDs) and was not perimenstrual during her event. She has never had any allergic symptoms while exercising and runs regularly. She denied history of atopic disease and physical examination was normal. Skin prick testing was negative for IgE-mediated response to crab, lobster or shrimp and was not performed for beef as she had tolerated consumption before and after her event without any symptoms. Specific serum IgE testing for crab, lobster, and shrimp was not performed. Additionally, IgE immunoassay to galactose- α -1,3-galactose was not performed due to her tolerance of mammalian meat without any symptoms.

She successfully passed an oral food challenge to crab whereby incrementally increasing portions of commercially purchased crab cake were eaten at 0, 15 and 30 min under close clinical observation and vital sign monitoring. The patient was then observed for 60 min without symptoms and subsequently ran on a treadmill at the 90 min mark for 15 min at a moderate pace, with appropriate cardiac response to exercise and without any anaphylactic symptoms during oral food exercise challenge (OFEC). She was then observed for another 60 min without symptoms and ran again on a treadmill at the 165 min mark for 15 min. During the second run, the patient developed urticaria on her face and the OFEC was terminated. She was treated with 10 mg cetirizine and her urticaria resolved. Serum tryptase levels were not evaluated at the time of laboratory testing. The patient's clinical history and evaluation confirmed a diagnosis of FDEIAN to crab.

INVESTIGATIONS

Obtaining a thorough clinical history is the most critical element of diagnosing FDEIAN. When suspicion is high, skin prick testing or food-specific IgE testing should be performed, as the vast majority of reported cases are associated with demonstrable sensitisation to the trigger food.¹ In vitro specific IgE testing for crabs/crustaceans was not evaluated in this patient after the negative skin prick testing and may have been positive if it had been performed.

Reproduction of symptoms consistent with immediate hypersensitivity during OFEC testing confirms the diagnosis of FDEIAN. However, a negative OFEC does not rule out the diagnosis, as symptoms can be difficult to induce in the laboratory setting due to the lack of standardisation in testing and the usual absence of accelerants that may have been present in vivo. Tryptase levels are not routinely evaluated in FDEIAN as elevations in

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Table 1 Food triggers associated with food-dependent exercise-induced anaphylaxis

Dairy	Cow's milk, cheese
Egg	Chicken egg
Fruit	Apple, nectarine, grape, kiwi, lychee, orange, peach, pear, strawberry
Grains	Rye, wheat
Legumes	Chickpea, soy bean, peanut
Meats	Pork, beef, chicken
Nuts/Seeds	Hazelnut, pistachio, almond, mustard, poppy seed, walnut
Seafood	Shrimp, crab, snail, octopus, cuttlefish, oyster, squid
Vegetables	Cabbage, celery, fennel, garlic, lettuce, mushroom, onion, potato, tomato

serum tryptase immediately after an episode of symptoms can support the diagnosis of anaphylaxis but do not provide information about exercise or food/exercise as the trigger, and tryptase levels often fail to increase during the OFEC.² Eliciting the most minimal symptoms in laboratory testing to make the diagnosis without causing a severe anaphylactic reaction is the goal in evaluation of FDEIAN. Careful monitoring for early symptoms and performing testing in appropriate facilities that can respond to anaphylaxis is paramount.

DIFFERENTIAL DIAGNOSIS

Exercise-induced anaphylaxis.

Anaphylaxis to food.

Cholinergic urticaria.

Clandestine insect envenomation.

FDEIAN.

Idiopathic anaphylaxis.

TREATMENT

Patient education and strict avoidance of combining trigger food and exercise is of paramount importance in the management of FDEIAN. Continued consumption of the trigger food is encouraged with the avoidance of exercise 4–6 hours afterwards. Since cases of FDEIAN have been reported with consumption of trigger food just after vigorous exercise, it is also recommended that trigger food be avoided for 2–4 hours after exercise. Cases of FDEIAN with ubiquitous foods like wheat, and in children, athletes and people with physically demanding jobs can be more difficult to manage and require nutritionist referral. Continued participation in exercise is encouraged for all patients. There are no randomised control trials addressing pharmacotherapy for prevention of symptoms in FDEIAN. Routine use of antihistamines is not generally recommended as they may mask early symptoms but can be considered for continuation in patients already taking these medications. Sodium cromoglycate was identified in a 2009 case report as effective in preventing FDEIAN symptoms in two paediatric patients with wheat as food trigger.³ Misoprostol was reported by Takahashi *et al*⁴ as effective in preventing FDEIAN symptoms in a 47-year-old Japanese man with FDEIAN to wheat when pretreated with 200 µg prior to exercise after consumption of trigger food. In 2012, Bray⁵ described the successful treatment FDEIAN with omalizumab in a 14-year-old competitive male athlete. Though these pharmacological treatment modalities may have promise, they require further evaluation. The cornerstone of management in FDEIAN is avoidance of the trigger food and exercise combination and the establishment of an anaphylaxis action plan with maintenance of an epinephrine auto-injector.

