CASE REPORT

Food-dependent exercise-induced anaphylaxis with negative allergy testing

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SUMMARY

Food-dependent exercise-induced anaphylaxis (FDEIA) is a disorder where exercise following allergen ingestion triggers anaphylaxis although exercise and allergen exposure are independently tolerated. The diagnosis of FDEIA is based on a characteristic clinical history. The culprit allergen is usually confirmed through the use of skin prick testing (SPT) serum-specific IgE levels and a food–exercise challenge. We present a case of FDEIA suggested by clinical history and open food–exercise challenge with negative specific IgE levels and SPT that highlights the challenges involved in diagnosing and managing this rare disorder.

BACKGROUND

Anaphylaxis is a severe allergic reaction defined by symptoms involving at least two organ systems (cutaneous, gastrointestinal, cardiovascular or respiratory) or when hypotension develops after exposure to a known allergen.^{1 2} The main triggers are food, medications and venom as well as certain physical conditions including cold, heat and exercise.³

Food-dependent exercise-induced anaphylaxis (FDEIA) is a distinct allergy syndrome. Anaphylaxis develops when exercise follows food allergen exposure although exercise and the food allergen are independently tolerated. It is a rare disorder that may affect up to 0.017% of the population.⁴ The pathogenesis of FDEIA remains poorly understood. The most common food triggers are reported to be wheat, crustaceans and tomato.^{5–7} However, FDEIA may be triggered by a multitude of food allergens and exercise of varying forms, durations and intensities. Furthermore, anaphylactic episodes may only develop in the presence of specific cotriggers and cofactors including simultaneous ingestion of a second food, non-steroidal anti-inflammatory drugs (NSAIDs) or exposure to extremes of temperature or aeroallergens. IgE-mediated food hypersensitivity is thought to be the principal underlying pathogenic mechanism. It is suggested that exercise induces physiological changes that increase absorption of undigested forms of allergen in the gut.^{7–10}

Diagnosis hinges on a detailed clinical history, which may identify a suspected food allergen, the relationship of anaphylaxis to exercise and exclusion of other diseases that may manifest similarly. Skin prick testing (SPT) and/or measurement of specific IgE levels usually identify a causal food allergen; oral food–exercise challenge (OFEC) confirms the diagnosis. Even after identifying a causal allergen, diagnosing FDEIA may be difficult.

Anaphylactic episodes are rarely stereotypical and are not always reproducible. No widely accepted protocol for exercise testing exists and false-negative results are common.^{8–10}

We present a case of FDEIA suggested by clinical history and diagnosed by OFEC. SPT and specific IgE levels were negative to possible causal allergens. This case highlights the challenges involved in diagnosing and managing this rare disorder.

CASE PRESENTATION

An 11-year-old girl presented to the emergency department with anaphylaxis following exercise. She ate a cookie containing wheat, oats and soy, with possible traces of peanuts and tree nuts 1 h before playing basketball indoors at school. She developed periorbital oedema, throat itching and tightness and dyspnoea half an hour after the onset of physical exertion ([figure 1A](#)). She was treated with intramuscular epinephrine in the emergency department and her symptoms resolved thereafter ([figure 1B](#)).

Figure 1 (A) An 11-year-old girl presenting to the emergency department with angioedema and dyspnoea following exercise. (B) Resolution of symptoms within minutes after epinephrine administration.

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The patient had eaten this brand of cookie on previous occasions without incident. She had previously tolerated postprandial exercise on multiple occasions. She had no prior history of anaphylaxis, asthma, seasonal allergies, eczema, pollen-food allergy syndrome, exercise intolerance or personal or family history of angioedema. She ingested no other food or medication (including NSAIDs) in the hours prior to exercise and was not exposed to latex, insect venom or extremes of temperature at the time of anaphylaxis.

INVESTIGATIONS

The patient was referred for outpatient investigations at the allergy clinic. SPTs were negative to an extract prepared from the cookie as well as to potential allergens contained therein, including oats, soy, wheat, barley, cashew, peanuts, hazelnuts, walnuts and pecans. Specific IgE for the aforementioned allergens (including omega-5 gliadin) were also below threshold for detection. Serum levels for tryptase, C1 esterase inhibitor and C4 were within the normal range.

The patient underwent OFEC. Two trials were conducted in a controlled environment 2 weeks apart in late fall (figure 2A,B).

The patient had no symptoms of upper respiratory tract infection prior to either trial. Each involved running on a treadmill in a monitored setting with pulmonary function tests (PFTs) measured prior to the onset of exercise and at regular intervals during exercise. For the first challenge, the patient was fasting 2 h prior to exercise testing. For the second challenge, she ingested the cookie in question 1 h prior to exercise testing. While fasting, the patient completed the exercise challenge without symptoms of anaphylaxis and without change in PFTs. However, after eating the cookie, the patient experienced dyspnoea, throat tightness and wheezing (though no frank angioedema was noted) following 5 min of exercise. This was accompanied by a decline in forced expiratory volume in 1 s to 68%. The challenge was stopped and the patient's symptoms resolved under observation without treatment.

