

Delayed food-dependent, exercise-induced anaphylaxis

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ABSTRACT

Food-dependent, exercise-induced anaphylaxis (FDEIA) is a clinically distinct form of anaphylaxis in which symptoms occur only when the patient exercises within a few hours of eating the food. Its precise mechanism remains unclear and has been reported to have a wide spectrum of presentations. The objective of this report is to show that the onset of FDEIA can be delayed for several hours and to emphasize the critical need for having self-injectable epinephrine available at all times. Our patient had several episodes of FDEIA to wheat shortly after exercise since the age of 11 years. At 16 years of age, 5 hours after exercise that followed eating a wheat-containing meal, the patient developed severe anaphylaxis with loss of consciousness. Skin-prick test was positive (4+) to wheat but negative to 41 other foods. Serum tryptase level 2 hours after onset of anaphylaxis was elevated. Other laboratory findings were within normal ranges. This case indicates that FDEIA can have a delayed onset for several hours. Because such delayed onset is unpredictable and can be life-threatening, it might be prudent for such patients to avoid the offending food totally or to avoid exercising for at least 6 hours after eating the food and to keep self-injectable epinephrine easily available at all times.

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Food-dependent, exercise-induced anaphylaxis (FDEIA) is a clinically distinct form of anaphylaxis. It was first described in 1983 by Kidd *et al.*¹ to celery and later other foods (*e.g.*, wheat, shellfish, egg, and pistachio) have been reported^{2–5} with wheat being the most common. In a series of 24 subjects with acute allergic reaction to wheat, anaphylaxis accounted for about one-half of them.⁶ This suggests that wheat-induced anaphylaxis may be underdiagnosed. The incidence of FDEIA seems to be increasing, possibly because of the increasing popularity of exercising, and has exhibited a wide spectrum of presentations. In most cases, symptoms appear during or shortly after exercise that follows ingestion of the offending food. We report here a case of a near-fatal anaphylaxis that developed 5 hours after exercise that followed ingestion of wheat.

CASE REPORT

A 16-year-old male subject was referred for allergy evaluation because he had an episode of severe anaphylaxis 3 weeks earlier. Within 1 hour after ingesting a cheese steak sandwich, peanut bar, and coke, he played basketball for ~1 hour. He did not develop any

symptoms during or after exercise. However, ~5 hours later, while he was home alone, he suddenly developed generalized urticaria, abdominal pain, and dyspnea. He started to call for emergency care but he rapidly lost consciousness before he could talk. He also could not get to his epinephrine autoinjector (EpiPen, Dey, Napa, CA) that he kept because he had had previous episodes. The paramedics arrived a few minutes later, forced the door open, and found him unconscious on his bedroom floor. He was breathing, but his pulse was barely palpable and his blood pressure was so low and it could not be assessed. He was given intramuscular epinephrine (0.3 mg), supplemental oxygen, and i.v. normal saline solution. He regained consciousness and was transported to the hospital.

In the Emergency Department, he was fully alert but in moderate respiratory distress—HR, 142/minute; RR, 48/minute; blood pressure, 90/48 mmHg; O₂ saturation, 98% on 50% O₂ by face mask—and had generalized urticaria and bilateral expiratory wheezing. He was given another dose of intramuscular epinephrine (0.3 mg), nebulized albuterol (2.5 mg), and i.v. diphenhydramine (50 mg). He was then admitted overnight for observation and was discharged the following day on prednisone, 20 mg b.i.d., for 5 days and diphenhydramine, 25 mg q. 6 hours p.r.n.

A review of his medical history revealed symptoms suggestive of perennial allergic rhinitis. He had experienced several episodes of anaphylaxis in association with exercise after ingestion of wheat-containing foods since the age of 11 years. Symptoms developed usually within <1 hour after exercise and consisted of hives, abdominal pain, hoarseness of voice, and shortness of

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breath. He lost consciousness on two previous occasions. Exercise by itself or exercise after nonwheat-containing meals did not trigger any symptoms. His first few episodes of anaphylaxis were treated at the local hospital Emergency Department but he was not given a prescription for self-injectable epinephrine. After 2 years of recurrent episodes, he was given a prescription for an epinephrine autoinjector (EpiPen) by a dermatologist who found serum-specific IgE negative to milk, chocolate, chicken, peanut, and tomato but was not checked for wheat. Subsequent episodes of anaphylaxis were self-treated with EpiPen.

