

Subspecialty Clinics: Allergic Diseases

Exercise-Induced Urticaria and Anaphylaxis

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Exercise-induced urticaria and anaphylaxis have become increasingly recognized during the past 2 decades as more people participate in physical activities. These syndromes can be categorized as cholinergic urticaria or exercise-induced anaphylaxis based on the clinical manifestation. Newer subsets such as food-dependent and familial exercise-induced anaphylaxis have also been recognized. Further studies are needed to characterize the variables involved in mast cell activation and mast cell mediator release in these syndromes. The management strategy for patients who have exercise-induced syndromes with

skin manifestations only differs from the management for those with systemic symptoms. Currently, antihistamines, as a single agent or in combination with other agents, may be helpful prophylactically in both groups. Avoidance of precipitating factors, modification of exercise, and use of a self-injectable epinephrine kit are recommended for patients with anaphylaxis.

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FEV₁ = forced expiratory volume in 1 second; MIAA = 1-methyl-4-imidazoleacetic acid

Exercise-induced urticaria and anaphylaxis have become increasingly recognized as more people participate in physical activity. As this trend continues, exercise-induced conditions will probably become more common. The symptoms in these exercise-induced syndromes range from mild urticaria with warmth and flushing to life-threatening laryngeal edema and vascular collapse. These syndromes are distinct from exercise-induced asthma in which bronchospasm is the primary symptom and skin manifestations are not observed. Traditionally, investigators believed that these syndromes represented two distinct clinical entities—cholinergic urticaria and exercise-induced anaphylaxis. Because of the common overlap of symptoms, increased histamine levels in both, and variant types of these entities, these syndromes may represent a continuum rather than discrete clinical entities. In addition, other subtypes of exercise-induced syndromes have been described, including familial and food-dependent, exercise-induced anaphylaxis. Persons with exercise-induced anaphylaxis may be unable to exercise or even perform daily activities. Because of the often self-imposed limitations and possible severity of the disease, exercise-induced urticaria and anaphylaxis must be diagnosed and treated appropriately.

CLASSIFICATION

The three major types of exercise-induced urticaria and anaphylaxis, as described by Sheffer and associates,¹ are as follows: cholinergic urticaria, classic exercise-induced anaphylaxis, and variant type of exercise-induced anaphylaxis. These are based on the precipitating event triggering the urticaria, the morphology of the urticaria, and the association with vascular collapse. The clinical characteristics of each are summarized in Table 1.

Cholinergic Urticaria.—Cholinergic urticaria is characterized by generalized flushing and distinctive, punctate 2- to 4-mm pruritic wheals surrounded by a red flare. The reaction occurs in response to an increase in core body temperature. This increase can be due to an active process such as exercise or to a passive process such as fever, emotional stress, or a hot bath. Classic exercise-induced cholinergic urticaria is not usually associated with vascular collapse,² although in severe cases, angioedema, bronchospasm, and hypotension can be observed.^{3,4} Other symptoms of cholinergic stimulation include lacrimation, salivation, and diarrhea. Symptom onset typically occurs in patients between the ages of 10 and 30 years and can persist for many years.² Cholinergic urticaria induced by exercise usually manifests approximately 6 minutes after onset of exercise and increases for approximately 12 to 25 minutes. Generally, urticaria begins on the upper part of the thorax and neck but may occur anywhere on the body. The lesions spread distally to involve the face, back, and extremities. Patients

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Table 1.—Classification of Exercise-Induced Syndromes

Type	Precipitating event	Urticarial morphology	Vascular collapse	Pulmonary symptoms
Cholinergic urticaria	Heat, stress, exercise	Punctate (2-4 mm)	Rare	Bronchospasm
Exercise-induced anaphylaxis	Exercise only	Conventional (10-15 mm)	Yes	Laryngeal edema
Food-dependent, exercise-induced anaphylaxis	Food in combination with exercise	Conventional (10-15 mm)	Yes	Laryngeal edema
Variant exercise-induced anaphylaxis	Exercise only	Punctate (2-4 mm)	Yes	Laryngeal edema
Exercise-induced asthma	Exercise only	None	No	Bronchospasm

without angioedema usually recover in 2 to 4 hours.⁵ Most patients with classic cholinergic urticaria do not have development of systemic symptoms, and symptoms are reproduced when the body becomes warm.

