Food-dependent exercise-induced anaphylaxis

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This article describes four cases of exercise-induced anaphylaxis occurring only in temporal relationship to the ingestion of food. One individual developed anaphylaxis if exercise followed the ingestion of any food within 2 hr. Three other individuals had symptoms only if celery was ingested in relation to exercise. Skin reactivity to fresh celery extracts was demonstrated in all three individuals. The episodes were prevented by avoidance of food ingestion in relation to exercise. This syndrome appears to be a variant of exercised-induced anaphylaxis. (J ALLERGY CLIN IMMUNOL 71:407, 1983.)

Anaphylaxis may becaused by a variety of antigenic and physical stimuli.[1-9] Certain foods such as fish and nuts may induce anaphylaxis as a result of an IgE antibody-mediated reaction due to the ingestion of the antigenic substance in a previously sensitized individual.[3, 4] Sheffer and Austen[6] reported that exercise may precipitate attacks of anaphylaxis, probably representing a form of physical allergy in which exercise causes mast cell release of mediators.[7, 8] One case of anaphylaxis associated with both the ingestion of shrimp and exercise has recently been reported.[10]

We have recently evaluated four patients with exercise-related anaphylaxis occurring only in relation to the ingestion of food. In one patient, anaphylaxis was brought on by exercise, but only if exercise followed the ingestion of a meal. In three other patients, anaphylaxis was precipitated by exercise only if it followed the ingestion of celery. In another, anaphylaxis was precipitated by celery, but only if ingestion followed exercise.

The conditions of patients were different from other exertion-related syndromes such as exercise-induced asthma, cholinergic urticaria, or exercise-induced anaphylaxis. The patients appeared to have a mixed clinical syndrome of a food antigen–induced and exercise-related anaphylactic syndrome.

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CASE REPORTS

Patient 1

A 29-yr-old athletic man presented with a 9 yr history of cutaneous itching, hives, nausea, dizziness, and extreme weakness associated with exercise occurring within 2 hr after meals. His first episode was in 1972 while in basic training in the Marine Corps. These symptoms occurred at irregular intervals throughout the years, with the frequency diminishing as he recognized their cause. Solid food of any kind followed by exercise within 2 hr resulted in symptoms within 2 to 5 min lasting 30 to 120 min. The ingestion of fluids alone was not associated with exercise-induced symptoms. The symptoms abated with diphenhydramine when taken after exercise; there was no effect if the drug was taken prior to exercise. Symptoms did not follow either vigorous exercise or eating.

The patient was evaluated at the Wood Veterans Administration Medical Center in May 1981. There were no significant abnormalities on physical examination or laboratory evaluation, including complete blood cell count, urinalysis, and blood chemistries.

On a subsequent visit, a meal consisting of a cheeseburger with tomato, lettuce, and catsup, a cola drink, and fried potatoes was ingested; 30 min later the patient was instructed to run in place. After 3 min of vigorous exercise, the patient experienced cutaneous itching, dizziness, nausea, and weakness but no laryngeal or respiratory complaints. Physical examination at that time revealed a blood pressure of 60/40, pulse 110/min, and respiration 16/min. Pinpoint (1 to 2 mm) cholinergic-like urticarial lesions were present on his upper anterior chest, neck, upper arms, and thighs, which coalesced within 10 min into giant hives. There was no pharyngeal or uveal edema, the lungs were clear to auscultation, and there was sinus tachycardia without gallops or murmurs. The abdominal examination was normal.

Subcutaneous epinephrine (0.3 ml of 1:1000) was administered every 15 to 20 min for a total of four doses.

TABLE I. Clinical features of patients with food-dependent exercise-induced anaphylaxis

Patient	Age/Sex	Presenting symptoms	Activity precipitating attack	Food related to attack	Relationship of eating and exercise*	Time between eating and exercise*
1	29/M	Cutaneous itching, hives, dizziness, weakness	Basketball, lawn mowing	Any	Eating before exercise	Within 2 hr
2	34/F	Cutaneous itching, hives, wheezing, abdominal cramping, dizziness, weakness	Tennis	Celery	Eating before exercise	Within 2 hr
3	20/M	Cutaneous itching, hives, angio-edema, dizziness, weakness	Racquetball	Celery	Eating before exercise	Within 2 hr
4	39/F	Cutaneous itching, hives, abdominal cramping, dizziness, weakness	Tennis	Celery	Exercise before eating	Within 2 hr

*Precipitating an attack.

Physiologic saline and 50 mg of diphenhydramine were administered intravenously. There was a decrease in the extent of urticaria, which then reappeared within 15 min. After an additional dose of epinephrine the urticaria began to resolve; complete resolution occurred within 2 hr.

