Exercise-induced Anaphylaxis

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Exercise-induced anaphylaxis has been recognized with increasing frequency since its original description in 1980. Recent studies suggest food-induced reactions may occur frequently in this syndrome, which is a mast cell–dependent phenomenon. In this article, the clinical manifestations of exercise-induced anaphylaxis are reviewed, and food-related factors contributing to the disorder are considered.

Introduction

Exercise-induced anaphylaxis (EIA) is a clinical syndrome in which anaphylaxis occurs in conjunction with exercise or other significant physical activity [1]. EIA was described over three decades ago. Several hundred cases have since been reported, 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. The clinical presentation includes cutaneous symptoms such as pruritus, flushing, urticaria, and angioedema; laryngeal edema or bronchospasm; abdominal pain and nausea; and vascular collapse. As in other allergic syndromes, mast cells play a prominent role, and most symptoms of EIA can be explained on the basis of mast cell–derived mediator release. The natural history of EIA is incompletely understood, but most patients recognize the association with such triggers as medication, food, and temperature. Recently, a new syndrome has been described: food-triggered-EIA (FT-EIA), an entity in which wheat has a prominent role as one of the foods most frequently implicated. FT-EIA can be controlled by avoidance of food before exercise. Because of the severity of the symptoms and their potential fatal outcome, EIA and FT-EIA should be recognized by all practicing physicians.

Clinical Presentation and Natural History

EIA is a physical allergy that was initially described in 16 patients who had been exercising for several years before developing anaphylaxis related to athletic activity [2]. Clinical criteria for the diagnosis of EIA were based on the description of symptoms experienced by those 16 patients and is consistent with the presence of exertion-related onset of such cutaneous symptoms as pruritus and a generalized feeling of warmth, urticaria (which can become generalized and is the hallmark of the syndrome), flushing, profuse sweating, and angioedema (Table 1). Subsequently, gastrointestinal symptoms such as colicky abdominal pain, dysphagia, nausea, and diarrhea may develop. Respiratory distress caused by upper airway obstruction with laryngeal edema, or lower respiratory symptoms with shortness of breath, chest tightness, and wheezing, can precede vascular collapse and syncope. A frontal headache lasting several hours is often noted following recovery. Several hundred cases have been reported worldwide. The largest cohort of patients with EIA included 279 individuals identified through a medical questionnaire [3]. Those patients were followed for 10 years [4]. Females predominated, with a f:m ratio of 2:1 and a mean age of 37.5 years, with ages ranging from 13 to 77 years. Attacks were associated with jogging, aerobics, dancing, tennis, bicycling, racquetball, swimming, and skiing (Table 2). Minimal exertion, such as walking or walking briskly, was noted as a precipitant by many of the responders. Jogging was the activity most frequently reported, but its relative frequency may reflect a high practice in the US population. Additional reports have implicated other types of exercise, such as running, sprinting, and soccer [5•]. Raking leaves, shoveling snow, or horseback riding were less frequently reported, but no exercise was reliably safe. Premonitory symptoms of EIA attacks included diffuse warmth, pruritus, erythema, and sweating, followed by typical urticarial lesions and angioedema. The affected areas included face, palms and soles, upper and lower extremities, and abdomen. Attacks induced by jogging typically occurred within 30 minutes of initiating exercise. Vascular collapse occurred in many patients, particularly if exercise was not promptly discontinued. Resolution of symptoms occurred spontaneously in some patients, but others experienced vascular collapse even after exercise cessation. EIA attacks were not consistently elicited by the same type and intensity of exercise in a given patient, suggesting multifactorial triggers. Foods, temperature, drugs, and hormonal changes were important co-factors in the precipitation of attacks (Table 3). Patients commonly presented with attacks for over 10 years before the

symptoms were recognized, with an average of 14.5 attacks per year. The frequency of attacks was diminished in patients avoiding known triggers, or in patients who modified their exercise programs to a lower level.