Exercise-Induced Anaphylaxis.—The first group of patients with exercise-induced anaphylaxis was described in 1980 by Sheffer and Austen.⁶ These 16 patients, who ranged in age from 12 to 54 years, experienced exercise-induced anaphylactic reactions without a specific exogenous allergen exposure. The usual sequence of symptoms included fatigue, generalized warmth, pruritus, and erythema with exercise that progressed to an urticarial eruption that became confluent and angioedematous. Collapse with transient, brief periods of loss of consciousness occurred in 12 patients. With a completely developed attack, choking, respiratory stridor, gastrointestinal colic, and nausea and vomiting were also noted. The completely developed symptom complex lasted from 30 minutes to 4 hours. Late sequelae included headaches that persisted for 24 to 72 hours. Wheezing and chest tightness were inconstant and occurred irregularly. Only 2 of the 16 patients had punctate wheals (2 to 4 mm) at the beginning of the attack; the other 14 had hives (10 to 15 mm), characteristic of anaphylaxis due to varying causes. In addition, the patients did not experience these attacks in response to a warm bath, emotional stress, or fever—only to exercise. Because of the size of the urticaria, precipitation of symptoms by exercise only, and progression to collapse, the syndrome was thought to be distinct from cholinergic urticaria and was labeled exercise-induced anaphylaxis.

An epidemiologic questionnaire survey of 199 persons believed to have exercise-induced anaphylaxis showed an age range of 4 to 74 years at time of onset of symptoms; the mean age at onset was 24.7 years.⁷ The frequency of attacks ranged from a single episode to innumerable attacks. The severity of the response could be decreased with early discontinuation of the exercise. Many of the patients were well-trained athletes. Jogging was the most common activity to induce the attacks, but several other activities have

been implicated, including bicycling, racquet sports, walking, and skiing. Fortunately, of almost 1,000 reported cases, only 1 death due to exercise-induced anaphylaxis occurred;⁸ however, unless a postmortem examination is performed that is capable of distinguishing whether premortem anaphylaxis occurred, the number of deaths due to exercise-induced anaphylaxis could be underestimated.

Variant Type of Exercise-Induced Anaphylaxis.—The variant type of exercise-induced anaphylaxis is characterized by the development of punctate urticaria (2 to 4 mm) with exercise that progresses to vascular collapse. Despite the cholinergic-type rash, this variant is precipitated by exercise only and not by passive warming.⁹ In the first study by Sheffer and Austen,⁶ their two patients with punctate urticaria were thought to have the variant type. This type seems to be less common than the other subtypes and accounts for approximately 10% of exercise-induced anaphylaxis. Why such patients do not have development of the large hives typical of exercise-induced anaphylaxis is unknown.

In addition to these categorizations, "overlap syndromes" have been reported. Studies have described patients with symptoms suggestive of variant exercise-induced anaphylaxis, but the symptoms were also reproduced with passive warming.^{3,10,11} Whether these patients' conditions represent a severe type of cholinergic urticaria or a point on the continuum of exercise-induced anaphylaxis is unclear.

Familial Exercise-Induced Anaphylaxis.—Two reports have described familial exercise-induced anaphylaxis. Longley and Panush¹² described two siblings with exercise-induced anaphylaxis who share the HLA haplotype A3-B8-DR3 with their father who has atopy, a suggestion of a heritable predisposition for this syndrome in some families. Grant and colleagues¹³ reported exercise-related cutaneous and respiratory symptoms in seven males from three generations of one family. These findings were consistent with an autosomal dominant pattern of inheritance, but further data could not be obtained to establish such a pattern. In the one family member studied, levels of C2 and C5 were decreased

before exercise, and these levels further decreased during exercise. Because further studies could not be done with this patient or other family members, determining whether a complement defect rather than exercise-induced anaphylaxis was responsible for the symptoms was not possible.

