Exercise-Induced Anaphylaxis and Urticaria

ROBERT G. HOSEY, M.D., University of Kentucky School of Medicine, Lexington, Kentucky
PETER J. CAREK, M.D., M.S., Medical University of South Carolina, Charleston, South Carolina
ALVIN GOO, PHARM.D., Harborview Medical Center, Seattle, Washington

In a select group of persons, exercise can produce a spectrum of allergic symptoms ranging from an erythematous, irritating skin eruption to a life-threatening anaphylactic reaction. The differential diagnosis in persons with exercise-induced dermatologic and systemic symptoms should include exercise-induced anaphylaxis and cholinergic urticaria. Both are classified as physical allergies. Mast cell degranulation with the release of vasoactive substances appears to be an inciting factor for the production of symptoms in both cases. Exercise-induced anaphylaxis and cholinergic urticaria can be differentiated on the basis of urticarial morphology, reproducibility, progression to anaphylaxis and response to passive warming. Diagnosis is usually based on a thorough history and examination of the morphology of the lesions. Management of acute episodes of exercise-induced anaphylaxis includes cessation of exercise, administration of epinephrine and antihistamines, vascular support and airway maintenance. Long-term care may require modification of or abstinence from exercise, avoidance of co-precipitating factors and the prophylactic use of medications such as antihistamines and mast cell stabilizers. (Am Fam Physician 2001;64:1367-72,1374.)

O *A patient information handout on exercise-induced urticaria, written by the authors of this article, is provided on page 1374.*

AGF *This article exemplifies the AAFP 2001 Annual Clinical Focus on allergies, asthma and respiratory infections.*

Exercise-induced anaphylaxis is a distinct form of physical allergy and, although rare, has been consistently described in the literature since the 1970s.[1] This disorder is classically characterized by a spectrum of symptoms occurring during physical activity that ranges from mild cutaneous signs to severe systemic manifestations such as hypotension, syncope and even death.

Exercise-induced anaphylaxis has been described at all levels of physical exertion and during various athletic activities.[2,3] In susceptible persons, ingestion of certain foods or medications before physical activity may be a predisposing factor. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) have been the most frequently implicated medications.[4,5] Foods that have been implicated include seafood, celery, wheat and cheese.[1,4,6] A variant has been described in which seven members of the same family exhibited exercise-induced cutaneous, respiratory and occasional vascular symptoms that were attributed to exercise-induced anaphylaxis.[7]

In susceptible persons, ingestion of certain foods or medications before physical activity may be a predisposing factor for exercise-induced anaphylaxis.

Because symptoms may vary greatly, many persons with exercise-induced anaphylaxis are unaware of their condition. Similarly, because it is a relatively rare condition, it often goes undiagnosed. Primary care physicians should be able to recognize and manage exercise-induced anaphylaxis and help patients prevent the condition.

Epidemiology

Since the original case description during the 1970s, more than 1,000 cases have been described in the literature.[8] Despite the potential for full-blown anaphylaxis with exercise-induced anaphylaxis, only one death has been attributed to this disorder.[9] This statistic suggests that many people with this condition have milder symptoms or are able to recognize potentially life-threatening symptoms and limit their activity. Conversely, it is possible

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that deaths caused by exercise-induced anaphylaxis go unrecognized. Urticaria is a much more recognized phenomenon, affecting 10 to 20 percent of the population at some point in time.[10] Urticarial responses occurring exclusively during exercise are significantly less common.

Definitions and Classification

Urticaria, angioedema and anaphylaxis may occur separately or simultaneously. Urticaria, or "hives," is characterized by pruritic, white or erythematous, nonpitting edematous plaques. These plaques change in size over time and may coalesce to form larger "giant wheals."

Urticarial lesions are the result of capillary vasodilation followed by transudation of fluid into the superficial dermis. Angioedema typically involves accumulation of transudate in the deeper layers of skin and subcutaneous tissues, resulting in the development of thick, firm plaques. These lesions usually involve the larynx, lips and gastrointestinal mucosa, although they may form anywhere on the skin.

