

Food- and exercise-induced anaphylaxis: importance of history in diagnosis

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CHIEF COMPLAINT

A 42-year-old woman was seen in the fall of 1997 in the outpatient allergy clinic at McMaster University Medical Centre for evaluation of recurrent episodes of anaphylaxis. She was referred by her general internist.

HISTORY OF PRESENT ILLNESS

This woman was well until 5 years before the visit, when she began to develop urticaria if she ate and then exercised shortly thereafter. She was unable to recall any specific food that was linked to these events and rather felt that the urticaria occurred after eating a mixture of foods before exercising. She tried taking diphenhydramine with some improvement of the urticaria, with drowsiness as an unfavorable side effect.

This patient denied any episodes of loss of consciousness with the urticaria until December 1996. She was at a dinner-dance and remembered eating chicken, rice, salad, carrots, and bread (initially the patient did not recall eating any bread) at 7:30 PM. No alcohol was consumed. At 8:30 PM, 1 hour later, she proceeded to dance and 5 minutes later, at 8:35 PM, she developed generalized pruritus, urticaria, and palpitations. She initially sat down, and upon trying to stand, collapsed, and lost consciousness for 1 minute. She was nauseated and vomited when she woke up. She denied any sensation of throat swelling and did not go to the hospital.

Her second episode was in March 1997. She ate lasagna and bread for dinner and then went for a walk. Twenty minutes into the walk this patient developed urticaria on her neck that spread to her back, chest, face, and extremities. There was also a sensation of pressure on the top of her head, ringing in her ears, and a racing heart. She sat down and, upon attempting to stand, lost consciousness. No medical attention was sought.

In May 1997, this woman had her third episode of anaphylaxis after eating and exercising consecutively. She ate chicken, potatoes, and noodles for dinner and then went for a walk. As on her previous episode, she developed hives during

the walk followed by collapse and loss of consciousness. Once again, she did not go to the hospital.

Loss of consciousness in each of these episodes lasted 1 to 2 minutes. The patient experienced nausea and vomiting after each episode. No specific foods gave her a pruritic throat. There was no history of diarrhea or insect bites.

Past Medical History

The patient's medical history is significant for a systolic heart murmur since childhood, asthma from ages 7 to 15, and rheumatoid arthritis since 1990 requiring both medical and surgical therapies. The hands, wrists, elbows, shoulders, and cervical spine were involved. She had previously used methotrexate, prednisone, cyclosporin, and gold. However, after having undergone Swanson arthroplasties and tendon rebalancing of all the digits of the right hand, she only requires infrequent use of ibuprofen for pain relief. There was also a history of heartburn when eating large meals and she experienced seasonal rhinitis symptoms from the end of May through October each year. No medical therapy was used for these problems. Most recently, fibromyalgia was diagnosed in 1998. There was no history of eczema.

Family History

There was a family history of seasonal rhinitis in siblings and the patient's mother. However, there was no family history of food allergy, anaphylaxis, inherited metabolic disorders, or immunologic problems.

Dietary History

There was no history of food or drug allergies as a child or an adult. The patient denied any specific dietary restrictions or changes in her diet in the last few years.

PHYSICAL EXAMINATION

On examination, she was afebrile and vital signs were within normal limits. The oropharynx and nasal cavities were without lesion, and the lungs were clear. There was a soft early systolic murmur at the apex with radiation to the second right intercostal space. Abdomen was soft, bowel sounds normal with no organomegaly, masses, or ascites. Skin revealed mild dermatographia. Characteristic rheumatoid nodules were evident in the hands. No clubbing, cyanosis, or edema was noted. The neurologic examination was unremarkable.

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INITIAL LABORATORY DATA

Laboratory tests performed by her internist included a complete blood count which showed a white blood cell count of $6.8 \times 10^9/L$ with a normal differential count, a hemoglobin of 13.0 g/L, and a platelet count of $192 \times 10^9/L$. The serum electrolytes, blood urea nitrogen, creatinine, liver enzymes, bilirubin, prothrombin time, and partial thromboplastin time were all normal.