Food-triggered Exercise-induced Anaphylaxis

The ingestion of food before exercise as a trigger for EIA was first recognized in a patient who ate shellfish before exercise and developed anaphylaxis after exercising [6]. More than half of patients with EIA report the association of food ingestion as many as 4 to 6 hours before exercise, and in many cases a single specific food has been identified [4]. A new syndrome has been named describing the necessary association of ingestion of food prior to exercise for the development of anaphylaxis: food-triggered exercise-induced anaphylaxis (FT-EIA). The frequency of FT-EIA in a population of 76,226 junior high school students in Yokohama, Japan, was recently established through a questionnaire sent to school nurses [5•]. Thirteen cases (0.017%) of FT-EIA were identified, and an additional 24 (0.031%) students with EIA without apparent food trigger were reported. Most patients with FT-EIA were males (11/2), but there was an equal ratio of females versus males (12/12) in patients presenting with EIA that was not associated with a food trigger. In patients with FT-EIA, the interval between food ingestion and exercise ranged from 1 to 3 hours. The duration of exercise prior to the development of symptoms ranged from less than 30 minutes to a maximum of 45 minutes. All patients presented with cutaneous symptoms, including urticaria. Respiratory and abdominal symptoms were present in more than 50% of the patients. Vascular collapse occurred in approximately 25% of patients, but no deaths were reported. The frequency of the episodes varied from 1 to 10, with no seasonal pattern. Foods implicated included crustacea (shrimp and crab), wheat, vegetables, and buckwheat. In one case, the development of anaphylaxis required the ingestion of two foods together prior to exercise (wheat and umeboshi) [7]. All patients were 9 years of age or older except for one patient who was 5 years of age. Ten of the 13 patients with FT-EIA were atopic, with other allergic conditions, including allergic rhinitis, asthma, atopic dermatitis, or food allergies. Exercise challenge done 30 minutes after ingestion of the implicated food reproduced the symptoms in 5/5 patients [5•].

Another study of patients with FT-EIA in Japan revealed that 7 of 11 patients identified wheat as the trigger [8]. Skin test was positive for wheat in all 7 patients, but only one of four had a positive exercise challenge after wheat ingestion, with significant elevation of plasma histamine. In an individual report, a 16-year-old boy with severe EIA attacks associated with vascular collapse and angioedema had positive skin and radioallergosorbent (RAST) tests to wheat. Symptoms were reproduced only when wheat was ingested prior to exercise. The patient tolerated wheat without exercise, and a wheat flour–avoidance diet induced a permanent remission of symptoms [9].

Table 1. Clinical presentation of exercise-induced anaphylaxis

	%
Pruritus	92
Urticaria	86
Angioedema	72
Flushing	70
Shortness of breath	51
Dysphagia	34
Chest tightness	33
Syncope	32
Profuse sweating	32
Headache	28
Gastrointestinal symptoms (nausea, diarrhea, colicky pain)	28
Choking, throat constriction, hoarseness	25

Because wheat has emerged as the single most common food inducing FT-EIA, attempts to characterize the responsible wheat allergens have been undertaken. Water insoluble gliadins have been implicated as prominent factors [10,11]. In a study from Finland, 18 patients with wheat-triggered FT-EIA were tested for immunoglobulin E (IgE) antibodies by immunoblotting of wheat proteins in the presence of the patient's serum. Two proteins were identified by amino acid analysis: a new γ-gliadin of 65 kDa and an α-gliadin of 40 kDa. All 18 patients had IgE antibodies against the new γ-gliadin and 13 to the α-gliadin. In contrast, in 31 patients with wheat allergy, positive skin prick test, and positive RAST test to wheat, and 11 patients with celiac disease, none reacted to the γ- or α-gliadin. Gluten-free diet induced a complete remission of the symptoms in the 18 patients with wheat-associated FT-EIA [12•]. Further characterization of the wheat allergens responsible for FT-EIA has identified ω-5–gliadin (Tri a 19) as a major allergen with in vitro and in vivo cross-reactivity with rye allergens (secalin γ-70 and γ-35) and barley allergens (hordein γ-3) but not oat allergens [13••]. The formation of gliadin neoantigens from wheat during exercise may be implicated, because wheat ingestion alone does not induce symptoms in the absence of exercise [12•]. Other cereals such as rice, corn [14], millet, and buckwheat do not cross-react with wheat [10]. FT-EIA has been reported after the ingestion of several foods, including shellfish and seafood, celery, cabbage, alcohol, tomatoes, cereals, nuts, fruits, and peanuts (Table 4). Inhalant allergens have also been implicated. A 14-year-old boy presented with severe EIA after the ingestion of *Penicillium* mold–contaminated food. Challenge with food alone, *Penicillium* alone, or exercise alone did not elicit symptoms. Double-blind, placebo-controlled challenge with a *Penicillium* extract–contaminated food followed by exercise induced an attack of EIA [15]. In rare cases, dual food