TABLE 1
Etiologic Mechanisms of Urticaria/Anaphylaxis

Anaphylaxis is a life-threatening syndrome that occurs in previously sensitized persons. An anaphylactic reaction is manifested by respiratory distress, with or without vascular collapse. Urticaria or angioedema may or may not accompany an anaphylactic episode. Urticaria, angioedema and anaphylaxis may have numerous causes that are often difficult to identify and are best classified by an etiologic mechanism *(Table 1)*.[11]

Exercise-Induced Disease Types

According to the literature, three distinguishable exercise-induced urticarial disease types exist and include cholinergic urticaria, and classic and variant exercise-induced anaphylaxis *(Table 2)*.[11,12]

CHOLINERGIC URTICARIA

Cholinergic urticaria is a physical allergy manifested by small (2 to 5 mm) punctate papules that are usually surrounded by an erythematous halo. Often, however, only a pruritic macular erythema covers an area of skin 10 to 20 cm in diameter. Lesions usually begin on the upper thorax and neck but may spread to the entire body.[10]

A single lesion typically resolves in 15 to 20 minutes, although the episode that produces many lesions may persist for several hours. The lesions are known to occur in response to exercise, passive body warming and emotional stress. A rise in plasma histamine levels has been demonstrated in symptomatic patients.[3,13] If the inciting stimulus persists, the hives may coalesce and resemble angioedema, but vascular collapse is rare.[11] Pulmonary symptoms often occur,[3,11] but significant changes on peak flow measurements and formal pulmonary function tests are not consistently reproducible.[3,13]

CLASSIC EXERCISE-INDUCED ANAPHYLAXIS

Urticaria or angioedema with upper respiratory obstruction and hypotension precipitated by exercise are classified as classic exercise-induced anaphylaxis. Symptoms may

include generalized itching, a choking sensation, gastrointestinal colic, nausea, headache and wheezing. An episode may be precipitated by a variety of exercise activities at varying degrees of exertion. Most commonly, jogging and running have been described as the inciting activity.[2,4] Activities such as dancing, volleyball, skiing and even yard work also have been implicated. Symptoms typically last from 30 minutes to four hours after the cessation of exercise.[2] Frequency of attacks may vary considerably, from a single episode to several episodes annually. In addition, the episodes are not consistently reproducible and thus are unpredictable. They do, however, tend to decrease with time (the likely reason being that patients learn to avoid triggers).[4]

VARIANT EXERCISE-INDUCED ANAPHYLAXIS

The variant form of exercise-induced anaphylaxis is the least common form. Like cholinergic urticaria, variant exercise-induced anaphylaxis produces small, punctate, erythematous papules and is associated with increased plasma histamine levels. However, the variant form is provoked only by exercise and may progress to anaphylaxis. Several cases of the variant form have been described, and they may account for approximately 10 percent of all cases of exercised-induced anaphylaxis.[3,10]

Pathophysiology

The specific etiology of exercise-induced anaphylaxis is unclear. Results from skin biopsies reveal that skin mast cell degranulation occurs during symptomatic attacks.[14] It is likely that vasoactive mediators released by mast cells are responsible for the symptoms.[2] An increase in plasma histamine levels has been demonstrated in patients with classic and variant forms of exercise-induced anaphylaxis and cholinergic urticaria.[2,3,14] In addition, other products of mast cell degranulation, namely serum tryptase and leukotrienes, have been shown to be present at increased levels in symptomatic patients with exercise-induced anaphylaxis.[15,16]

An exaggerated cholinergic response to an increase in body temperature (or to anxiety, stress or exercise) seems to be the cause of cholinergic urticaria. Results of skin biopsies of cholinergic urticarial lesions reveal histologic characteristics identical with other forms of urticaria. Specifically, neutrophils, mononuclear cells and eosinophils are present in and around the walls of superficial subpapil-

TABLE 2
Patterns of Exercise-Induced Anaphylaxis

Type	*Reproducibility*	*Precipitating event*	*Urticarial morphology*	*Associated vascular collapse*	*Bronchospasm (clinical)*	*Bronchospasm (functional)*
Cholinergic	Reproducible	Passive warming, emotional stress, exercise	2 to 5 mm	Rare	Inconsistent	Yes
Classic	Variable	Exercise only	Conventional; 10 to 15 mm	Yes	No	No
Variant	Variable	Exercise only	2 to 5 mm; may progress to larger lesion	Yes	No	No

Information from Nichols AW. Exercise-induced anaphylaxis and urticaria. Clin Sports Med 1992;11:303-12, and Sheffer AL, Soler NA, McFadden ER, Austen KF. Exercise-induced anaphylaxis: a distinct form of physical allergy. J Allergy Clin Immunol 1983;71:311-6.