QUESTION

Based on the initial history, physical examination, and laboratory data, what other testing might be useful to determine the cause of this patient's recurrent anaphylaxis?

- A. Erythrocyte sedimentation rate
- B. Rheumatoid factor
- C. Food allergy skin tests
- D. Antinuclear antibody level
- E. Complement (C3, C4, CH₅₀, C1-esterase inhibitor) levels
- F. Aeroallergen skin testing
- G. Testing for physical urticarias
- H. Psychiatric evaluation
- I. Drug allergy testing
- J. Serum tryptase
- K. Radioallergosorbent test (RAST)
- L. Skin biopsy
- M. Pulmonary function tests (PFTs)

ADDITIONAL STUDIES AND DIFFERENTIAL DIAGNOSIS

The general internist had also ordered an erythrocyte sedimentation rate which was 12 mm/hour, rheumatoid factor <30 IU/mL, and complement levels which were normal. Antinuclear antibody was negative. The background history of rheumatoid arthritis might lead some physicians to suspect an autoimmune or systemic illness as the cause of her urticaria. This group would include Sjögren syndrome, hepatitis, and systemic lupus erythematosus with or without cryoglobulinemia. However, this patient seems to have an exclusively exercise-associated syndrome without fevers and arthralgias. Therefore, these tests should not routinely be part of this work-up.

Exercise-induced anaphylaxis (EIA) seems to fit this patient's clinical profile. Skin prick testing was positive to wheat (6-mm wheal) and weakly positive to rye (2-mm wheal); 10 mg/mL of histamine control produced a 2-mm wheal. Based on the history and positive skin prick testing, wheat was thought to be the culprit food eaten before exercising in all her episodes of anaphylaxis; that is, she had wheat-dependent EIA (a type of food-dependent EIA [FDEIA]). Based on this patient's history drug, aeroallergen, and venom skin prick testing are not indicated. RASTs are preferable in patients with significant dermatographism, as virtually all their skin prick tests will be positive. Patients with diffuse rashes (severe atopic dermatitis) or those who have difficulty stopping antihistamines would be best served with RASTs.

EIA is clinically distinct from other exercise-induced syndromes and causes of angioedema and urticaria (Table 1). Physical urticarias share the common property of being reproducibly induced by environmental factors such as a change in temperature or by direct stimulation of the skin from pressure, water, vibration, or light. Cholinergic urticaria (CU), an exercise-induced physical urticaria, is important to distinguish from EIA. Although exercise is the main precipitating stimulus of each disorder, CU can also be triggered by hot showers, sweating in the absence of exercise, and anxiety. The hives seen with EIA are usually large (10 to 15 mm) rather than the small, punctate lesions (2 to 4 mm) characteristic of CU. Classically, wheezing and bronchospasm are common in CU, whereas laryngeal edema with stridor and no change in pulmonary function are seen with EIA. This testing was not done in our patient as respiratory symptoms were not a dominant complaint and her hives were >4 mm. Although histamine levels are elevated in both disorders, CU is more reproducible than EIA with each exercise challenge.¹⁻⁷ Attacks of EIA are not usually consistently noted in a given patient even when undergoing apparently identical degrees of exertion.

Tryptase, a marker of mast cell activation and degranulation, is increased after an attack in EIA, whereas studies do not support such an increase in CU.⁸⁻¹⁰ An elevation in tryptase levels could have been missed as it is known that the kinetics of tryptase release require at least a 2-hour period for optimal detection.¹¹ A serum tryptase level was not performed in our patient because she was not seen at the time of an episode.

