

Cholinergic Urticaria and Exercise-Induced Anaphylaxis

Stefan L. Montgomery, MD

Abstract

In this article, we will present the physical manifestations of two similar conditions. The first is cholinergic urticaria. This is chronic urticaria precipitated by an elevated body temperature. The second is exercise-induced anaphylaxis. Anaphylaxis can be idiopathic, a result of a specific allergenic trigger (food, medication, or insect sting), or exercise induced. We will focus on the third subtype. We describe the causes, symptoms, pathophysiology, testing, treatment, and prognosis of these two conditions.

the most common. CU is the second most common physical urticaria (2).

CU — Causes and Symptoms

CU is induced by exercise, elevation in body temperature, strong emotions, ingestion of hot or spicy foods, or showering in hot water (4). CU is characterized by generalized flushing, an urticarial rash (2- to 4-mm wheal

surrounded by macular erythema), and pruritus (11). Many patients note a tingling, itching, or burning sensation of the skin before the appearance of the hives. As the response progresses, the macules may coalesce to form large areas of erythema that become more difficult to recognize as CU. Lesions can appear anywhere on the body, but it typically begins on the trunk and neck and spreads distally to involve the face and extremities. In rare cases, CU has been reported to progress to include systemic symptoms such as hypotension, angioedema, and bronchospasm (4). CU induced by exercise usually presents about 6 min after the onset of exercise. The symptoms and physical findings increase for approximately 12 to 25 min (12).

Introduction

Two physical manifestations of disease are described and differentiated here. The first is cholinergic urticaria (CU). This is chronic urticaria precipitated by an elevated body temperature. CU is believed to account for approximately 5% of all cases of chronic urticaria and approximately 30% of all cases of physical urticaria (4).

The second is exercise-induced anaphylaxis (EIA). Anaphylaxis can be idiopathic, a result of a specific allergenic trigger (food, medication, or insect sting), or exercise induced (8). We will focus on the third subtype. EIA was described over three decades ago. While rare, several hundred cases have been reported since and the incidence of EIA appears to be increasing possibly due to the popularity of physical fitness in developed countries. The true prevalence of this condition is unknown, and, although only one death has been reported, it is probably not an accurate statistic (3).

CU — Epidemiology

No easily accessible incidence data is available on CU. What is known, however, is that 15% to 20% of the population will experience urticaria of some type during their lifetime. The most common type is allergic urticaria, whether from drugs, insect bites, foods, illness, or chemical contact. The other type is physical urticaria, which is commonly due to scratching, pressure, warmth, or cold. Of these, dermatographism is

CU — Pathophysiology

CU has been associated with elevated levels of histamine in the serum during an attack. Adachi *et al.* reported a group of patients who seemed to have a Type I allergy to their own sweat. Twenty patients underwent autologous sweat testing and demonstrated an immediate skin reaction. A subgroup of patients with symptoms suggestive of CU may have allergic urticaria that is manifest only when they sweat (4). Fukunaga *et al.* (6) attempted to differentiate two subgroups of patients with CU on the basis of diluted sweat reaction. One group had a positive skin reaction to diluted sweat. Another distinct group had a positive reaction to an autologous serum skin testing. They labeled the groups non-follicular (responding to autologous sweat and not to autologous serum) and follicular (responding weakly to autologous sweat and strongly to autologous serum) (6).

CU — Testing

The presentation of the lesions of classic CU in the context of typical inciting triggers is often enough to suggest the

Stefan Montgomery, MD, Family and Sports Medicine, Orangeburg, SC

Address for correspondence: Stefan Montgomery, MD, ATC, 2850 Pelham Ct., Orangeburg, SC 29118; E-mail: stefanmontgomery@hotmail.com.

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diagnosis strongly, but confirmatory testing should be conducted. Confirmation is done by provocation testing using a variety of methods. Classically the methacholine injection should be positive in patients with CU. An intradermal injection of 0.01 mg of methacholine in 0.1-mL saline produces a local area of hives and is diagnostic. Unfortunately only about one-third of patients with CU demonstrate a positive test. Therefore this procedure cannot be used to rule out the diagnosis. Specific provocative challenges may be needed and may use the inciting event suspected in a particular patient. These challenges could include exercise, bathing, or ingestion of certain foods. The best diagnostic test is one that measurably raises the patient's core body temperature. To perform the test, a patient should be submerged partially in a hot water bath at 40°C until the core body temperature has increased by at least 0.7°C. The appearance of generalized urticaria confirms the diagnosis of CU (4).