A history of exercise-induced cutaneous warmth, erythema and pruritus with or without urticaria is highly suggestive of exercise-induced anaphylaxis or cholinergic urticaria.

lary dermal vessels.[13] It has been theorized that increased sympathetic nervous activity stimulates cholinergic fibers innervating eccrine sweat glands to release acetylcholine, leading to mast cell degranulation and liberation of vasoactive substances, including histamine, and resulting in urticaria. IgE, an intermediate substance, may be responsible for mast cell degranulation.[13]

Diagnosis

The diagnosis of exercise-induced urticaria or anaphylaxis can often made on the basis of the history. A history of exercise-induced cutaneous warmth, erythema and pruritus with or without urticaria is highly suggestive of either condition. Progression of symptoms to dysphagia, dyspnea, wheezing, dizziness or syncope is also consistent with exercise-induced anaphylaxis. Gastrointestinal symptoms of colic, nausea and vomiting also may occur. A history of atopy provides further evidence to support the diagnosis.

Observation of skin lesions and a history of symptoms with passive warming (i.e., during a shower or a bath) help differentiate cholinergic urticaria from exercise-induced anaphylaxis. If the diagnosis remains in doubt, a passive warming test can be performed. A rise in core body temperature of 0.5°C to 1.5°C (0.9°F to 2.7°F) can be achieved by immersing the patient in warm water or raising the ambient temperature in a controlled environment. This test will produce elevation of plasma histamine levels with or without urticaria in patients with cholinergic urticaria but not in those with exercise-induced anaphylaxis.[11]

If a patient is suspected of having exercise-induced anaphylaxis, an exercise challenge test can be conducted. This test can be carried out on a treadmill or exercise bicycle in a manner similar to a graded exercise stress test. Because the reproducibility of symptoms in exercise-induced anaphylaxis is variable, a negative test does not rule this out as a diagnosis. A positive test, however, helps confirm the diagnosis. The exercise challenge test should be conducted under controlled settings with emergency equipment available.

The methacholine skin test may elicit a positive response in patients with cholinergic urticaria. In this test, methacholine (100 units in saline solution) is injected intradermally, subsequently producing the characteristic micropapular hives. This test is positive in approximately one third of patients.[3,13] Thus, a negative test does not exclude cholinergic urticaria as a diagnosis. Typically, patients with a positive test tend to have more severe cholinergic urticaria.[3]

Treatment

Modification of activities and behaviors is the mainstay of treatment in patients with exercise-induced anaphylaxis. Patients should

The Authors

ROBERT G. HOSEY, M.D., is assistant professor of family medicine and associate director of the Primary Sports Medicine Fellowship at the University of Kentucky School of Medicine, Lexington. Dr. Hosey received his medical degree from the State University of New York Health Science Center at Syracuse College of Medicine, and completed a residency in family practice at the Medical University of South Carolina, Charleston. He completed a sports medicine fellowship at the University of California, Los Angeles, UCLA School of Medicine. He holds a certificate of added qualification in sports medicine.

PETER J. CAREK, M.D., M.S., is associate professor and residency program director in the Department of Family Medicine at the Medical University of South Carolina, where he completed a residency in family practice. He completed sports medicine fellowships at Ohio Physical Therapy and Sports Medicine, Cleveland, and the University of Tennessee–Medical Center, Knoxville. He holds a Master of Science degree in Human Performance and Sports Studies and a certificate of added qualification in sports medicine.