Classic CU is not usually associated with vascular collapse, although in severe cases hypotension can be observed. Kaplan et al¹² described two cases of typical CU in which

Table 1. Differential Diagnosis of EIA

EIA*
Food-dependent
Drug-dependent
Familial
Variant-type cholinergic (only induced by exercise)
Cholinergic urticaria (exercise-induced urticaria)
Exercise-induced asthma
Other physical urticarias:
cold, heat, solar, aquagenic, pressure, vibratory
Aeroallergen-mediated anaphylaxis (eg, pollens, molds)
Food- or food additive-dependent anaphylaxis
Drug- or chemical-dependent anaphylaxis (eg, penicillin, latex)
Drug-dependent anaphylactoid (eg, niacin, vancomycin [red man syndrome])
Venom-dependent anaphylaxis
Excessive endogenous histamine (eg, systemic mastocytosis)
Psychogenic (eg, panic attacks, somatoform anaphylaxis)
Chronic idiopathic urticaria
Idiopathic anaphylaxis

* Coprecipitating factors: climate, menses, previous aeroallergen exposure, food contaminants.

punctate lesions became confluent and there were recurrent episodes of hypotension. Neither patient had a change in PFTs (also known as variant-type EIA). Extreme cases of CU can resemble EIA, as these conditions lie on a continuum with any given patient having features that resemble one disorder more so than another.¹³⁻¹⁶ An important distinguishing feature of CU is that an increase in core body temperature $>0.7^{\circ}\text{C}$ using passive heat challenges (hyperthermic blankets or submersion in warmed water) causes anaphylactic symptoms in patients with CU but not in patients with EIA.^{12,17}

Exercise-induced asthma, defined as a transitory increase in airway resistance that follows vigorous exercise, is rarely associated with pruritus, urticaria, upper respiratory obstruction, or vascular collapse.^{18,19} PFTs could be helpful.

Systemic mastocytosis is a rare disorder characterized by skin manifestations such as urticaria pigmentosa and hyperplasia of mast cells in bone marrow, liver, spleen, bones, and lymph nodes. These patients can present with acute anaphylactic episodes because they exhibit uncontrolled release of mast cell mediators (tryptase and chymase) that can be spontaneous or triggered by nonspecific stimuli. Exercise is not a common trigger of acute mediator release in these patients.¹¹ Darier sign, skin biopsy with increased dermal mast cells, and raised α -tryptase level would be confirmatory.

Nonorganic disease may mimic anaphylaxis. Such episodes can be involuntary, such as panic attacks which are accompanied by shortness of breath, palpitations, tachycardia, flushing, gastrointestinal symptoms, and dizziness. Loss of consciousness is not usually a feature of panic attacks. Somatoform anaphylaxis is used to describe patients who present with manifestations that mimic idiopathic anaphylaxis but who lack objective confirmatory findings, do not respond to therapy, and exhibit psychologic signs of an undifferentiated somatoform disorder.⁶ These conditions would require a psychiatric evaluation to confirm once organic causes have been excluded.

INITIAL TREATMENT

What treatment strategy should be recommended for this patient?

- A. H_1 -antihistamines
- B. Patient education
- C. Wheat elimination diet
- D. Immunotherapy
- E. H_2 -antihistamines
- F. Sodium bicarbonate prophylaxis
- G. Medical alert bracelet
- H. Epinephrine

The management plan included education regarding avoidance of wheat in her diet before exercising, avoidance of exercise after eating wheat, acquiring a medical alert bracelet, use of H_1 -antihistamines to prevent and treat episodes of urticaria, use of H_2 -antihistamines to potentially prevent hypotension, the suggestion to consume a tablespoon of sodium bicarbonate before exercising to help prevent or reduce ana-

phylactic attacks, and self-administration of intramuscular epinephrine for acute symptoms of an attack. It was suggested that she exercise with a companion who was aware of her condition and capable of administering intramuscular epinephrine if required. There is no evidence that immunotherapy is beneficial for this condition and thus its use was not entertained.

FOLLOWUP EVALUATION

At her followup appointment 3 months later, the patient explained that when she eliminated wheat from her diet, she could exercise without developing anaphylaxis. She was also asymptomatic if she ate wheat alone without exercising. This woman did eat wheat and then walked on two occasions, and developed urticaria and lightheadedness each time. She sat down and the symptoms subsided with no treatment required. Interestingly, the patient did report being asymptomatic on a few occasions when combining wheat and exercise. No specific wheat dose-dependent response or culprit type of exercise could be elicited.