Subsequent studies carried out 2 wk later revealed a total serum IgE of 7 IU/ml, negative cutaneous (prick) and intracutaneous and radioallergosorbent tests with commercial food and common inhalant antigens, and a negative intradermal skin test with 0.01 mg of methacholine.

The patient has subsequently avoided all exertion for at least 2 hr after meals and has had no recurrence of symptoms.

Patient 2

A 34-yr-old woman presented with a 10 yr history of generalized itching, hives, wheezing, abdominal cramps, dizziness, and weakness associated with vigorous exercise occurring only within 2 hr after eating celery. No other food ingestion, in a temporal relationship to exercise, resulted in symptoms, and symptoms were avoided if there was a 2 hr waiting period between eating celery and exercising. Eating celery without subsequent exercise did not provoke symptoms. The episodes occurred after approximately 3 to 5 min of vigorous exercise, and the onset of generalized tingling and itching was followed by giant hives; all symptoms gradually resolved in 30 min to 2 hr. Initially, the episodes occurred on a weekly basis, especially with tennis preceded by eating celery; after several months they no longer occurred once the appropriate association was made and avoidance was practiced.

There was a history of mild springtime allergic rhinitis but no history of asthma, urticaria, eczema, or food allergy.

Physical examination at the time of an episode, which occurred while the patient played tennis shortly after eating celery, showed a blood pressure of 70/40, pulse 120/min, and respiration 16/min. Giant urticarial lesions were present on the upper chest, back, upper arms, neck, and abdomen. Examination of the nose and throat was normal; there was no uveal edema. Cardiac examination showed sinus tachycardia without gallops or murmurs. Auscultation of the chest showed mild inspiratory and expiratory wheezes. Treatment with three doses of 0.3 ml of 1:1000 subcutaneous epinephrine at 15 min intervals resulted in rapid resolution of symptoms.

Cutaneous (prick) testing with 1:10 w/v dilutions and intracutaneous testing with higher dilutions of commercial inhalant and food antigens several months later were negative. Cutaneous (prick) skin testing with 1:1 w/v saline dilutions of fresh milk, egg white, cheese, parsley, carrot, and celery revealed wheal and flare reactions to carrot and celery. Similar testing of these antigens on three nonsensitive individuals demonstrated no reactions.

The patient has subsequently avoided eating celery for at least 2 hr prior to exercise and has had no recurrence of episodes.

Patient 3

A 20-yr-old man presented with a 6 mo history of generalized pruritus, nasal obstruction, dyspnea, swelling of the lips, giant hives, and extreme weakness occurring 5 to 10 min after beginning strenuous exercise, but only if he ingested celery within 2 hr before the exercise. During the previous 6 mo he had experienced episodes twice a week. The patient was a health food enthusiast and thought that consuming copious amounts of celery prior to exercise would provide him with energy.

Prior to one episode the patient consumed four to five stalks of celery and played racquetball 1½ hr later. Approximately 5 to 10 min into the game he developed extreme weakness, generalized itching, and hives. His blood pressure was unobtainable by the paramedics who were summoned because of his symptoms. Intravenous fluids were begun and he was transported to the emergency room of a local hospital.

Upon admission his blood pressure was 112/68, pulse 110/min, and respiration 18/min. The patient was moderately apprehensive and anxious, but alert and oriented. There was giant urticaria on the anterior chest, arms, abdo-

men, neck, and thighs, and angioedema of the lips. Pharyngeal examination revealed slight erythema but no uveal edema. The nasal mucosa was slightly boggy and erythematous. Auscultation of the chest was normal. Heart examination revealed sinus tachycardia without gallops or murmurs. Abdominal examination was normal. After subcutaneous injection of three doses of 0.3 ml of 1:1000 epinephrine and intramuscular administration of 50 mg of dephenhydramine, the lesions cleared and the patient stabilized. The entire episode lasted approximately 1½ hr.

Subsequent laboratory evaluation showed a normal complete blood cell count. Total eosinophil count was 265/mm^3. Serum total IgE was 831 IU/ml. Wheal and flare skin reactions were demonstrated by prick test with commercial extracts of ragweed, soy, tomato, lobster, and celery in 1:10 w/v dilutions. Similar tests on nonsensitive controls were negative. There was a history of mild seasonal hay fever but no history of previous asthma, eczema, or food or drug allergy.

The patient has since continued to play racquetball daily. However, he has not eaten celery since the evaluation and no subsequent attacks have occurred in a 9 mo follow-up.

Patient 4

A 39-yr-old woman presented with a 2 yr history of cutaneous itching, abdominal cramping, dizziness, and weakness after the ingestion of celery. However, these symptoms occurred only if ingestion of the celery was preceded by vigorous exercise within 2 hr. Ingestion of celery without prior exercise or exercise without subsequent celery ingestion produced no symptoms. The attacks occurred almost immediately upon celery ingestion and lasted from 1 to 3 hr. She had three such episodes in the week immediately preceding testing. The symptoms were not relieved or prevented by oral dyphenhydramine but were alleviated with hydroxyzine. There was a history of mild seasonal allergic rhinitis and asthma. Asthma was also provoked by the ingestion of dill or mustard, but not in relation to exercise.