ALVIN GOO, PHARM.D., is clinical instructor in the Department of Family Medicine at the University of Washington in Seattle, and clinical pharmacist at Harborview Medical Center, also in Seattle. Dr. Goo received a doctorate of pharmacy degree and completed a general practice pharmacy residency at the University of Washington and Harborview Medical Center. He also completed a pharmacy residency in family medicine at the Medical University of South Carolina.

Address correspondence to Robert G. Hosey, M.D., Department of Family Medicine, University of Kentucky, K308 Kentucky Clinic, 740 S. Limestone, Lexington, KY 40536. (e-mail: rhosey@email.uky.edu) Reprints are not available from the authors.

be advised to exercise with a partner who is able to administer basic life support and epinephrine (i.e., EpiPen). Patients should be educated to (1) abstain from exercise four to six hours after eating; (2) avoid aspirin and NSAIDs before exercising; (3) refrain from exercise around menses; (4) cease exercise and self-administer subcutaneous epinephrine at the first indication of pruritus or flushing and (5) seek medical assistance if symptoms progress.[11,17-19] Management of an acute episode of anaphylaxis consists of maintaining airways, treating vascular collapse and resolving angioedema with epinephrine, fluids, vasopressor agents and intravenous diphenhydramine or hydroxyzine (Atarax).

Long-term management of episodes of exercise-induced anaphylaxis may require lifestyle modification, abstinence from exercise, avoidance of co-precipitating factors and the prophylactic use of medication.

Antihistamines are partially effective in preventing exercise-induced anaphylaxis.[10,18,20] Hydroxyzine, in a dosage of 25 to 50 mg four times daily, appears to be as effective as the newer antihistamines and is well tolerated.[11,18,20] The newer antihistamines may be preferred because of their more favorable side-effect profiles *(Table 3)*.[21]

The use of cromolyn (Intal), a mast cell stabilizer, has shown variable results in the prophylactic treatment of patients with exercise-induced anaphylaxis.[20,22] This agent prevents mast cell degranulation and release of plasma histamine and other inflammatory mediators, and may prove to be a viable option in this condition. However, it remains unknown if inhaled mast cell stabilizers, administered on a daily basis, maintain sufficient systemic concentration levels necessary to be adequately prophylactic against exercise-induced anaphylaxis.

Future treatment regimens may include the use of leukotriene modifying agents. Montelukast (Singulair), zafirlukast (Accolate) and zileuton (Zyflo) have recently been demonstrated to be as effective in preventing exercise-induced bronchospasms as inhaled salmeterol (Serevent).[23,24] The effectiveness of

TABLE 3
Histamine H_1 Antagonists in the Treatment of Exercise-Induced Urticaria

Agent	T_{max} (hour)	$T_{1/2}$ (hour)	Wheal suppression (hour)	Dosage	Cost*	Comments
Loratadine (Claritin)	1.0	7.8 to 24	12 to 24	10 mg daily	$66	Take on an empty stomach. Available in syrup form. Drug interactions that increase levels of loratadine include imidazoles, cimetidine (Tagamet), erythromycin, azithromycin (Zithromax), clarithromycin (Biaxin)
Fexofenadine (Allegra)	2.6	14.4	N/A	60 mg twice daily	53	Decrease dosage in patients with renal impairment. Active metabolite of terfenadine (Seldane†)

T_{max} = mean time to maximum plasma concentration; $T_{1/2}$ = mean elimination half-life.

**—Estimated cost to the pharmacist for one month's therapy, rounded to the nearest dollar, based on average wholesale prices in Red book. Montvale, N.J.: Medical Economics Data, 2000. Cost to the patient will be higher, depending on prescription filling fee.*
†—*Seldane was removed from the market in 1998.*

Adapted with permission from Simons FE. Recent advances in H_1-receptor antagonist treatment. J Allergy Clin Immunol 1990;86(6 pt 2):995-9.

leukotriene antagonists in the management of exercise-induced anaphylaxis remains to be determined.

When prescribing any medication to competitive athletes, physicians should take care to avoid medications that are banned by athletic governing bodies. Banned substances include medications commonly used in the treatment of symptoms that occur in patients with physical allergies.[17,19]

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