More recently, in the summer of 1999, the patient tried eating bread made with wheat flour at a dinner-party and then swam 30 minutes later. She developed urticaria, lightheadedness, and decreased level of consciousness within 10 to 15 minutes and was assisted out of the water by friends. One of them administered intramuscular epinephrine with good resolution of symptoms. She had minimal success with H_1 - or H_2 -antihistamines for symptom prevention or control, and she had not tried taking any sodium bicarbonate to prevent attacks. She does not wear a medical alert bracelet.

DISCUSSION

EIA is a form of physical allergy that was first noted in 1969.^{18,20,21} The first description of a group of patients with this disorder was published by Sheffer and Austen in 1980.²² Approximately 1000 cases have since been identified.¹¹ This life-threatening exercise-associated clinical syndrome is characterized by symptoms similar to those of other immunoglobulin (Ig)E-dependent anaphylactic reactions mediated by mast cells. The symptomatology of an attack can be divided into *prodromal*, *early*, *fully established*, and *late* components. The *prodromal* symptoms include fatigue, generalized warmth, pruritus, and cutaneous erythema. The *early* manifestations are highlighted by an urticarial eruption that often becomes confluent and even angioedematous. The most commonly affected areas include the face, palms, and soles. Gastrointestinal colic with nausea and vomiting, choking, respiratory stridor, vascular collapse with hypotension, and loss of consciousness may occur with *fully established* attacks. *Late* sequelae in the form of headaches persist for 24 to 72 hours. A typical attack may begin within 10 minutes after initiation of exercise. The episode may persist for 30 minutes to 4 hours after discontinuing the exercise. A tendency toward personal and family history of atopy has been noted, especially when the age of onset is less than 20 years old.^{11,23,24} A familial predisposition to EIA has been suggested

by the presence of several affected members in certain families.^{25,26} Multiple reviews of EIA and other exercise-induced allergies have been published since 1980.^{11,27–35}

The variability and the unpredictability of attacks of EIA have suggested that in some patients other variables, immune or nonimmune, are necessary for the priming of mediator release. Exercise is therefore seen as a subthreshold stimulus for mast cell degranulation. A subset of these patients noticed that ingestion of a specific food, or alternatively, exercise in the postprandial state without requirement for a specific food, is essential for the development of EIA. The first case report of FDEIA was published in 1979 by Maulitz et al.³⁶ The authors described recurrent episodes of anaphylaxis in a 31-year-old atopic male who would ingest shrimp or oysters up to 24 hours before long-distance running events.

Since that first report, numerous other case reports of FDEIA have been published (Table 2). The following foods have been reported: shellfish,^{24,36–39} squid and octopus,⁴⁰ shrimp,^{24,41} snail,⁴² wheat products (including barley, oats, and rye),^{13,24,39,43–50} poppy seed,⁵¹ soybean,⁴⁶ celery,^{39,52,53} peaches,^{39,54} grapes,^{23,53} nuts (hazelnuts, peanuts, walnuts),^{13,46,55} apples,^{46,56,57} cheese,^{39,58,59} cuttlefish,⁶⁰ egg,^{24,41,42} chicken,^{60,61} corn,⁶³ rice,^{45,48} tomatoes,^{13,39,46,49,50} pears,⁴⁶ strawberries,³⁹ kiwis,⁴⁰ litchis,⁶⁴ oranges,⁶⁵ mustard,⁴⁶ milk,³⁹ alcohol,³⁹ matsutake mushrooms,⁴⁰ lettuce,⁵⁰ fennel,⁵⁰ and potatoes¹³ have been reported. Although some patients only experience anaphylaxis with one food, others find that separate ingestion of different specific foods can trigger symptoms after exercise challenge.^{13,46} One case has been described where anaphylaxis was precipitated by celery, but only if ingestion followed exercise.⁵³ It seems that almost any intensity of exercise, from walking to long distance running, can be sufficient to provoke an episode.¹¹