Table 2. Exercise associated with exercise-induced anaphylaxis

Jogging	Racquet ball
Running	Basketball
Aerobics	Soccer
Walking	Swimming
Dancing	Skiing
Tennis	Cross-country
Bicycling	Downhill
Others: stairmaster, horseback riding, volleyball, shoveling snow, raking leaves	

Table 3. Triggers associated with exercise-induced anaphylaxis

Food ingestion 4 to 6 hours before exercise
Warm temperature
Cold temperature
High humidity
Drug ingestion (aspirin and nonsteroidals) 4 to 6 hours before exercise
Menstrual cycle
Seasonal allergies

intake is necessary to induce EIA. One case has been reported of the association between wheat and umeboshi for the induction of EIA, neither of the two allergens alone being sufficient to trigger symptoms upon exercise [7].

Other Triggers for Exercise-induced Anaphylaxis

Medications

Patients have reported the ingestion of a variety of medication within a few hours of exercise as EIA triggers or cofactors [3,4]. Aspirin and nonsteroidal anti-inflammatory agents have been the most frequently reported medications in connection with EIA [16], followed by penicillin and cephalosporins. Aspirin has been reported to facilitate positive exercise challenge in patients with wheat-triggered FT-EIA [17].

Hormones

Women with EIA have associated the occurrence of EIA with different phases of the menstrual cycle [3,4]. Pre-menstrual association of EIA has been reproducible in some patients, such that exercise has had to be limited to the noncritical phase of the cycle.

Atopy

There is a strong association between EIA and FT-EIA and the presence of an atopic condition, such as a history of eczema, asthma, or allergic rhinitis [3,4,5•]. First-degree relatives of patients with EIA have increased incidence of atopic symptoms [4]. Most patients who present with EIA before age 20 years are atopic [4,5•]. In contrast, patients who develop EIA symptoms after the age of 30 years tend not to have atopic personal or family histories [4].

Diagnosis of Exercise-induced Anaphylaxis

Clinical history

Recognition of the exercise-associated nature of the anaphylactic event is key, and may well require a complete and exhaustive clinical history of the attacks [1]. Of additional importance is the association with food and medication [2–4,5•]. The same level of exercise may not trigger the same symptoms unless associated with prior food or medication ingestion. Walking briskly, a frequently reported triggering activity in patients with EIA, may sometimes be overlooked as exercise. Environmental factors, such as temperature and humidity, are important adjuvant factors. Aspirin and cyclo-oxygenase inhibitors should be considered as precipitating factors if consumed within 4 to 6 hours before exercise. As noted, antecedent ingestion of specific foods may be a requirement, although in some patients the postprandial state per se appears to be an adjuvant factor [10,11,12•].

Double-blind placebo-controlled food exercise challenges

Double-blind, placebo-controlled food exercise challenges are the gold standard to prove the association between a specific food and the development of EIA [2,5•]. Patients are asked to eat the specific food implicated in the reaction by history, and to exercise on a treadmill using the standard Bruce protocol, within a few minutes and up to 3 hours after ingestion [5•]. A positive test provides definite diagnosis. A negative test does not rule out the diagnosis because of the potential necessary association of additional cofactors.

