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## Clinical Communications: Adults

### EXERCISE-INDUCED ANAPHYLAXIS AS A CAUSE OF SYNCOPE

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**Abstract—Background:** Exercise-induced anaphylaxis (EIA) is an under-recognized condition that is a distinct physical allergy. Triggers include varying amounts of exercise, alone or in combination with certain foods or medications (food-dependent EIA, or FDEIA). Therapy is identical to that of any immunoglobulin E-mediated allergic reaction. **Objectives:** This case is reported to increase awareness among emergency physicians of EIA and FDEIA. **Case Report:** A 57-year-old man was found with a diffuse erythematous rash after eating a wheat bagel and walking up five flights of stairs. Emergency medical services found him hypotensive and combative. In the Emergency Department, the patient's blood pressure was 72/27 mm Hg, with an oxygen saturation of 97% on non-rebreather mask. The physical examination was notable for bilateral inspiratory crackles in the lower one-third of the lungs. He received intravenous (i.v.) diphenhydramine 25 mg, i.v. methylprednisolone 125 mg, and 1 L of normal saline, after which his blood pressure improved to 110/54 mm Hg. He was admitted to the hospital where his recovery was uneventful. **Conclusion:** EIA and FDEIA are uncommon forms of physical allergy, but they represent important entities for emergency physicians to consider. Recognition of the association with exercise is key, as recurrences can be prevented by avoiding triggers. © 2010 Elsevier Inc.

**Keywords—**exercise; anaphylaxis; allergic reaction; syncope; shock

#### INTRODUCTION

Exercise-induced anaphylaxis (EIA) and food-dependent exercise-induced anaphylaxis (FDEIA) are distinct phys-

ical allergies that previously seemed uncommon, but have been recognized with increasing frequency and have been increasingly reported in the sports medicine and allergy literature in recent years; it is possible that EIA and FDEIA may simply be under-diagnosed. Over 1000 cases have been reported since Maulitz et al. first reported on EIA in 1979 (1). The actual incidence and prevalence of these conditions are unknown (2,3). A death due to FDEIA also has been published (4). Because prevention of EIA and FDEIA episodes is paramount, recognition of these conditions is important to avoid potentially life-threatening symptoms. A case of FDEIA is reported, along with a review of the currently understood pathophysiology and treatment.

#### CASE REPORT

A 57-year-old man presented to the Emergency Department (ED) after being found confused and diaphoretic, with a diffuse erythematous rash, after a syncopal episode. This patient had a known history of FDEIA, with recurrent episodes of flushing and urticaria that usually resolved with oral diphenhydramine and cessation of exercise. Other past medical history included hypertension and hyperlipidemia. Home medications included diltiazem, aspirin, and multivitamins. He had no known drug allergies. He worked as an accountant, was married with two daughters, occasionally smoked cigars, and rarely drank alcohol. He denied any illicit drug use. The

patient's usual morning routine was to eat a wheat bagel at home for breakfast and then drive to work. On the day of hospital presentation, he instead had eaten a wheat bagel during the drive to work, where on arrival he proceeded to walk up five flights of stairs. He then started feeling flushed and mildly short of breath, after which he had a syncopal episode.

Upon arrival of paramedics, the patient was hypotensive, vomited once, and was confused and combative, refusing an intravenous (i.v.) line. Fingerstick blood sugar was 156 mg/dL. He received oxygen by non-rebreather mask en route. The patient was transported to the ED of a small community hospital, where he was afebrile, with a heart rate of 87 beats/min, blood pressure of 72/27 mm Hg, respiratory rate of 18 breaths/min, and an oxygen saturation of 97% on non-rebreather mask. On examination, he was diaphoretic and confused, mucous membranes were moist, and he had no evidence of airway compromise or stridor. The physical examination was also notable for bilateral inspiratory crackles in the lower one-third of the lungs. The heart beat was regular and the abdomen was soft, non-tender, and non-distended. The skin was cool and moist without any rash being present at that time.