In some cases of specific-FDEIA, an attack will only occur if a large enough quantity of the culprit allergen is ingested before exercising. This could explain certain false negative results in food-exercise challenges. It is unknown whether induction of FDEIA by allergenic food is a dose-dependent response or shows a discrete threshold, (ie, an all-or-none response).^{48,53,62}

If FDEIA is suspected, it would be important to obtain a detailed history of all foods ingested up to 24 hours preceding the episodes of anaphylaxis, the quantity of the suspected foods ingested, the length of time between ingestion and development of symptoms, and the importance of exercise

(type, intensity, and duration) in the chain of events.⁵⁰ Frequently, patients are unaware of the foods that cause their adverse reactions. This was illustrated in a study evaluating adverse reactions to foods in adult patients (not FDEIA-related). Sixty percent of the participants failed to correctly identify the culprit food.⁶⁶ One should also look for a personal and/or family history of atopy. Knowing these specific details, together with results of skin prick tests, can help increase the likelihood of reproducing the symptoms in a controlled setting of a patient-individualized, food-exercise challenge. Although this is the gold standard test for FDEIA, a “negative” exercise challenge does not rule out the condition. Contributing factors, such as climatic conditions, menses, seasonal allergic rhinitis, or use of certain drugs (acetylsalicylic acid, caffeine), should be elicited on history. Patients with a positive skin prick test result and a clear history of severe anaphylaxis after isolated ingestion of a specific food before exercising need not be challenged; instead, an elimination diet would suffice.³⁵

In a review of 179 adult patients who underwent an evaluation for anaphylaxis, Yocum and Khan⁶⁷ identified 12 cases (7%) of EIA. A similar review of 76 Italian children found that exercise accounted for 9% of the cases of anaphylaxis and generally occurred in older children.⁶⁸

Wade et al²⁰ performed an epidemiologic study of 199 patients with EIA to elucidate, among other things, the factors noticed by patients to precipitate an attack. Overall, women were twice as likely to have EIA than men. Any food ingestion within 3 to 4 hours before exercise or intake of specific foods was thought to be an important precipitant of EIA in 54% of cases. Specific food groups cited were shellfish in 8%, celery or cabbage in 6%, and alcohol in 5% of cases.

Shadick et al³⁹ reported that 103 (37%) patients in a cohort of 279 with EIA had one or more food triggers that contributed to an attack. Shellfish was the most common trigger (16% of the cohort) followed by alcohol (11%), tomatoes (8%), cheese (8%), and celery (7%). Wheat products served as a trigger for EIA in 5% of cases.

Cross-reactions between food and inhaled allergens (shared epitopes) have been noted in some patients with FDEIA. These include celery-specific FDEIA and mugwort allergic rhinitis, and snail-specific FDEIA and house-dust mite (*Dermatophagoides pteronyssinus*) allergy.^{42,69–71}

A case involving contaminants in food and EIA has been reported. Specifically, ingestion of any food contaminated by the mold spore *Penicillium lanoso-caeruleum* followed by exercise produced anaphylaxis, whereas neither ingestion of any of these foods, nor *P. lanoso-caeruleum* alone, nor exercise alone was sufficient to trigger the reaction. Such foods included salami, pasta, Parmesan cheese, beef, bread, and apple.⁷²

EIA is generally a permanent disorder marked by significant morbidity if patients are not diagnosed correctly. Avoidance of exercise will prevent anaphylaxis but, of course, will remove health benefits attributable to exercise. Some have been able to modify their exercise routine so as to avoid

Table 2. Most Common Foods Associated with FDEIA

Grains: wheat, rye, barley, oats
Shellfish and seafood: shrimp, crab, oyster
Nuts: hazelnut
Legumes: peanut
Fruits: apple, tomato, peaches, grapes
Vegetables: celery, cabbage
Dairy: cheese, eggs
Alcohol

anaphylaxis while still maintaining physical fitness.²⁰ There has only been one death attributed to EIA and it was not food-dependent.⁷³ It is likely that others have unknowingly died from this disorder. Castells et al¹¹ have suggested measuring tryptase levels at the time of death as a useful screen for the presence of premortem anaphylaxis in those patients suspected of dying from EIA. Recently, a case of acute liver injury was reported in a patient who drank alcohol the night after he experienced postprandial FDEIA. This was felt to be attributable to an interaction between anaphylactic shock and alcohol.⁷⁴