In vivo testing

Skin testing, with a panel of foods containing those identified by the patient and other common allergens, should be done in all patients with EIA and FT-EIA [18]. Skin test will identify the potentially implicated foods, which may then be confirmed by challenge. A negative skin test will not rule out the diagnosis, because specific tissue sensitization has been described.

In vitro testing: CAP/RAST-tryptase

For patients with negative skin testing and a history of severe anaphylactic reaction, CAP/RAST (ImmunoCap; Pharmacia, Peepack, NJ/radioallergosorbent) testing to identify potential food triggers may be undertaken [18]. The correlation between skin test and CAP/RAST is very high for most food allergens. A positive CAP/RAST test will identify candidate foods, which will need to be confirmed by challenge. A negative CAP/RAST test will not rule out the diagnosis of FT-EIA.

Table 4. Foods associated with food-triggered exercise-induced anaphylaxis

Grains: wheat, rye, barley, oats
Shellfish and seafood: shrimp, crab, oyster
Nuts: hazelnut
Legumes: peanut
Fruits: apple, strawberries, peaches
Vegetables: celery, cabbage, tomatoes
Milk
Alcohol
Contaminated food with inhalant allergens: *Dermatophagoides farinae, Penicillium*
Other

Tryptase, a product of mast-cell activation, is released in the blood within 30 minutes of a severe anaphylactic reaction associated with vascular collapse [19]. Tryptase levels have been elevated in patients with EIA and FT-EIA, providing evidence of mast-cell involvement [20]. A serum tryptase level should be drawn within 30 minutes (or as soon as feasible) of a suspected episode of EIA/FT-EIA to confirm mast-cell activation and the anaphylactic nature of the event.

Pathophysiology

Mast cells have been implicated in the pathophysiology of FT-EIA and EIA. There is evidence of the release of mast cell products such as tryptase and histamine during anaphylaxis induced by exercise [20]. In addition, there is anatomical evidence of mast-cell degranulation following exercise. Five patients with EIA were challenged by treadmill running until symptoms of urticaria appeared. Plasma histamine levels demonstrated a significant elevation not seen in control patients, and skin biopsies taken after exercise demonstrated ultrastructural evidence of mast-cell degranulation in vivo [21]. Such changes were not observed in biopsies taken before exercise challenge or in control subjects.

Plasma histamine levels have also been found transiently elevated in 5 patients who presented with FT-EIA on challenge with the implicated foods, suggesting the participation of mast cells [5•]. Because histamine is found in basophils, the participation of those cells needs also to be considered.

Differential Diagnosis

Cholinergic urticaria

Cholinergic urticaria is a syndrome characterized by generalized small (2–4 mm) pruritic wheals with erythematous macular flares, developing in response to elevation in body temperature induced actively (*eg*, by exercise) or passively (*eg*, after a hot bath or shower or with fever and emotional stress). Angioedema, bronchospasm, and hypotension with vascular collapse are rarely associated. Lacrimation, salivation, and diarrhea can occur, also infrequently. Age at onset is typically 10 to 30 years, and the condition tends to persist for many years. The lesions of cholinergic urticaria occur within minutes of exercise, start on the upper thorax and neck, and become generalized within minutes. In almost all episodes, symptoms are limited to the skin. A study in which seven patients with cholinergic urticaria were challenged on a treadmill, while wearing occlusive suits, showed an elevation of histamine in the serum of all patients [22]. All patients had typical, small, generalized wheals of cholinergic urticaria. Tryptase has not been found elevated in five patients with reproducible symptoms and increased peak histamine levels [23]. Most patients with EIA develop larger urticarial plaques than the discrete, small, urticarial papules seen in cholinergic urticaria. However, the occasional patient with EIA may present with lesions suggestive of cholinergic urticaria.