The patient was kept on a continuous cardiac monitor. Given his known history of FDEIA, he received diphenhydramine 25 mg i.v., methylprednisolone 125 mg i.v., and 1 L of normal saline, after which his blood pressure improved to 110/54 mm Hg. His blood work was essentially unremarkable, including negative cardiac enzymes, except for an arterial blood gas with a partial pressure of oxygen of 82.1 mm Hg, consistent with hypoxia. The chest X-ray study demonstrated bilateral lower lobe infiltrative disease consistent with either an infectious etiology or pulmonary edema. He was then transferred to a tertiary care center for further management. His vital signs before transfer included a blood pressure of 140/72 mm Hg and a heart rate of 101 beats/min. En route he required continuous oxygen to maintain a saturation level in the high 90s.

At the ED of the tertiary care center, the patient was feeling improved, though he still complained of persistent swelling in his fingers. His vital signs included a heart rate of 98 beats/min and a blood pressure of 145/91 mm Hg, as well as an oxygen saturation of 94% on 2 L of oxygen by nasal cannula. The physical examination was notable for bilateral inspiratory crackles in the lower one-third of the lungs. The heartbeat was regular, the abdomen was soft, non-tender, and non-distended, and he was alert and oriented to person, place, and time. No rash was noted, but the fingers did appear puffy. The patient was in no acute distress. He received furosemide 20 mg i.v. due to the possibility of a component of congestive heart failure. His repeat chest X-ray study at the

tertiary care hospital showed asymmetric left-greater-than-right patchy opacities, so the patient also received azithromycin 500 mg per oral to treat a possible case of underlying pneumonia. An electrocardiogram showed sinus tachycardia, an incomplete right bundle branch block, and T wave flattening in leads aVL, V5, and V6. His vital signs remained stable in the ED and he was subsequently admitted to the hospital, where his recovery was uneventful and he was discharged the following day.

## DISCUSSION

The differential diagnosis for this patient with hypotension, confusion, and syncope is broad, but was successfully narrowed due to his known history of FDEIA. Even with the presence of a rash, the proper diagnosis likely would not have been recognized given that EIA and FDEIA are uncommon entities. As mentioned, EIA and FDEIA are distinct physical allergies. Many patients with EIA or FDEIA have a personal history or family history of atopy (5). Triggers can include varying amounts of exercise, alone (as in EIA) or in combination with certain foods or medications (as in FDEIA); in FDEIA, the culprit foods in the absence of exercise do not cause a reaction (6). The two most common causes of FDEIA are the wheat gliadin protein and shellfish, which when consumed within 4–6 h of exercise can induce an allergic reaction (7). Additional foods that have been linked to FDEIA include nuts (e.g., hazelnuts, almonds, peanuts, pistachio), vegetables (e.g., celery, onions, tomatoes, corn, matsutake mushrooms, lentils, chickpeas), fruits (e.g., pomegranate, grapefruit, apples, oranges, grapes, and peaches), and some other types of food (e.g., snails, cuttlefish, tofu, egg, cow's milk, poppy) (4,8–31). Perkins and Keith present a list of culprit foods with their literature references (32). Some patients require ingestion of multiple foods in combination with exercise to provoke symptoms (33). There is also a subtype of FDEIA, *unspecific* food-dependent EIA, in which filling of the stomach— independent of the actual food ingested—followed by exercise brings about symptoms (34). Examples of medications that in combination with exercise can trigger EIA are aspirin and non-steroidal anti-inflammatory drugs (35,36). Aspirin is further thought to enhance the process of FDEIA in some patients (37). Bito et al. report on a case in which FDEIA was triggered only in the setting of cows' milk, aspirin, prior skin sensitization to cows' milk, and the premenstrual or ovulatory phase of the patient's menstrual cycle (38). Sanchez-Borges et al. report on a case of dust mite ingestion-associated EIA (5).

Exercise itself has a variable effect, in that the same amount of exertion may not always result in a reaction. Walking and jogging are the most frequent causes of triggering EIA, though lower impact activities, such as

gardening, also have been implicated (7,36). Stress, and labor and delivery have been reported to lead to EIA symptoms as well (39). Environmental conditions, such as exercise in the setting of cold water or cold weather, also have been described to play a role in FDEIA (40,41).