Food-Dependent, Exercise-Induced Anaphylaxis.—In another subset of patients, ingestion of a specific food or any solid food before exercise produces symptoms of exercise-induced anaphylaxis.¹⁴ Patients sensitive to specific foods usually have positive results to prick skin tests to those foods. Patients who experience exercise-induced anaphylaxis after ingestion of any food generally have negative skin test results.

The first case of food-dependent, exercise-induced anaphylaxis was described in 1979 by Maulitz and coworkers.¹⁵ In their report, a 31-year-old man experienced urticaria, facial flushing, and laryngeal edema after ingesting shellfish 5 to 24 hours before long-distance running. Neither exercise alone nor shellfish alone by challenge would reproduce the symptoms. Prick skin testing was positive to oysters and shrimp. Since that report, numerous foods have been implicated in food-dependent, exercise-induced anaphylaxis, including wheat, raw celery, shellfish, cabbage, peaches, grapes, chicken, hazelnuts, and apples.^{14,16-19} Most events occur within 2 to 3 hours after ingestion. Other ingestants that have precipitated exercise-induced anaphylaxis are alcohol and various medications, including aspirin, nonsteroidal anti-inflammatory drugs, antibiotics, and cold remedies.^{7,17} In general, patients with food- or medication-dependent exercise-induced anaphylaxis are able to exercise without symptoms when the offending agent is avoided before exercise. Of interest, such patients almost invariably have large urticaria typical of exercise-induced anaphylaxis rather than punctate (cholinergic) urticaria. Unlike exercise-induced anaphylaxis in which symptom reproduction with challenge varies, food- and medication-dependent exercise-induced anaphylaxis is highly reproducible.¹⁷

PRECIPITATING FACTORS

Other factors associated with or predisposing to attacks were noted on the questionnaire survey of patients with exercise-induced anaphylaxis.⁷ Of the 199 patients with exercise-induced anaphylaxis, almost 50% with classic exercise-induced anaphylaxis had atopy, defined as a history of eczema, asthma, or allergic symptoms to airborne allergen (in comparison with approximately 20% of the general population).⁷ More than 50% of first-degree relatives of patients with exercise-induced anaphylaxis had allergic symptoms.⁷ Exercising in a warm, humid, or cold environment was thought to increase the likelihood of an attack in 64%, 32%, and 23%, respectively.⁷ Food ingestion within 3 to 4 hours before exercise or intake of specific foods was thought to be a factor

in the development of attacks in 54% of the respondents. Of the women who responded, 19% thought that the menstrual cycle affected the onset of exercise-related symptoms.⁷ In a separate study, 43% of patients with cholinergic urticaria had atopy.² In addition, patients with other types of physical allergy, especially cold urticaria, pressure urticaria, and dermatographism, are overrepresented in groups with the exercise-induced syndromes.²⁰ This may reflect an enhanced mast cell lability in these patients.

PATHOPHYSIOLOGY

Cholinergic Urticaria.—The exact mechanism of cholinergic urticaria is unknown, but this disorder seems to result from an exaggerated cholinergic response to body warming. Acetylcholine is released, an outcome that may cause mast cell degranulation through unknown and probably indirect mechanisms, and subsequent histamine release provokes the urticarial eruption. It is unclear whether this represents excessive acetylcholine secretion, increased acetylcholine receptor sensitivity, excessive histamine release after cholinergic stimulation, or reduction in the amount of the protease inhibitor α_1 -antichymotrypsin, a mediator that may inhibit a protease causing mast cell activation.²

A few studies have analyzed the mediators in cholinergic urticaria under various exercise conditions. These reports mainly involved individual patients or small groups of two to four patients. Most of the study patients had systemic symptoms induced by exercise and not skin manifestations alone. In one of the larger reports, Soter and associates²¹ studied seven patients with a history of exercise-induced cholinergic urticaria and respiratory complaints by having them exercise on a treadmill at their own pace for a mean of 7 minutes while wearing plastic occlusive suits. All the patients experienced cholinergic urticaria, and six experienced dyspnea or wheezing. Increased histamine levels were detected in all the patients. The level of histamine increased as early as 6 minutes, peaked at 20 minutes, and returned to baseline at 40 minutes. Eosinophil and neutrophil chemotactic activity peaked at 6 minutes and returned to baseline at 20 to 30 minutes. Assessment of CH_{50} levels in each of the seven subjects and functional analyses of C1, C4, C2, C3, and C9 in one subject did not change from baseline levels. In another study, Sigler and colleagues²² had a patient with cold urticaria and cholinergic urticaria run in place for 20 minutes. Histamine levels increased 5 minutes after exercise and peaked 30 minutes after exercise. Another representative study³ involved four patients who exercised on a stationary bicycle; histamine levels peaked 10 to 25 minutes after onset of exercise. Cholinergic urticaria was noted in all four patients and dyspnea in two. Kaplan and coworkers¹⁰ had two patients exercise on a bicycle ergometer and noted peaks in histamine levels at 20 minutes. Both these patients had a