Laboratory studies revealed an IgE concentration of 33 IU/ml. Immediate wheal and flare skin reactivity was demonstrated by prick test with commercial extracts of 1:10 w/v dilutions of celery, dill, milk, mustard, tomato, beef, ragweed, grass, and tree. Studies on nonsensitive controls were negative.

Since the evaluation, the patient has avoided celery consumption after exercise and has not had another attack.

RESULTS

The patient group (Table I) consisted of four subjects, two men and two women, ranging from 20 to 39 yr of age (mean age, 30 yr). The duration of the symptom complex ranged from 6 mo to 10 yr. The number of episodes varied, but each patient reported symptoms each time he or she exercised in association with the particular food.

The symptoms and signs experienced by the patients included, in decreasing order of frequency, giant urticaria in all, abdominal cramping in two, and wheezing, dyspnea, angioedema, and cholinergic urticaria in one each. The attacks began in all patients with generalized tingling, itching, and warmth, followed by giant hives on the anterior chest, upper arms, thighs, neck, and face. The onset of symptoms occurred within 2 to 15 min into strenuous exercise and lasted from 1 to 4 hr after the attack began. As the attacks progressed, a generalized feeling of extreme weakness and dizziness occurred; all subjects stopped exercising at that time for fear of collapse. None of the patients reported syncope during the attacks.

TABLE II. Immunologic features of patients with food-dependent exercise-induced anaphylaxis

Patient	Atopic symptoms	IgE (IU/ml)	Positive skin tests	
			Food	Inhalant
1	None	7	None	None
2	AR	132	Fresh celery, fresh carrots	Grass, trees
3	AR	831	Celery, soy, tomato, lobster*	Ragweed
4	AR	33	Celery, dill, milk, mustard, tomato, beef*	Ragweed, grass, trees

AR = allergic rhinitis.
*Commercial extracts.

All patients were experienced amateur athletes in the sport in which they participated; athletic activities were carried out daily. The types of physical activity provoking the attacks included tennis, racquetball, and basketball. All subjects recognized the association of food and exercise with symptoms and had modified their eating and exercise routines to avoid precipitating an attack.

The foods associated with exercise and symptoms included celery in three patients and any food in one individual. All patients had symptoms if exercise occurred within 2 hr after eating; both food and exercise were necessary to induce symptoms. In three patients, ingestion of food prior to exercise was necessary to induce an episode of anaphylaxis; in one patient, ingestion of food after exercise was required.

Physical examination was done in three patients during an attack and revealed hypotension and urticaria in all. Wheezing, as well as angioedema of the lips, was detected in one patient. No uveal or laryngeal edema was detected.

Laboratory evaluations, including complete blood

cell count, blood chemistries, urinalysis, total hemolytic complement activity, and C3 and C4 levels, were normal in all patients.

Immunologic evaluation (Table II) revealed that one patient was probably nonatopic. He had no present or prior history of rhinitis, asthma, eczema, or urticaria, a total serum IGE level of 7 IU/ml, and no skin or radioallergosorbent test reactivity to common food and inhalant antigens. The three patients with symptoms related to celery ingestion were probably atopic. All had histories of seasonal allergic rhinitis. Total serum IgE level was elevated in two of three, and immediate wheal and flare skin reactions were demonstrated with food antigens as well as with common inhalant antigen extracts in all.

All the patients had treated themselves prior to seeking medical attention by avoiding the temporal sequence of the offending food and exercise. Three patients (Nos. 1, 2, and 3) first sought medical attention by presenting to the emergency room for immediate medical treatment of anaphylaxis. Patient 4 initially presented her history during an evaluation of rhinitis. The patients were treated in emergency facilities with standard treatment of an anaphylactic episode, i.e., administration of subcutaneous epinephrine, antihistamines, and intravenous fluids and maintenance of adequate airway. All patients responded well to treatment within the first hour and have since prevented further episodes by avoidance of the evoking events.

DISCUSSION

A syndrome characterized by hives, cutaneous itching, dizziness, weakness, abdominal cramping, and angioedema associated with certain foods and exercise has been presented. History and laboratory evaluation indicate that there are probably at least two subsets of this food-dependent exercise-related syndrome. The nonspecific food-dependent anaphylactic syndrome in patient 1 was not associated with symptoms or signs of atopic disease. Exercise within 2 hr of solid food ingestion would produce an attack. Exercise without prior food ingestion or exercise occurring longer than 2 hr after meals would not produce an attack. It is probable that digestion and subsequent exercise somehow triggered mast cell release of mediators and the resultant anaphylactic syndrome.