DIFFERENTIAL DIAGNOSIS

The patient presented with respiratory and mucocutaneous symptoms of anaphylaxis following exercise. Given negative SPT and specific IgE levels to all potential consumed allergens and prior tolerance to the cookie in question, a food allergy unrelated to exercise is unlikely. She was not exposed to venom, latex or extremes of temperature at the time of anaphylaxis. She has never developed anaphylaxis after playing basketball or following any other form of exercise, making exercise-induced anaphylaxis unlikely.

Dyspnoea following exercise may be due to asthma exacerbation or exercise-induced bronchoconstriction. This is improbable in this case, given prior and ongoing exercise tolerance, absent history of asthma, seasonal allergies or atopy, lack of upper respiratory tract infection symptoms prior to presentation and exercise trials, as well as the presence of angioedema. Furthermore, the normal pulmonary function testing during exercise seen in the first challenge is not consistent with exercise-induced bronchoconstriction.

Hereditary and acquired angioedema as well as systemic mastocytosis may present with dyspnoea and angioedema. This patient had no family history of angioedema, and levels of tryptase, C4 and C1 esterase inhibitor were normal. Physical examination did not reveal lesions consistent with mastocytosis, and tryptase levels during the episode were within normal range. These are, therefore, improbable diagnostic possibilities.

Given anaphylaxis following exercise, positive OFEC to the suspected food and the continued ability to tolerate exercise without incident, FDEIA remains the most likely diagnosis.

TREATMENT

The patient and her mother were informed about the dangers of anaphylaxis. The patient has since been careful not to exercise within 2 h of eating. An emergency action plan was implemented, including informing school staff, prescription of an epinephrine autoinjector and recommending supervision during exercise.

OUTCOME AND FOLLOW-UP

The patient has not experienced another episode of anaphylaxis during the following year and has been able to tolerate exercise without incident.

DISCUSSION

This case exemplifies some of the diagnostic and management challenges in caring for patients with FDEIA. Episodes of FDEIA are rarely stereotypical, often require certain cofactors and cotriggers, and hence the clinical presentation may differ even in the same patient. This may account for the clinical variability in FDEIA observed in our patient. While on initial presentation to the emergency department, the symptoms involved the cutaneous and respiratory systems, following challenge the symptoms were restricted to the respiratory system.

Although negative allergen testing, as in our case, is unusual in FDEIA, SPT and specific IgE levels may not always reveal a causal allergen. Definitive diagnosis often relies on food-exercise

Figure 2 Pulmonary function tests (A) control exercise trial (fasting) and (B) food-exercise trial 1 h after ingesting the cookie in question.

challenge.^{8–10} A Japanese study of 50 cases of wheat-dependent EIA documented by food–exercise testing showed (among other epitopes tested) sensitivities of 48% and 80% for wheat-specific IgE and omega-5 gliadin-specific IgE, respectively. Some patients without omega-5 gliadin-specific IgE responded to other epitopes, while three patients had no positive IgE levels whatsoever.¹¹ This underlies the fact that each patient may develop an allergic response to a different epitope within the same protein and some may have a negative in vitro response to allergen, possibly because they respond to an epitope outside the testing panel. This may be the case for our patient.

FDEIA has been categorised into specific FDEIA (sFDEIA) and non-specific FDEIA (nsFDEIA). In sFDEIA, anaphylaxis is triggered by a specific food identified by allergy testing. In nsFDEIA, ingestion of any food prior to exercise triggers anaphylaxis and allergy testing is often negative.¹⁰ There is little discussion of nsFDEIA in the literature, though it has been documented in individual case reports as well as in larger studies.^{12–16} Although our patient had negative allergy tests, it is unlikely that she experienced nsFDEIA, because prior to presentation, she had engaged in postprandial exercise on multiple occasions without incident. However, because the candidate allergens are contained in numerous foods the patient eats, we advised that she should fast for a minimum of 2 h prior to exercise to avoid inadvertently triggering anaphylaxis. As such, we cannot with certainty attribute the absence of anaphylaxis to the exclusion of a specific allergen prior to exercise.

Management of FDEIA is predicated on avoiding the culprit allergen and any cotriggers or cofactors prior to, during and immediately after exercise as well as providing the patient with an epinephrine autoinjector. Our case poses significant challenges to diagnosing and managing FDEIA. Given that we are unable to identify a culprit allergen among many candidates, we have recommended broader dietary restrictions.

Learning points

- ▶ Consider food-dependent exercise-induced anaphylaxis (FDEIA) when anaphylaxis follows exercise.
- ▶ Skin prick testing and specific IgEs may not reveal a candidate allergen.
- ▶ FDEIA remains as a clinical diagnosis.
- ▶ Food–exercise testing is the gold standard for diagnosing FDEIA.

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