

Food-Dependent, Exercise-Induced Anaphylaxis

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SYSTEMIC anaphylactic reactions are rare consequences of the ingestion of certain foods, administration of drugs, or exposure to stinging insects. Recently, exercise has been recognized as an additional cause of anaphylaxis.¹ The entity of exercise-induced anaphylaxis has been further modified by the recognition that in some susceptible persons, exercise must be preceded or followed by the ingestion of any food or of specific foods for anaphylaxis to occur.^{2,3}

This report concerns a patient with food-dependent, exercise-induced anaphylaxis. The patient underwent exercise challenge both with and without prior food ingestion; plasma histamine determinations were performed during and after exercise.

Report of a Case

A 24-year-old woman was initially seen in July 1982 for evaluation of an episode of pruritus, urticaria, angioedema, abdominal cramping, and diarrhea, accompanied by impending loss of consciousness. This episode began after the patient had jogged 1 mile in 20 minutes. Despite symptoms, the patient was able to return to her home, where she ingested 100 mg of diphenhydramine hydrochloride. Cutaneous symptoms began to subside, but severe abdominal cramps and diarrhea persisted for two hours. She had eaten a peach immediately before exercise.

The patient had a history of seasonal rhinitis and asthma during childhood. While at high school, she occasionally had urticaria after dancing. She also had urticaria, periorbital edema, respiratory distress, and abdominal cramping after eating nuts and sesame seeds. She ate peaches and other fresh fruits without adverse reactions. Neither heat nor cold exposure caused urticaria.

Physical examination disclosed no ab-

normalities. The hematocrit level was 38%; WBC count, 7,200/cu mm; ESR, 5 mm/hr; total eosinophil count, 142/cu mm. Skin tests were performed; the patient had multiple positive wheal and flare reactions to a variety of pollen, mold, animal dander, house dust, and house dust mite extracts and a negative saline control.

The patient was told she had exercise-induced anaphylaxis. She was instructed to carry a syringe and epinephrine and to exercise with a "buddy." The role of an ingested food antigen was unclear at this time. It was suggested that she avoid eating for two hours before exercise because of the possibility that food ingestion might have played a role in initiating symptoms.

She returned nine days later. An episode of facial swelling and throat tightness had occurred after she danced for 40 minutes. The patient administered 0.3 mL of 1:1,000 epinephrine subcutaneously. She required two injections ten minutes apart. All symptoms resolved after the second epinephrine injection. She had eaten a fresh peach before dancing. During the interim, she had eaten peaches, not followed by exercise, without adverse reactions. A scratch test with fresh peach juice produced a wheal and flare reaction; saline control was negative. Avoidance of all foods, especially peaches, before exercise was stressed.

When the patient was seen one month later, she reported jogging many times without symptoms until Aug 22, 1982. On that occasion, she ate grapes immediately before jogging. Cutaneous pruritus, swelling, urticaria, wheezing, and throat tightness developed after she jogged 2.5 miles. She chose not to treat herself with epinephrine because she considered this episode to be milder than the previous one, and she found the side effects of epinephrine to be objectionable. Symptoms subsided after one hour of rest. The result of a scratch test with fresh grape juice was negative.

During the past eight months, the patient has fasted for two hours before jogging; no further episodes of anaphylaxis have occurred.

Exercise Challenge

To determine whether the patient had food-dependent, exercise-induced anaphylaxis, she was tested twice in the stress-

testing laboratory of the Cardiac Unit at Massachusetts General Hospital, Boston. An anesthesiologist, allergist, and cardiologist were present; resuscitative equipment was available. Informed consent was obtained from the patient before each challenge; permission for the studies was obtained from the Human Studies Committee.

The patient ingested a fresh peach one hour before the first exercise study. She fasted for three hours before the second exercise study. Baseline BP, pulse rate, and physical examination results were recorded before she started exercise. An 18-gauge plastic catheter was inserted into a forearm vein; patency was maintained with a normal saline solution. Blood for baseline histamine values was taken before exercise. Further blood samples were drawn during and after exercise at times indicated in the Table. A modified Bruce exercise protocol⁴ was used. Exercise was continued for 18 minutes in both studies. Plasma histamine levels were determined by a radioenzymatic assay.⁵

Results

The first exercise study performed one hour after peach ingestion was followed by cutaneous warmth, redness, pruritus, and swelling. Agitation, cough, and sensation of throat discomfort also developed. According to the patient, this episode was similar to the others she had experienced. She did not experience hypotension or abdominal pain. There was an eight-fold increase in plasma histamine level from 506 pg/mL at baseline to 4,174 pg/mL at 14 minutes after exercise was stopped. No further blood samples were obtained because it was considered indicated to treat the patient with epinephrine and diphenhydramine at this time.