The remaining patients had a specific food-dependent anaphylactic syndrome and signs and symptoms indicative of atopic disease. They had histories of seasonal rhinitis and skin-test reactivity to pollens. All had symptoms related to celery ingestion and exercise, and all had skin test reactivity to celery. In two of these patients, ingestion of celery within 2 hr before exercise precipitated an attack, while in one patient exercise before ingestion of celery was necessary.

This syndrome appears to be intermediate between the exertion-related syndromes and anaphylaxis secondary to food antigens. Anaphylaxis presents with symptoms in any of four organ systems: the respiratory tract, with wheezing or laryngeal edema; the skin, with pruritus, urticaria, or angioedema; the cardiovascular system, with hypotension, weakness, and dizziness; and the gastrointestinal tract, with cramping, nausea, vomiting, and diarrhea.[1, 5] Several clinical conditions may present during exercise and manifest as one or more symptoms attributed to anaphylaxis. These conditions include exercise-induced asthma, physical urticaria such as cholinergic urticaria, and exercise-induced anaphylaxis.

Exercise-induced asthma is a common syndrome more frequently seen in young male subjects than in female subjects.[9] It manifests as wheezing associated with vigorous exertion occurring during, or more commonly, after exercise. None of the patients in the current study had a history of exercise-induced asthma unless a particular food was also eaten.

Patients who show signs and symptoms of allergic reactions as the result of physical stimuli are described as having physical allergy. Certain physical allergies present with symptoms similar to those of anaphylaxis. Urticaria and sometimes wheezing may be associated with cholinergic urticaria,[11, 12] which is considered to be a heat-induced syndrome, and usually the symptoms occur with warm stimuli such as hot showers or in hot weather conditions. Frequently exercise may produce enough heat to precipitate an attack of cholinergic urticaria. The urticarial lesions of this condition are typically small (1 to 2 mm) raised hives, first seen on the thorax or neck, and can often be reproduced by an intradermal injection of methacholine (0.01 mg). In this article, patient 1 had pinpoint, cholinergic-like urticaria that appeared at 2 min into strenuous exercise but then rapidly progressed into giant hives. The patient did not have hives with warm stimuli such as hot showers or with exercise prior to food consumption; there was no skin reactivity to intradermal methacholine. On clinical grounds, none of the other patients were considered to have cholinergic urticaria as a basis for the syndrome.

Of the exertion-related syndromes producing anaphylactic symptoms, the recently described exercise-induced anaphylaxis most closely resembles our patients' conditions. The presenting symptoms, hives and cutaneous itching with exercise, and the time of onset of these symptoms are strikingly similar.[6–8]

Since the ingestion of food was required for exercise to provoke an attack, this syndrome might also be

considered a subset of food allergy. It is possible that food and exercise are related to mediator release from mast cells, especially in the presence of IgE as demonstrated by skin tests. Increased absorption of the appropriate food antigens might also occur with exercise. The sensitivity to celery as demonstrated by skin-test reactivity might then become clinically significant with exercise. A similar phenomenon occurs in some atopic patients who exercise after a battery of inhalant skin tests and react; this may be related to increased absorption of the inhalant antigens from the skin-test sites.

Celery is a member of the parsley family, which includes carrot and dill.[13] Two patients had skin-test reactivity to dill and carrot but did not exhibit clinical sensitivity after eating these members of the parsley family; they also had no symptoms after eating the foods and undergoing exercise. This may be related to the presence of a unique antigen in celery that is related causally to anaphylaxis (Heiner D, personal communication). Atopic patients with sensitivity to other common foods such as egg, peanut, and shellfish probably will also predispose some individuals to food-dependent exercise-induced anaphylaxis.

The diagnosis of food-dependent exercise-related anaphylaxis should be evident after a careful history evaluation. In patients with exercise-induced anaphylaxis, or perhaps with other exercise-induced syndromes, careful questioning concerning a temporal relationship to foods may be rewarding. In some cases, skin tests with suspected foods may help clarify the diagnosis; antigens prepared from fresh food antigens may be more reactive than the commercial variety.[14]

Treatment of food-dependent exercise-induced anaphylaxis centers about recognition of the events necessary to produce the attack. Avoidance of a food or group of foods for a given period of time before or after exercise can be preventative. Prior therapy with antihistamines appears to have little effect on the subsequent episode. It is apparent that the patients in the present study can exercise vigorously without difficulty as long as the offending food is not ingested for 2 hr before or after exercise.

The recent popularity of exercise and physical fitness has led to some morbidity and mortality from a variety of disorders.[15–17] One such disorder is food-dependent exercise-induced anaphylaxis, which should be considered in the differential diagnosis of anaphylaxis.

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