Exercise-induced asthma

Patients with asthma typically respond to exercise by increasing airway resistance and by the development of bronchospasm without skin lesions or vascular collapse [25]. Exercise-induced asthma is usually controlled with the use of inhaled beta agonists or cromolyn prior to exercise. In patients with EIA, cutaneous symptoms herald the onset of the episode, and vascular collapse may occur. There is no evidence that pretreatment with inhaled beta agonists or cromolyn is protective in EIA.

Idiopathic anaphylaxis

Urticaria, angioedema, bronchospasm and vascular collapse occur unassociated with exercise during acute attacks of idiopathic anaphylaxis [26]. Anaphylactic manifestations do not differ from those seen in EIA. The true incidence of idiopathic anaphylaxis is unknown. Most of the patients need daily medication with systemic steroids and antihistamines. Because minimal exercise such as walking has been found to be a trigger for EIA, a careful history is needed in patients with idiopathic anaphylaxis to exclude this possibility [5•].

Systemic mastocytosis

Systemic mastocytosis can present with anaphylaxis, but without particular association with exertion. Most patients have evidence of cutaneous involvement (*eg*, urticaria pigmentosa), and history suggests evidence of other manifestations of the condition (*eg*, dyspepsia, abdominal cramps, diarrhea, bloating). Bronchospasm is uncommon in mastocytosis. Patients can present with acute anaphylactic episodes that can be initially categorized as idiopathic [26]. However, history and clinical examination will suggest the diagnosis of mastocytosis, and anatomic evidence of mast-cell hyperplasia and correlative biochemical evidence of the condition (elevated alpha-tryptase) can be sought.

Variant Type of Exercise-induced Anaphylaxis

Exercise induces a small urticarial rash in some patients, with wheals similar to those seen in cholinergic urticaria but with symptoms usually progressing to vascular collapse. Passive warming of the body does not induce lesions; however, cholinergic urticaria does. This variant form of EIA is uncommon and accounts for perhaps 10% of patients with EIA [2]. Other overlap syndromes have been described in which patients develop symptoms in association with increases in body temperature. These syndromes are considered sometimes as severe as cholinergic urticaria [2].

An increase in histamine levels has been found in patients with variant EIA, similar to the elevations found in cholinergic urticaria, peaking with peak clinical symptoms.

Familial Exercise-induced Anaphylaxis

A heritable predisposition has been suggested by the presence of several affected members in certain families [27]. Two reports have identified families with several affected siblings. In one report, seven males from three generations were described with cutaneous and respiratory symptoms induced by exercise. One of the affected members had decreased levels of complement C2 and C5, but further studies were not done [28].

Treatment

Acute

The emergency management of EIA is the same as that for anaphylaxis [28]. Early administration of intramuscular (IM) or subcutaneous epinephrine (0.3–0.5 mL of 1:1000 solution for average adults) is associated with decreased mortality in patients with all forms of anaphylaxis. Antihistamines (diphenhydramine 25–50 mg oral or IM, cetirizine 10 mg oral, or hydroxizine 10–25 mg oral) are helpful in blocking vasodilation, pruritus, and bronchoconstriction mediated by H1 histamine receptors. Ranitidine, 150 mg, or cimetidine, 20 mg, are helpful at blocking the vasodilation and increased vascular permeability mediated by the H2 histamine receptors. Once epinephrine is self-administered, the patient requires immediate attention in a medical facility for intravenous volume repletion, oxygen therapy, and repeated epinephrine as necessary. Careful treatment of compromised airway will include inhaled bronchodilators, endotracheal intubation, or tracheostomy for severe angioedema. Severe bronchospasm will require continued inhaled bronchodilator therapy. Late-phase reactions in EIA have not been documented, but observation is required for at least 6 hours after a severe attack. Corticosteroids are not part of the acute treatment of EIA, but a brief course of systemic corticosteroids may be prudent in all cases, and should be strongly considered following a severe episode. The use of beta adrenergic blocking agents can adversely affect the course of anaphylaxis by inducing refractory symptoms despite the administration of epinephrine [29]. Patients on beta blockers who present with anaphylaxis that is unresponsive to standard therapy may benefit from administration of glucagon. Patients on angiotensin-converting enzyme inhibitors should be carefully monitored because lack of angiotensin II generation and increased bradykinins can severely affect plasma volume repletion during anaphylaxis. Avoidance of beta blockers and ACE inhibitors should be considered in the patient with a history of EIA/FT-EIA.