Our evaluation included skin-prick testing (SPT), which was strongly positive (4+) to wheat but negative to 41 other foods. It was also moderately positive (3+) to house-dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) but negative to 36 other aeroallergens. Serum tryptase was 18.0 ng/mL (NI < 11.4) at 2 hours after onset of an episode of anaphylaxis. He had normal serum complement hemolytic assay CH50 (37 U/mL), C2 (31 U/mL), and C4 (21 mg/dL) levels. Complete blood count, erythrocyte sedimentation rate, blood chemistry, and thyroid function were normal also. Latex-specific IgE antibody, ANA titer, hepatitis profile, *Helicobacter pylori* antibody, and thyroid autoantibodies were negative.

He was given intensive education about easy accessibility and prompt use of epinephrine autoinjector, wearing of Medic-Alert identification, and avoidance of exercise for at least 6 hours after meals that may contain wheat products. This patient has been following the foregoing regimen and enjoying eating and exercising without any recurrence of anaphylaxis for the past 3 years.

DISCUSSION

The incidence of FDEIA is increasing, possibly because of increasing engagement in physical activities.⁷ Although several foods have been implicated, wheat seems to be the most common, perhaps partly because of its common consumption.⁸ Wheat also contains several water/salt-soluble and -insoluble protein fractions. Palosuo *et al.*⁹ identified omega-5 gliadin (*Triticum aestivum*) as a major wheat allergen in FDEIA. The same group¹⁰ also showed cross-reactivity of this allergen with gamma-70 and gamma-35 secalins in rye as well as with gamma-3 hordein in barley. According to Battais *et al.*,¹¹ the major IgE-binding wheat allergens are gliadin, low molecular weight glutenin subunits, and some water/salt-soluble proteins, whereas high molecular weight glutenins are only minor allergens. In certain patients, wheat α -amylase inhibitor subunits can be the offending allergen.¹²

Postulated mechanisms linking exercise with induction of symptoms of FDEIA include enhanced intestinal

allergen absorption secondary to increased intestinal permeability,¹³ provocation of abnormal responses of the autonomic nervous system,¹⁴ decreased threshold of IgE-mediated mast cell degranulation,¹⁵ and activation of tissue transglutaminase¹⁶ by exercise. Transglutaminase is located beneath the intestinal epithelium and is activated by mucosal inflammatory injury or by oxidative stress such as occurs during exercise. It catalyzes the formation of irreversible protein cross-links which enhances the IgE binding affinity. This enzyme may be particularly important in wheat-dependent, exercise-induced anaphylaxis because gliadin is among its substrates.¹⁶

Information is accumulating to indicate that FDEIA can have varying presentations. Although in most reported cases the symptoms appeared during or shortly after exercise, our patient did not have any symptoms until 5 hours after exercise and 6 hours after eating the offending food. His presentation was also unusual in that anaphylaxis developed very fast and was near fatal. The elevated serum tryptase level confirms a systemic mast cell degranulation.¹⁷ In cases with normal tryptase levels, other mechanisms should be considered.

In some reported patients, FDEIA occurred only when additional factors were involved such as menstruation,¹⁸ ingestion of aspirin¹⁹ or NSAIDs,²⁰ or a combination of multiple foods.^{21,22} Wheat was identified as the offending food allergen in this patient. Because of the very convincing history and severity of symptoms, intentional food-exercise challenge was not performed. The precise mechanism underlying the delayed onset of symptoms in our patient or in other previously reported cases is unknown. Isolated late-phase response or delayed gastric emptying are possibilities.

CONCLUSION

This case supports the few previous reports on the varying presentations of FDEIA, particularly regarding the time of onset after exercise. Because delayed reactions may occur after several hours, progress rapidly, and can be life-threatening, all patients with FDEIA should be advised to totally avoid the offending food or to avoid exercise for at least 6 hours after eating the food. Self-injectable epinephrine should be prescribed as soon as the diagnosis is made and should be made easily available for administration at all times.

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