The mechanism of EIA and FDEIA remains unclear but is thought to be related to increased mast cell degranulation due to higher alpha-adrenergic tone and higher serum osmolality from dehydration during exercise (28,39). In those with FDEIA, a greater systemic exposure to food allergens from increased entry of recently ingested (but incompletely digested) food proteins (along with the inherent allergens) into the circulation and increased splanchnic blood flow on exertion may also contribute (28,42). Inomata speculated that activated tissue transglutaminases may increase allergenicity in patients after wheat ingestion (43). Elevated plasma histamine, tryptase, and leukotriene levels, consistent with mast cell activation, have been demonstrated (4,34,44). Elevated plasma noradrenaline level also has been reported in FDEIA (45). High levels of gliadin-specific immunoglobulin E (IgE) levels in several patients with wheat-dependent FDEIA also have been found. (Simple food anaphylaxis, such as to shellfish and peanuts, is believed to be entirely IgE mediated) (46).

The primary conditions to consider in the differential diagnosis of EIA/FDEIA include exercise-induced asthma and cholinergic urticaria, though clearly, primary cardiovascular causes of symptoms such as syncope and hypotension must be considered as well. Exercise-induced asthma presents with a similar bronchospastic component; exercise-induced asthma, however, should not have the associated vasomotor instability seen in EIA. Although cardiac dysrhythmias and other cardiovascular etiologies must be considered, cutaneous findings suggest an allergic component. Cholinergic urticaria and EIA/FDEIA have similar skin changes, but cholinergic urticaria is induced by passive elevation in body temperature alone and does not result in vascular collapse (44,47). An exercise challenge in a controlled setting, with emergency equipment available, can be undertaken to confirm the diagnosis of EIA. In FDEIA, diagnosis is based upon history, skin testing, and in vitro food-specific IgE assays, in combination with an exercise challenge after consumption of the assumed culprit food (5,6). Although Matsuo et al. found that measurement of IgE levels specific to epitope peptides of omega-5 gliadin and a high-molecular-weight glutenin subunit was useful as an in vitro tool for diagnosing patients with wheat-dependent FDEIA, it is not necessary to have a high specific IgE level for the culprit food in FDEIA and, moreover, low-positive results are frequent (8,48,49).

Treatment for EIA/FDEIA should include the immediate cessation of exercise as soon as symptoms occur, which

may suffice to halt their evolution to life-threatening manifestations. Pharmacologic therapy is identical to any IgE-mediated allergic or anaphylactic reaction and includes H<sub>1</sub> blockers such as diphenhydramine, H<sub>2</sub> blockers such as ranitidine, steroids, bronchodilators for bronchospasm, and, depending on severity, intramuscular or intravenous epinephrine for hypotension and airway compromise (6). Aggressive airway management with intubation or cricothyrotomy in severe angioedema should be considered early. Patients ought to be observed for symptom recurrence (e.g., for at least 6 h) before discharge.

Although difficult to characterize due to the small number of cases, the natural history of EIA/FDEIA suggests that the frequency of episodes experienced over a lifetime decreases or at least stabilizes over time (7). This is likely due to appropriate preventive measures taken by patients once the condition is recognized. Specifically, patients should be educated in carrying an epinephrine self-injector at all times and stopping exercise as soon as symptoms develop. For those patients with FDEIA, they should be cautioned against ingestion of their triggers within a certain time frame before and after exercising or exerting themselves. Premedication, for example, with antihistamines, has not been proven effective to prevent episodes of EIA, though it seems beneficial in some reports and so should be offered to patients (37). Although there is some indication that cromolyn (or sodium cromoglycate), a mast cell stabilizer, may help prevent severe reactions, results have been mixed and this has not been adopted as standard preventative therapy (37). Katsunuma et al. reported a case of successful pretreatment with sodium bicarbonate, but again, this has not been adopted as standard therapy (50).

## CONCLUSION

Exercise-induced anaphylaxis, occasionally associated with food or medication triggers, previously has been considered an uncommon form of physical allergy but may be just under-recognized. EIA and FDEIA have been reported with increasing frequency in the recent medical literature and represent important entities for health care professionals to be aware of and to consider in the differential diagnosis of syncope or hypotension. Treatment is like for any allergic reaction. Recognition of the association with exercise is key, as recurrences can be prevented by avoiding triggers.

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