significant decrease in blood pressure in addition to a typical cholinergic urticarial skin exanthem. In a free running challenge of three patients with cholinergic urticaria, one of whom had hypotension with challenge, an increased histamine level was noted only in the patient with hypotension.²⁰ This increase in histamine was rapid, and the maximal increase occurred with peak symptoms. Serum complement levels (C3 and C4) were normal in all three subjects. This is the only study that did not show an increase in histamine levels in patients with exercise-induced cholinergic urticaria.

In studies evaluating other mediators, serotonin levels were not increased except in one patient.²² Tryptase, a mast cell marker, was not found to be increased in five patients with variant and overlap types of cholinergic urticaria despite increased levels of histamine and reproduction of symptoms.^{3,23} Sampling continued up to 20 minutes after exercise in four of the patients and up to 50 minutes in the other patient. Because of the late release of tryptase from the mast cell, sampling may not have been done for a long enough period after exercise to detect an increase, or, possibly, these patients have more than mast cell involvement. Overall, levels of histamine are consistently increased with cholinergic urticaria, and investigators generally agree that histamine is the major mediator involved in cholinergic urticaria. Complement activation does not seem to have a role, and thus far studies have not detected increased levels of bradykinin.

Because pulmonary symptoms are often a prominent systemic component of exercise-induced cholinergic urticaria, pulmonary function tests have also been performed in an exercise-challenge setting. These studies are typically done concomitantly with mediator measurement during exercise challenge. Soter and associates²¹ noted a significant decrease in forced expiratory volume in 1 second (FEV_1), maximal midexpiratory flow rate, and specific conductance in seven patients who experienced cholinergic urticaria when undergoing challenge consisting of wearing a plastic occlusive suit while running on a treadmill. In four of the patients, wheezing also developed, as detected on auscultation. These findings of bronchospasm are not ubiquitous, however, because other patients with cholinergic urticaria had no changes in pulmonary function with exercise.⁴ In two patients studied by Kaplan and colleagues,¹⁰ no significant changes in FEV_1 were noted on challenge despite reproduction of symptoms and a significant decrease in blood pressure. On the basis of these studies, some patients with cholinergic urticaria can have a significant decrease in the FEV_1 , especially when undergoing challenge with plastic occlusive suits, but this phenomenon is not observed in all patients.

Exercise-Induced Anaphylaxis.—Exercise challenges performed with patients who have classic exercise-induced anaphylaxis have also shown increased serum histamine lev-

els;^{1,24} however, symptom reproduction during exercise challenge is not as consistent as in patients with cholinergic urticaria despite use of high exertion challenges. Sheffer and coworkers¹ noted increased histamine levels in four of seven patients who had symptoms during challenge consisting of running while wearing an occlusive suit. The histamine levels peaked 5 to 10 minutes after onset of exercise and returned to normal after about 20 minutes when the clinical symptoms were subsiding. In another study, Sheffer and associates²⁴ performed skin biopsies before and after exercise that revealed an exercise-induced loss of ultrastructural detail within the mast cell granules. These changes are similar to those observed in *in vivo* mast cell degranulation induced by intradermal injection of ragweed extract into persons allergic to ragweed.²⁴ In the four patients, histamine levels were measured, and increases were noted with exercise. Further evidence of mast cell activation has been suggested by an increased tryptase level during the height of an attack in a patient with classic exercise-induced anaphylaxis during a jogging challenge;²⁵ however, no baseline levels of tryptase were obtained in this patient.