Experimental data, including postexercise electron microscopy of skin biopsies, show that EIA is associated with mast cell degranulation and a rise in plasma histamine and serum tryptase.^{2,8,14,21,22,75-79} Unfortunately, no histochemical studies have defined the type of mast cells that participate in EIA.^{11,80,81} Basal eosinophil hyperactivity has been demonstrated in patients with FDEIA.⁸²

It is poorly understood why exercise can produce anaphylaxis in some people and not in others (Table 3). Small intestinal permeability has been shown to increase in proportion to the intensity of exercise. One of the mechanisms is felt to be increased paracellular transport through "leaky" tight junctions. This leakiness would allow food allergens to cross the intestinal epithelia and stimulate neutrophil migration. Elevation in core temperature coupled with reduced blood flow to the gut (gut vasoconstriction) during exercise may be additional factors that increase small intestinal permeability.⁸³⁻⁸⁹ Certain medications, such as nonsteroidal anti-inflammatory drugs, are known to exaggerate these responses.⁹⁰⁻⁹² This sequence of events suggests how exercise may allow food allergens to penetrate the systemic circulation and generate FDEIA.

EIA appears to involve either an abnormal release of a mast cell degranulating factor, or an exaggerated response to a degranulating factor ordinarily released during exercise that is capable of altering mast cell threshold.^{17,24,93} With respect to the latter possibility, it is known that exercise is associated with a rise in opioid peptides. Lin and Barnard⁹⁴ suggest that exercise might provide an opioid stimulus that can trigger mast cells, already primed by a subthreshold amount of

IgE-mediated mast cell cross-linking after food allergen ingestion, to degranulate.⁹⁵ Experiments implicate both opioid and nonopioid receptors on mast cells.⁹⁶ Gastrin is also released in response to exercise,^{97,98} and has been shown, in both in vitro and in vivo studies, to induce histamine release from human cutaneous mast cells and from rat and human gastric mucosa.⁹⁹⁻¹⁰² It is conceivable that the effects of exercise on mast cell degranulation may be potentiated by the postprandial release of gastrin, which in combination may produce overt clinical symptoms of FDEIA.

Exercise could also be speculated to induce changes in gastrointestinal mucosal enzymes that might facilitate the absorption of peptides from the gut. Conformational changes of a protein attributable to exercise- and gastrin-induced lowering of blood and gastric pH respectively, together with generation of new epitopes by enzymatic modification, could provide the suitable immunomodulatory stimulus for IgE-dependent mast cell degranulation. This concept of new epitope generation by enzymatic modification was recently illustrated in celiac disease.¹⁰³

Using skin prick testing, Kushimoto and Aoki⁴³ showed that digestion of wheat with pepsin increased, whereas digestion with trypsin decreased the activity of wheat allergens in patients with wheat-dependent FDEIA. Sensitive immunoblotting techniques have confirmed that the IgE antibodies of these patients are directed against components of gliadin.⁴⁷ Recently, the major allergenic component was identified as a 64-kD γ -like gliadin.⁴⁵ The allergenic activity of gliadin, the alcohol-soluble fraction of gluten (the chief component of wheat proteins), could thus be enhanced in the stomach and maintained in the duodenum, where the allergens could be absorbed during exercise.