Prevention and Pregnancy

Successful strategies for preventing attacks in 256 patients surveyed for 10 years included the avoidance of exercise in extremely humid, hot, or cold weather and during the allergy season and the avoidance of food and medication identified as triggers [4]. Additional measures include the avoidance of exercise on the day of allergen immunotherapy injections for inhalant and venom allergens because changes in blood flow consequent to exercise can enhance the absorption and tissue distribution of the allergens. The prophylactic use of antihistamines before exercise has not been successful at blocking EIA, in particular severe attacks. However, this has not been systematically studied. An objection to the use of pre-exercise antihistamines on a prophylactic basis may be that such agents will block cutaneous symptoms, which warn of the impending EIA attack and, therefore, alert the patient to discontinue exercise. Anticholinergic, beta-adrenergic, and phosphodiesterase inhibitors have not been shown to provide prophylactic benefits. Oral or inhaled disodium cromoglycate, a mast-cell stabilizer, has partially blocked EIA [29]. In one patient, sodium bicarbonate was helpful at preventing wheat-induced FT-EIA.

It is important that the patient can recognize the prodromal manifestations of EIA so that exercise can be discontinued at the earliest warning signs, and the progression to vascular collapse can be prevented. Modification of exercise programs by reducing the intensity or the duration of activity may be required [1]. Identification and avoidance of foods and medications (for 4 to 6 hours before exercise) that have been implicated as cofactors can induce complete remission of FT-EIA and EIA. Ideally, patients affected with EIA need to exercise with a companion who is aware of the condition and can provide emergency treatment. Self-injectable epinephrine should be carried at all times when patients are exercising [28]. A medical identification bracelet indicating the condition is needed to allow emergency personnel to assess the nature of the attack in an unresponsive individual.

Seven patients who had EIA during pregnancy delivered healthy babies without complications [4]. All reduced the exercise regimens during pregnancy and one had worsening of the symptoms during pregnancy. Five had an increase in the severity of the symptoms when resuming exercise after delivery. Only one woman had mild pruritus and urticaria during labor [4].

Mortality

Because the true incidence of EIA is not known, the number of deaths caused by EIA may be underestimated. Approximately 1000 cases of EIA have been reported, with one fatality. Tryptase level is a useful screening test for the presence of pre-mortem anaphylaxis and should be drawn in cases in which EIA (or anaphylaxis of another cause) is suspected as cause of death. Elevations of tryptase are associated with anaphylaxis and have been shown to correlate with the severity of the symptoms [19]. Patients with vascular collapse have elevated tryptase levels, whereas patients with only skin manifestations may lack that elevation.

Conclusions

EIA is a unique physical allergy with increasing recognition and, probably, incidence as the exercising population is increasing. Clinical features are indistinguishable from IgE-mediated anaphylaxis in which the offending allergen is known (*eg*, food, drug, or insect sting). Recognition of the association with exercise is crucial. A wide variety of activities, including brisk walking, can induce the symptoms. Symptoms may not always be reproduced by the same amount and type of exercise in a given patient, suggesting that other associated trigger factors may be required. FT-EIA is a new syndrome recognized with increasing frequency, in which wheat has been the most frequently associated trigger. Avoidance of the known associated triggers such as food, aspirin, or nonsteroidal anti-inflammatory agents, induces the remission of EIA and FT-EIA. Treatment is not different from that for anaphylaxis of any other cause. General recommendations for patients with EIA include avoidance of exercise 4 to 6 hours postprandially and avoidance of aspirin and nonsteroidals before exercise. Discontinuation of exercise at the earliest warning symptom is critical to avoid vascular collapse.

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