The second study, performed after the patient had fasted for three hours, did not precipitate any unusual symptoms. The patient did become flushed and perspired profusely, but she stated that she felt well. Histamine levels remained within the normal range during this study.⁵

Comment

Exercise-induced anaphylaxis consists of the symptom complex of pruritus, erythema, urticaria, and/or angioedema. These cutaneous manifestations may be followed by upper respiratory tract obstruction, gastrointestinal distress, and loss of consciousness. Elevated plasma histamine levels have been recorded dur-

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Reprints not available.

Clinical and Plasma Histamine Response to Exercise With (Study 1) and Without (Study 2) Prior Food (Peach) Ingestion

Plasma Histamine Levels, pg/mL		Symptoms and Signs		Time, min	Exercise Protocol (Duration, min)
Study 1	Study 2	Study 1	Study 2		
506	541	None	None	0	Resting
365	931	None	None	6	Bruce level 1 (3) Bruce level 2 (3)
394	570	Fatigue, perspiration	Fatigue, perspiration	12	Bruce level 3 (3) Bruce level 4 (3)
308	425	Fatigue, perspiration, erythema	Fatigue, perspiration, erythema	18	Bruce level 4 (2) Bruce level 3 (4)
345	233	Erythema of face, chest, and extremities	Fatigue, perspiration, erythema	19	Resting
954	441	Agitation, groin pruritus, erythema of face and hands	Erythema of face	22	Resting
1,355	385	Facial swelling, hand swelling, diffuse pruritus	None	25	Resting
4,174	181	Facial swelling, diffuse, pruritus, cough*	None	32	Resting

*Treatment included diphenhydramine hydrochloride, 50 mg intravenously, and epinephrine, 1:1,000, 0.3 mL subcutaneously.

ing laboratory exercise challenge in patients who became symptomatic.⁶ Based on the demonstration of histamine release, exercise-induced anaphylaxis has been classified as a physical allergy akin to cholinergic and cold urticaria.

Both Kidd et al¹ and Maulitz et al² have described patients in whom the combination of food ingestion and exercise was required to precipitate anaphylaxis. In these patients, neither exercise alone nor food ingestion alone caused symptoms. In the report of Kidd and co-workers, three patients had food-specific (fresh celery), exercise-related symptoms. All three patients had wheal and flare responses on testing with celery. Their fourth patient experienced symptoms after eating various solid foods followed by exercise. Results of skin tests and radioallergosorbent tests with commercial food and common inhalant antigens were negative in this patient. The patient of Maulitz and colleagues had symptoms only after ingesting shellfish, followed by exercise. This patient had wheal and flare responses on testing with clam, oyster, shrimp, and crab extracts.

Our patient at first seemed to have food-specific, exercise-induced anaphylaxis. However, her third episode occurred after ingestion of a different fruit to which her skin test result was negative. Failure to obtain a skin test result positive to grape may reflect

the absence of IgE antibody to this fruit or the inadequacy of the test used to detect this antibody. If the patient does not have IgE (or other homocytotropic) antibodies to this fruit, then the positive response to exercise after grape ingestion suggests that a variety of mechanisms may be involved in the induction of anaphylaxis by the combination of food ingestion and exercise. Our patient was not tested in a doubly masked protocol, nor was she subjected to laboratory challenge with grapes or other foods, to minimize the risks and discomforts inherent in testing.

In normal persons, plasma histamine levels are generally less than 1 ng/mL.^{5,7} A wide range of plasma histamine values have been reported in patients with anaphylactic and anaphylactoid reactions.^{8,9} Systemic reactions are generally accompanied by plasma histamine levels of greater than 1 ng/mL.⁷ Our patient's peak histamine value was 4 ng/mL. This is consistent with the systemic nature of her reaction. If the reaction had been allowed to progress untreated, higher plasma histamine values might have been found and hypotension might have developed. Failure to obtain precise correlations between symptoms and plasma histamine levels may be explained by the rapid destruction of locally released histamine before "spillover" into the blood

can take place. Furthermore, it seems likely that, as in other physical allergies, additional mediators are involved in the production of symptoms.

The mechanism of food-dependent, exercise-induced anaphylaxis is still unknown. Several factors should be considered. Patients with physical allergies are considered to have enhanced mast cell responsiveness to physical stimuli.⁹ Patients with food hypersensitivity¹⁰ may have increased spontaneous leukocyte histamine release. In certain instances, antigen-IgE antibody-mediated mast cell degranulation may be occurring. Possibly a combination of immunologic and nonimmunologic factors may be contributing to mediator release. The present case may exemplify one or more of these mechanisms.

Food-dependent, exercise-induced anaphylaxis has been reported in relation to ingestions of celery, shellfish, fruit, and a variety of solid foods. With the strong emphasis on physical fitness in our society, physicians may see additional patients with this syndrome. The diagnosis can generally be made by history alone. Fasting for two to four hours before exercise has been preventative.

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