

A case of food-dependent exercise-induced angioedema

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Clinical Implications

- We report for the first time a case of food-dependent exercise-induced angioedema. We presume that among the patients with idiopathic histaminergic angioedema might be some cases of food-dependent exercise-induced angioedema that may possibly be revealed by thorough anamnestic evaluation.

TO THE EDITOR:

We present our patient who was diagnosed with food-dependent exercise-induced angioedema. The patient appeared to be sensitized to milk proteins (lactalbumin, casein, and cow's milk), diagnosed by skin prick tests (SPTs) with ALK-Abelló allergens.

A 26-year-old woman was referred to our allergy clinic complaining of eyelid, face, lips, and extremities edema. A thorough history-taking revealed that angioedema episodes occurred when the patient exercised (running) 1 to 4 hours after eating or after ingesting milk and resolved within 2 to 4 days. The patient had experienced similar episodes 7 times while running and 4 times within 2 hours after jogging in the past 16 months. She experienced no urticarial rash, pruritus, nausea, vomiting, and/or diarrhea during angioedema episodes. She denied any allergic diseases in the past. Complete physical examination was normal, as were complete blood cell counts, biochemistry, urinalysis, and complement levels. Total serum IgE level was 94 kUA/L. We performed SPTs (ALK-Abelló, Copenhagen, Denmark) with a wide range of food allergens, and wheal and flare reactions were found positive with lactalbumin (6/10 mm), casein (9/12 mm), and cow's milk (9/14 mm). SPT results with other food allergens were negative. Specific IgE antibodies to cow's milk (CAP-FEIA; Pharmacia, Uppsala, Sweden) were 8.6 kUA/L and specific IgE antibodies to other food allergens were all less than 0.35 kUA/L (Table 1). An open oral challenge test with cows' milk in progressively increasing doses (5, 10, 30, 75, 125, and 250 mL) every 15 minutes was tolerated well by the patient. An exercise test was carried out on 3 different days and consisted of running on a motor-driven treadmill for 15 minutes. Speed was adjusted during the running to achieve at least 80% of calculated maximum age-related heart rate during the running time. Heart rate, blood pressure, and oxygen saturation were monitored throughout the exercise. A fasting exercise challenge was performed, followed by an exercise challenge 1 hour after a meal without consumption of cow's milk and finally an exercise challenge 1 hour after the ingestion of 250 mL of cow's milk. Exercise challenge test results in the fasting state and 1 hour after a meal not containing cow's milk were

negative. However, the exercise challenge 1 hour after the consumption of cow's milk resulted in appearance of angioedema on the eyelids, lips, and hands, without pruritus, urticarial lesions, and/or any systemic signs of allergic reaction. Her angioedema resolved within 5 hours after treatment with fexofenadine 180 mg, and she was discharged after 8 hours of observation. On discharge, she was advised to avoid exercise within 6 hours of consuming milk products, and antihistamine fexofenadine 180 mg was prescribed. A serum total tryptase level drawn shortly after the onset of angioedema was normal.

She has since avoided any exercise for a minimum of 6 hours after consuming any milk products. She has not had angioedema attacks and she carries fexofenadine tablets while exercising.

To our knowledge, this is the first case of food-dependent exercise-induced angioedema. The patient's history, the positive SPT responses with cow's milk, the negative treadmill exercise challenge test results in the fasting state and 1 hour after a meal not containing cow's milk, the appearance of angioedema without urticaria after food-dependent exercise challenge after consumption of cow's milk, and the negative open oral challenge test result with cow's milk indicate that the patient had IgE-mediated food-dependent exercise-induced angioedema to cow's milk.

Adult cow's milk allergy (CMA) is generally acquired at an adult age and is severe in nature.^{1,2} Both casein and whey proteins are involved in IgE-mediated adult CMA.² Most adult patients with CMA experience pulmonary and cardiovascular symptoms, and 27% even experience an anaphylactic shock.³ Moreover, 63% of these patients suffer from an allergic reaction upon accidental ingestion of milk products, and spontaneous tolerance in adult CMA occurs rarely.³ Nevertheless, in some adult patients, the main organ manifestations of CMA are the skin and/or the respiratory tract symptoms.¹ These patients are likely to be misdiagnosed for years because of symptoms that initially often refer to only 1 organ system.¹ But our patient was completely asymptomatic and did not avoid cow's milk before developing the episodes of cow's milk-dependent exercise-induced angioedema. It is also noteworthy that food-dependent exercise-induced angioedema in our patient was not associated with urticaria, bronchospasm, or other signs and symptoms of mast cell mediator release. There were no clinical manifestations of bradykinin-mediated angioedema, such as abdominal pain, nausea, vomiting, and/or diarrhea. A trial of nonsedating antihistamine fexofenadine 180 mg was effective after appearance of angioedema similar to idiopathic histaminergic angioedema without urticaria.