Fukutomi et al⁴¹ have demonstrated abnormalities in the responses of the autonomic nervous system in some patients with FDEIA. The result could be increased perfusion of the gastrointestinal tract with consequent increased distribution of food allergens to various parts of the body. This could explain the systemic nature of the attack.¹⁰⁴

The treatment of FDEIA consists of the reversal of acute anaphylactic reactions and the prevention of recurrent attacks. Management of an acute episode of FDEIA is symptomatic as for any other cause of anaphylaxis.^{18,30} No large controlled trials have shown a definitive and effective treatment regimen, and responses to single-agent and multiple-agent regimens in individual patients have been disappointing.³⁵ Bronchodilators for bronchospasm, H₁- and H₂-antihistamines, intramuscular epinephrine for impending airway closure or vascular collapse, and corticosteroids may be helpful. Late-phase reactions in EIA have not been clearly documented. Nonetheless, patients should be observed for at least 6 hours after a severe attack.¹¹

Patients with specific FDEIA should avoid the culprit food item for at least 24 hours before exercise. Those with non-specific (postprandial) FDEIA should avoid all food for 6 to 8 hours before exercise.⁵⁸ Patients should be cautioned to stop exercising at the slightest provocation of symptoms (pruritus, flushing, or onset of urticaria). They should also be taught to

Table 3. Potential Mechanisms of EIA

Change in small intestinal permeability
exercise increases permeability to food allergens (paracellular leakiness)
Mast cell degranulation
? novel/abnormal exercise-induced release of a degranulating factor
exaggerated exercise-induced release of a degranulating factor, eg, opioids, gastrin
New epitope formation
exercise-induced changes in pH and gastrointestinal enzymatic function
Autonomic nervous system abnormalities
modified gastrointestinal blood supply causes systemic distribution of food allergens

self-administer intramuscular epinephrine with the onset of symptoms. Patients should be instructed to always exercise with a partner who is aware of their condition and who knows how to administer epinephrine. Use of a medical alert bracelet may be helpful.³²

Modification of the individual's exercise program by reduction in intensity or duration of exertion may be required. There are anecdotal reports of success of a graduated exercise program in which the patient developed a "tolerance" to exercise.²⁰ These patients, however, usually have a clinical picture that overlaps CU. Patients should search for and avoid factors that may precipitate an episode. For example, use of certain medications before exercising (eg, nonsteroidal anti-inflammatories) should be avoided. A patient should avoid exercising in weather conditions found to contribute to his/her episodes of FDEIA. For example, some patients with FDEIA have more attacks during the summer months,^{22,23} whereas others find winter a particular problem.¹⁰⁵ Some women should avoid exercising around the time of their menses.

The episodic nature and variability in reproducing symptoms during exercise challenge make it difficult to evaluate the actual efficacy of prophylactic medications. Antihistamines have not been universally successful in the prevention of EIA.¹¹ However, case reports of successful prophylaxis, including one using terfenadine, have been published.¹⁰⁶ Ketotifen, an inhibitor of mast cell degranulation and an H₁-antihistamine, has been shown to reduce symptoms and histamine levels in a patient with EIA.¹⁰⁷ Unfortunately, fatigue and drowsiness have been noted with the sedating antihistamines. Case reports of success with oral or inhaled cromolyn prophylaxis can be found.^{108,109} The importance of low pH is highlighted by a case report documenting successful prophylaxis of wheat-dependent EIA using 3.0 g of sodium bicarbonate orally before exercising. Neither the decrease in pH nor the elevation in plasma histamine levels occurred.¹¹⁰ However, the patient may have been in a refractory state as prophylaxis was carried out shortly after an event had been induced. Others have not confirmed success with sodium bicarbonate.^{111,112} No trials or case reports have been published on the efficacy of corticosteroids in prophylaxis. Considering the many side effects of long-term use of corticosteroids, most physicians do not recommend them for this condition.³⁵ Anticholinergic agents, β -adrenergic agonists, and phosphodiesterase-inhibiting agents have provided no benefit when given prophylactically.²³

FDEIA is an important condition to consider in the differential diagnosis of EIA. The physician is very dependent on the accuracy of a complete and exhaustive clinical history from the patient to make the connection between food ingestion and exercise. There are still many gaps in our knowledge and understanding of FDEIA. Additional studies are required to determine why certain people are susceptible to EIA and what the roles of exercise and food are in producing FDEIA. Clinical trials are needed to determine the efficacy of the

various treatment modalities. Once the condition is recognized, it is easily preventable.

FINAL DIAGNOSIS

Wheat-dependent EIA.

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