The cause of the histamine release from the mast cell is unclear. Because patients with classic exercise-induced anaphylaxis do not have a response to passive body warming, investigators have suggested that an immunoglobulin-antigen complex similar to an IgE-mediated anaphylactic event may provoke the anaphylactic response.^{1,16} The lack of predictability in reproducing exercise-induced anaphylaxis under similar exercise stimuli and the ingestion of specific foods before exercise suggest that a "priming" phenomenon may be needed for mediator release.²⁶ The mechanism of this priming, however, is unknown.

Changes in spirometry (FEV_1) are uncommon in classic exercise-induced anaphylaxis.⁹ Choking and stridor due to upper airway edema can occur in some patients with exercise-induced anaphylaxis. In four subjects tested by Sheffer and colleagues,¹ no significant changes were noted in FEV_1 , airway conductance, or residual volume despite reproducibility of pruritus, erythema, angioedema, and increased histamine levels. This differs from classic cholinergic urticaria in which bronchospasm and wheezing are commonly reported.

Variant Type of Exercise-Induced Anaphylaxis.—In patients with the variant type of exercise-induced anaphylaxis, increased histamine levels have been documented with experimental challenge on a bicycle or ergometric exerciser.^{9,10} The time course of the increase was similar to that with cholinergic urticaria and classic exercise-induced anaphylaxis.

Food-Dependent, Exercise-Induced Anaphylaxis.—Mast cell release has been studied with skin testing to compound 48/80, a marker for mast cell releasability, and co-

deine. Kivity and coworkers²⁷ described five patients with a history of exercise-induced anaphylaxis and positive results of prick skin tests to foods. Prick skin testing to histamine, control, and compound 48/80 were performed before and after challenge with exercise alone, food alone, and food ingestion followed by exercise. In four of the patients, symptoms were produced with the combined food and exercise challenge only. The before and after histamine and control skin responses were unchanged. With the compound 48/80, however, a substantially increased wheal response was noted after exercise with prior food ingestion. In one patient, the symptoms could not be reproduced, and no changes occurred in any of the skin testing before and after challenge. The observation that the skin response was increased only to compound 48/80 and not to the histamine or the control suggests a direct effect on mast cell releasability and not an increased sensitivity to histamine. This also implies that the interaction between the food antigen and IgE can lower the mast cell threshold to another stimulus—in this case, exercise—that enables the mast cell release to become clinically apparent. Lin and Barnard²⁸ noted increases in the wheal size with skin testing to codeine after exercise alone in a patient with food-dependent, exercise-induced anaphylaxis. During the challenge, no symptoms were elicited, and no changes were noted in the histamine, food, and control skin tests before or after exercise. This implies that exercise may provide a nonspecific stimulus for mast cell degranulation. In theory, the food allergen may lower the threshold of the mast cell such that exercise may provide enough stimulus for mast cell release. The precise sequence of events, however, remains unclear.

DIAGNOSIS

Exercise-induced syndromes can usually be diagnosed by elicitation of the history. The size of the hives, precipitating factors such as food and passive warming, and clinical course relative to vascular collapse and type of pulmonary involvement should be noted.

The methacholine skin challenge test involves intradermal injection of 100 µg of methacholine chloride in 0.1 mL of saline solution. Patients with cholinergic urticaria will experience a localized hive and occasionally satellite lesions around the site. Unfortunately, sensitivity is only 33%, although specificity is high.⁴ Therefore, the skin test can only be used to confirm the diagnosis of cholinergic urticaria. Another method of documentation is a passive warming test. This can be performed by using a heating blanket to increase the body temperature approximately 1°F or by placing an extremity in hot (104°F) water. The patient with cholinergic urticaria should have an increased histamine level and urticaria, whereas the patient with classic exercise-induced anaphylaxis will not.