Box 1 Reported accelerants/cofactors

- ▶ Alcohol.
- ▶ Non-steroidal anti-inflammatory drugs.
- ▶ Perimenstruation.
- ▶ Seasonal aeroallergens.
- ▶ Increased ambient temperature.
- ▶ Cannabis.
- ▶ Opioids.
- ▶ Stress.
- ▶ Infection.

OUTCOME AND FOLLOW-UP

The patient has moved to Hawaii, is adherent to her plan of care and has had no further episodes of FDEIAN. She remains on active duty and continues to perform physical training with an epinephrine autoinjector and cell phone with her at all times.

DISCUSSION

Clinical manifestations of FDEIAN can include urticaria, fatigue, diarrhoea, respiratory symptoms, hypotension, syncope and rarely death. The timing of symptom onset is highly variable in relation to food consumption. Delayed and near-immediate onset have been reported. Usually FDEIAN presents when trigger food is consumed prior to exercise; however, there have been rare cases reported of consumption of food after vigorous exercise leading to symptoms as well.⁶ The exact pathogenesis of FDEIAN remains unclear, but several hypotheses exist. Increased permeability of the gastrointestinal tract during exercise has been suggested and demonstrated in a murine model.^{7,8} In a human model, intestinal absorption of the peanut allergen Ara h 6 was shown to increase after intense exercise, suggesting this mechanism of antigen exposure may play a role in the pathogenesis of FDEIAN.^{7,9} Another leading hypothesis is that a lowered threshold for basophil activation and mast cell degranulation exists during aerobic exercise, leading to symptoms in susceptible patients. Other suggested possibilities include autonomic dysregulation, alterations in blood flow and mobilisation of immune cells from gut during exercise as contributory to FDEIAN.⁷ The role of

Learning points

- ▶ Food-dependent exercise-induced anaphylaxis (FDEIAN) is a rare but potentially fatal, subset of IgE-mediated food allergy. Thorough clinical history and appropriate diagnostic testing is essential to making the diagnosis. Our patient's negative skin prick testing to crab is a unique element of this case.
- ▶ FDEIAN should be treated like any other type 2 hypersensitivity reaction with institution of an anaphylaxis action plan and maintenance of an epinephrine autoinjector as the cornerstone of care.
- ▶ FDEIAN is a difficult diagnosis to make. Discordance between in vivo and laboratory settings may lead to falsely negative food exercise challenge testing. Lack of associated accelerants can also complicate testing.
- ▶ Modern grocery and the age of processed foods and multifeed meals can make identifying a trigger food a difficult undertaking. Diligence must be taken to get an extremely thorough history from patients when FDEIAN is suspected.

accelerants and cofactors is important in FDEIA (see [box 1](#)). A broad set of contributors have been reported in cases of FDEIA including seasonal aeroallergens, perimenstruation, opioids, stress, infection, increased ambient temperature and cannabis.¹⁰ The most commonly identified accelerants in reported cases are NSAIDs and alcohol. The role of NSAIDs was demonstrated by Matsuo *et al*¹¹ who measured increased serum gliadin peptide levels in patients with wheat-dependent exercise-induced anaphylaxis, who were given aspirin. The authors suggest that NSAIDs may contribute to intestinal tight junction dysregulation and increased systemic absorption of trigger food antigen.

Similarly, Brockow¹² demonstrated increased intestinal permeability in 16 patients with wheat-dependent exercise-induced anaphylaxis and exposure to alcohol using a mean intestinal permeability index, affirming alcohol as an accelerant in FDEIA.

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