The exact mechanisms of food-dependent exercise-induced angioedema are unknown, although an IgE-mediated mechanism may be suggested in light of the SPTs and specific IgE results for cow's milk. Nevertheless, it is not clear which exercise-specific factors facilitate the appearance of angioedema after consumption of the causative food. The following mechanisms have been proposed: IgE cross-links with a specific food allergen and, when linked with exercise, it lowers the threshold for mast cell and

TABLE I. SPT and specific IgE antibodies (CAP-IEIA) to food allergens

ALK-Abelló allergens used for SPT	SPT (mm)	CAP-IEIA (kUA/L)
Almond Food SCR; 1:10	Negative	<0.35
Apple Food SCR; 1:10	Negative	—
Apricot SCR; 1:10	Negative	—
Avocado SCR; 1:10	Negative	—
Beef SCR; 1:10	Negative	<0.35
Brazil Nut SCR; 1:10	Negative	<0.35
Casein SCR; 1:100	9/12	—
Celery SCR; 1:10	Negative	<0.35
Chicken Meat SCR; 1:10	Negative	<0.35
Cocoa, Whole Bean (Chocolate) SCR; 1:10	Negative	<0.35
Coffee SCR; 1:10	Negative	—
Crab SCR; 1:10	Negative	<0.35
Egg, White SCR; 1:100	Negative	<0.35
Fish, Mixed (NY) SCR; 1:10	Negative	<0.35
Lactalbumin (Cow Alpha) SCR; 1:100	6/10	—
Milk, Whole Cow's SCR; 1:10	9/14	8.6
Olive (Food) SCR; 1:10	Negative	—
Orange (Food) SCR; 1:10	Negative	—
Oyster SCR; 1:10	Negative	<0.35
Pea, Green (English) SCR; 1:10	Negative	—
Peach SCR; 1:10	Negative	—
Peanut SCR; 1:10	Negative	<0.35
Pecan (Food) SCR; 1:10	Negative	<0.35
Pistachio Nut SCR; 1:10	Negative	<0.35
Potato, Sweet SCR; 1:10	Negative	—
Potato, White SCR; 1:10	Negative	—
Rice SCR; 1:10	Negative	—
Salmon SCR; 1:10	Negative	—
Sesame Seed SCR; 1:10	Negative	<0.35
Shrimp SCR; 1:10	Negative	<0.35
Soybean SCR; 1:10	Negative	<0.35
Strawberry SCR; 1:10	Negative	—
Sweet Corn (Food) SCR; 1:10	Negative	—
Tomato SCR; 1:10	Negative	—
Tuna SCR; 1:10	Negative	—
Vanilla SCR; 1:10	Negative	—
Walnut, English (Food) SCR; 1:10	Negative	<0.35
Wheat Grain SCR; 1:10	Negative	<0.35
Yeast (<i>Saccharomyces cerevisiae</i>) SCR; 1:10	Negative	—

CAP-IEIA, ImmunoCAP solid-phase IgE assay (Phadia, Uppsala, Sweden); SCR, scratch; SPT, skin prick test.

basophil degranulation with release of histamine and vasoactive mediators to cause histaminergic angioedema.^{4,5} Moreover, after consumption of milk products, increased gut permeability during

exercise^{6,7} and possible abnormalities of the autonomic nervous system⁸ could potentially trigger histaminergic angioedema. Additional factors in the pathophysiology of this phenomenon may possibly be changes in pH and increases in blood flow to muscle during exercise, exposing more muscle tissue mast cells to cow's milk allergens.^{5,9}

Idiopathic histaminergic angioedema is the term applied to angioedema without urticaria responding to antihistamine medications, for which no explanation can be found after a thorough evaluation to exclude allergic disorders, drug reactions, and defects in complement pathways.

We presume that among patients with idiopathic histaminergic angioedema might be some cases of food-dependent exercise-induced angioedema that may possibly be revealed by thorough anamnestic evaluation.

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