Exercise challenge testing can be performed to reproduce the symptoms if the clinical picture is unclear. This should be done under controlled conditions in which resuscitation equipment and skilled personnel are readily available. In patients with classic exercise-induced anaphylaxis, reproducing the symptoms in a controlled setting can be difficult because of the variability of symptom occurrence. Thus, a “negative” exercise challenge does not rule out the disease. Several methods can be used to perform exercise testing, including running on a treadmill in an occlusive suit,^{21,24} jogging in place,²² riding a bicycle ergometer exerciser,¹⁰ and free running.^{5,25} During the challenge, mediator measurements such as histamine and tryptase are typically obtained through an intravenously placed catheter at predetermined time points before, during, and after exercise. At set time points or when the patient is symptomatic, pulmonary function testing is also typically performed. The forced vital capacity and FEV₁ can be determined by having the patient expire forcefully into a spirometer. In order for the physician to perform these maneuvers while the patient continues to exercise, the patient should be on a bicycle or treadmill. We perform exercise testing in the exercise laboratory of our pulmonary testing center. While the patient is exercising on a bicycle ergometer, a 1-minute, 20-W incremental protocol is used to a maximal workload of approximately 140 W. A physician is in attendance, and emergency equipment is available. The heart rate is constantly monitored, and blood pressure readings are taken periodically. An indwelling catheter is used to obtain blood samples. Spirometry is performed with the patient remaining on the bicycle during exercise.

In addition to exercise testing, prick skin testing or *in vitro* testing for specific IgE antibodies to foods may be helpful. If the clinical history suggests a specific food as a precipitant of exercise-induced anaphylaxis, a positive result of prick skin testing to that food may confirm the diagnosis. Often, prick skin testing to other foods that have not been clinically associated with the episodes and aeroallergens also shows positive results.¹⁷ Therefore, further recommendations relative to food intake must consider the clinical history and not just skin test positivity.

The differential diagnosis in these patients is limited. The key is to confirm that symptoms occur only with exercise or, in the case of cholinergic urticaria, with passive warming. The other major diagnostic considerations are idiopathic anaphylaxis and mastocytosis. In idiopathic anaphylaxis and systemic mastocytosis, symptoms occur at times other than with exercise. If the patient is unsure whether symptoms occur at times other than with exercise and if mastocytosis is suspected, an initial work-up including determination of serum tryptase and 24-hour urine 1-methyl-4-imidazoleacetic acid (MIAA) levels would be

reasonable; further evaluation would depend on the clinical situation.

TREATMENT

The treatment of an acute attack of exercise-induced anaphylaxis is the same as that for anaphylaxis of any cause and consists of subcutaneously administered epinephrine, intravenously administered fluids, oxygen, antihistamines, and airway maintenance. Preventing future episodes is difficult. No large controlled trials have shown a definitive effective treatment regimen for either cholinergic urticaria or exercise-induced anaphylaxis, and responses to single-agent and multiple-agent regimens in individual patients have been disappointing. Of importance, a detailed history must be obtained in regard to any precipitating factors such as specific foods, food in general, and prescription and over-the-counter medications. When implicated, elimination of all food 6 hours before exercise and avoidance of the medication are the easiest strategies. A food diary may be helpful if the patient is unable to recall ingestants before exercise. Because of the importance of the postprandial state as a promoting factor and the limitations of our knowledge of the pathogenesis of exercise-induced anaphylaxis, all patients with exercise-induced anaphylaxis should wait 4 to 6 hours after eating before they exercise, not just those with obvious food provocation.¹⁷

Because symptoms of cholinergic and exercise-induced urticaria sometimes overlap, the best treatment approach, after a thorough review for precipitating factors, is to categorize the patients into two groups—those who have skin symptoms only (usually mild cholinergic urticaria) and those who have skin and systemic symptoms with exercise (usually severe cholinergic urticaria and exercise-induced anaphylaxis). For patients with skin symptoms only, the usual first line of treatment is the H_1 receptor antagonists. Hydroxyzine is often effective possibly because of its concomitant anticholinergic properties. Hydroxyzine can be administered at dosages as high as 100 to 200 mg/day in divided doses.⁴ The main side effect is drowsiness. H_1 antagonists such as terfenadine and acrivastine have been tried, and results have varied.^{5,29} Other nonsedating antihistamines probably have similar efficacy. Typically, an H_1 antagonist will decrease the patient's symptoms. If the patient continues to have troublesome symptoms, other H_1 antagonists or the addition of an H_2 antagonist should be considered. Because patients with reproducible symptoms limited to the skin should not be expected to experience systemic symptoms, severe limitations and modifications of exercise and the carrying of a self-injectable epinephrine kit are not indicated.