CU — Treatment

Identification and avoidance of known triggers are the first steps in controlling CU. Bathing in hot water and performing strenuous exercise during hot weather are to be avoided. Medical therapy is predominantly oral antihistamines. Hydroxyzine is the classic agent of choice and generally is believed to be more effective than other antihistamines. A low dose should be initiated and increased gradually until the urticaria is controlled, which typically occurs at doses of 100 to 200 mg divided over 24 h. Oral anticholinergic agents have not been shown to be effective (4). One case report of using a preexercise beta blocker (propranolol at a dosage of 80 mg twice daily) prevented debilitating symptoms of CU. Unfortunately this has not been studied extensively due to the observed adverse effects of beta-blockers in allergic and anaphylactic conditions (1).

CU — Prognosis

The prognosis for CU is generally favorable. Hirschmann reported only 31% of patients with persistence of symptoms greater than 10 years. Sibbald estimated that the average duration of symptoms is 7.5 years, with a range of 3 to 16 years.

EIA — Presentation and Symptoms

Most of the cases of EIA present within 45 min of instituting exercise (3). The main symptoms of EIA include bronchospasm, laryngospasm, and/or vascular collapse. Other symptoms include sudden fatigue, warmth, flushing (7), sudden itching, gastrointestinal upset, hives, throat tightness, vocal changes, and trouble breathing. In contrast to CU, the wheal is 10 to 15 mm in EIA (5). If left unchecked, urticaria, bronchospasm, and airway edema progress to vascular collapse (8).

EIA — Causes and Pathophysiology

Attacks have been linked with jogging, aerobics, dancing, tennis, bicycling, racquetball, swimming, and skiing. Minimal exertion, such as walking or walking briskly, was noted as a trigger in many cases. Jogging was the activity most frequently reported, but its relative frequency may reflect the popularity of this exercise in the U.S. population. Additional reports have implicated other types of exercise, such as running, sprinting, and soccer. Raking leaves, shoveling snow,

or horseback riding were reported less frequently, but no exercise was reliably safe (3). Trigger foods that have been reported include *Crustacea* (shrimp and crab), wheat, grains, nuts, fruits, vegetables, legumes, and seeds. Less commonly implicated foods are meats, eggs, and cow's milk. Interestingly there is a case reported in an individual with food-dependent EIA (FDEIA) provoked by ingestion of tofu before exercise; however ingestion of soy milk had no such effect, suggesting the significance of food processing (7). With FDEIA, the ingestion of the causative agent could be delayed for as much as 6 h. Aspirin and nonsteroidal anti-inflammatory drugs have been the most frequently reported medications in connection with EIA, followed by penicillin and cephalosporins (3). EIA is caused by the sudden release of basophil and mast cell mediators (7).

EIA — Testing

The gold standard for testing is an exercise challenge, especially with FDEIA. A serum tryptase level drawn within 30 min of anaphylaxis supports the diagnosis of EIA since this is a mast cell activation by-product (3).

EIA — Treatment

This condition is treated in a similar fashion to any anaphylactic event. Subcutaneous or intramuscular epinephrine is the first line for symptom control. Epinephrine may need to be given by IV if the athlete is in severe shock. Diphenhydramine also is given via IM or IV (25 to 50 mg). Corticosteroids are used to prevent a delayed (biphasic) reaction. Transfer to an acute care facility for further monitoring is warranted due to the potential for rebound anaphylaxis. It is essential for any athlete diagnosed with EIA to carry an epinephrine autoinjector while exercising (8). Ranitidine 150 mg or cimetidine 20 mg can be used to block the vasodilatation and vascular permeability associated with the H₂ response (3). In addition, the combination of cetirizine and montelukast has been helpful in preventing symptoms on an exercise challenge (10). Some studies have cited that cromolyn pretreatment before exercise has been helpful. In addition, attempts of pretreatment with sodium bicarbonate before exercise to avoid the drop in blood pH secondary to histamine elevation have been made (5). In patients with FDEIA, there appears to be development of a tolerance to exercise over time, with a decreased frequency of attacks. The theory is that, over time, exercise will lead to a lessened inflammatory response of leukocytes and proinflammatory cytokine release as well as a down-regulation of toll-like receptor 4 expression on the surface of immune cells. This diminishes the overall immune response to exercise. In fact, one 10-year study showed either stabilization or regression of episode severity in 93% of patients (9).

Conclusions

CU can be differentiated from EIA using the size of the rash (2- to 4-mm wheal in CU vs 10- to 15-mm wheal in EIA). In addition, the emergency nature of EIA makes it a more worrisome condition. The acute treatment differences (oral antihistamines in CU versus epinephrine and IV or IM antihistamines in EIA) and later use of corticosteroids and oral antihistamines in EIA lead to a much different treatment course. Exercise challenge is still useful in both

conditions. In addition, methacholine injection and passive warming in CU versus serum tryptase elevations in EIA differentiate the testing and clinical picture. It is useful for any sports medicine practitioner to be familiar with these rare but distinct entities.

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