For patients with systemic symptoms (severe cholinergic urticaria and exercise-induced anaphylaxis), the usual first

line of treatment to prevent or decrease symptoms is the H_1 antagonists. In general, they are most effective for milder types of exercise-induced syndromes. Fortunately, in normal subjects, the H_1 antagonists have not been shown to compromise athletic performance,³⁰ an important factor because many patients are well-trained athletes. Because of breakthrough symptoms while a patient is taking a single agent, combination antihistamine regimens have been tried (for example, the addition of cyproheptadine hydrochloride, 8 to 16 mg/day, to hydroxyzine).⁴ In refractory cases, the H_1 antagonist cimetidine and the tricyclic antidepressant doxepin hydrochloride have been added to H_1 antagonists. Ketotifen, an H_1 receptor antagonist, mast cell stabilizer, and up-regulator of β -adrenergic receptors, which is not yet available in the United States, was helpful in four patients with refractory systemic cholinergic urticaria and the variant type of exercise-induced anaphylaxis.³ Anticholinergic agents such as atropine and propantheline bromide, β -adrenergic antagonists, and phosphodiesterase-inhibiting agents have provided no apparent benefit when given prophylactically.¹⁹ In case reports involving only one patient each, results have varied with oral cromoglycate therapy, from 400 mg to 2.4 g a day, and inhaled cromolyn therapy, two puffs four times a day.^{11,20,31} Sodium bicarbonate was helpful in one patient with wheat-dependent, exercise-induced anaphylaxis.³² No reported trials or case reports have studied the efficacy of corticosteroids in patients with these syndromes. Because of the side effects associated with prolonged use of corticosteroids, we cannot recommend them for most patients. Overall, the episodic nature and variability in reproducing symptoms during exercise challenge make it difficult to evaluate the actual efficacy of these prophylactic medications. We recommend an H_1 antagonist for initial treatment. If symptoms persist, we add an H_2 blocker. If symptoms are still uncontrolled, we add another antihistamine such as doxepin. These medications are summarized in Table 2.

Because of the difficulty associated with medical therapy, the mainstay of treatment is modification of each individual person's exercise program and education. Avoidance of exercise on warm or humid days and a reduction in the intensity of the exercise may be necessary. Exercise should be discontinued at the first signs of flushing, pruritus, urticaria, or malaise. Some patients with severe cholinergic urticaria have benefited from a graduated exercise program in which they can develop a "tolerance" to exercise.¹⁰ This type of program should be implemented under close medical supervision. All patients with exercise-induced anaphylaxis should be instructed in the use of a self-injectable epinephrine kit and should carry one with them. Exercise should always be done with a partner who is aware of the patient's condition and capable of providing emergency assistance.

Table 2.—Management of Exercise-Induced Urticaria and Anaphylaxis

Nonpharmacologic management	
Exhaustive search for other precipitating causes	
Modification of exercise regimen	
Avoidance of all food 4 h before exercise	
Pharmacologic management	
H ₁ antagonists	
	Hydroxyzine, 10-50 mg every 6 h
	Terfenadine, 60 mg twice daily
	Astemizole, 10 mg daily
	Loratadine, 10 mg daily
	Doxepin, 25-100 mg at night
H ₂ antagonists	
	Cimetidine, 150 mg twice daily
	Ranitidine, 150 mg twice daily
	Famotidine, 20 mg twice daily
Mast cell stabilizers	
	Cromolyn sodium, 2 puffs every 4 h
	Ketotifen, 1-4 mg twice daily
Emergency	
Self-administration of injectable epinephrine	

CLINICAL VIGNETTES

The following two clinical vignettes highlight the severe symptoms that can be associated with exercise-induced syndromes and the subsequent assessment, diagnosis, and treatment.

Case 1.—A 14-year-old female adolescent was referred to Mayo Clinic Rochester because of a 3-year history of exercise-related pruritus. Throughout the years, she noticed pruritus followed by small skin lesions (less than 5 mm in diameter) whenever she would exercise enough to feel "hot." In addition, she noted similar symptoms when taking a warm bath or shower. During the preceding 6 months, the symptoms occurred daily and progressed to the point that they would occur when she climbed two flights of stairs. She also noted occasional chest tightness and such weakness that she would have to sit down or she would lose consciousness. No correlation was noted with food ingestion before these episodes. The symptoms would usually resolve in approximately 20 to 30 minutes. Use of a self-injectable epinephrine kit was needed on two occasions to relieve her symptoms.

On the basis of the patient's clinical history of small urticaria and reproduction of symptoms with passive warming, we believed that she had severe cholinergic urticaria. This condition differs from mild cholinergic urticaria in which systemic symptoms do not occur. The diagnosis of the variant type of exercise-induced anaphylaxis could not be made because of her symptoms with passive warming. Further evaluation included an exercise challenge test. After approximately 5 minutes of exercise challenge (as previously described), she had pinpoint urticaria characteristic of

cholinergic urticaria. During the next 10 minutes, her blood pressure progressively decreased to a nadir of 45/24 mm Hg; thus, a supine position and subcutaneous administration of epinephrine were necessary. She did not experience loss of consciousness. Spirometry showed an 11% decrease in her FEV₁, which corresponded to her symptoms of chest tightness and dyspnea before the decrease in her blood pressure. Her symptoms resolved within 1 hour. The diagnosis of severe cholinergic urticaria was confirmed. Because she had had a poor response to antihistamines in the past, astemizole, 10 mg/day, and doxepin, 10 to 20 mg/night, were initiated. She was instructed in the use of a self-injectable epinephrine kit and given exercise safety guidelines.

Case 2.—A 26-year-old man sought medical attention because of an 8-month history of pruritus, hives, and angioedema associated with exercise. He described pruritus, large hives, and periorbital and perioral edema occurring repeatedly during extensive physical activity. He had had three episodes that resulted in loss of consciousness and hypotension that necessitated treatment at an emergency department. No correlation was noted with food ingestion before these episodes. These hypotensive episodes occurred only with exercise. He noted small hives (less than 5 mm in diameter) while taking a warm bath or shower but had no other symptoms at those times.

On the basis of the patient's clinical history, we believed that he had classic exercise-induced anaphylaxis because of the large hives, angioedema, and occasional loss of consciousness and hypotension associated with exercise. We believed that he also had mild cholinergic urticaria based on the small punctate rash he noted during warm baths or showers. Because of his severe symptoms with exercise and reliable history, an exercise challenge was not performed. Further evaluation included serum-specific IgE tests to basic foods, results of which were either negative or equivocal. Results of screening tests for mastocytosis, including calcitonin and 24-hour urine MIAA, were in the normal range. The patient's symptoms partially decreased while he was taking a regimen of astemizole, 10 mg/day; hydroxyzine, 50 mg/day; famotidine, 40 mg twice a day; and cromolyn, two puffs twice a day and using an albuterol inhaler as needed. Prednisone therapy was subsequently initiated, which seemed to help slightly; however, he was instructed to taper the dose of prednisone. He was advised about exercise safety and the use of a self-injectable epinephrine kit. Fasting at least 4 hours before any exercise was recommended.

CONCLUSION

Exercise-induced urticaria and anaphylaxis can be classified into cholinergic urticaria and exercise-induced anaphylaxis on the basis of the patient's history relative to size of the urticarial lesions, development of hypotension, precipitating

factors such as passive warming and food, type of airway involvement, and reproducibility under similar conditions. Because of overlap of symptoms, it is unclear whether these syndromes represent a continuum of one process or subsets with different pathogenesis and mediator release patterns. The threshold of mast cell responsiveness seems to be influenced by heat, food, and, possibly, currently unknown stimuli. Additional studies are needed to characterize further the mast cells in these patients in regard to mediator release (other than histamine) and morphologic changes during the event.

Prophylactic treatment for patients with skin involvement only consists of antihistamines. For those with systemic symptoms, management includes modification of exercise relative to intensity, duration, and weather conditions and abstaining from food before exercise. All patients with systemic symptoms should carry an epinephrine kit and exercise with a partner. Larger controlled trials must be performed to determine the efficacy of the various antihistamines and other treatment modalities.

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