

Exercise-Induced Anaphylaxis (EIA)

***Mariana C. Castells,* Richard F. Horan,
and Albert L. Sheffer***

*Division of Rheumatology, Immunology and Allergy,
Department of Medicine, Brigham and Women's Hospital,
Harvard Medical School, Boston, MA 02115*

Introduction

Exercise has become an integral part of the American lifestyle in the last three decades. There has been a marked increase in the number of people engaging in physical fitness programs. In 1970, the first case of exercise-induced anaphylaxis (EIA) was reported (1). In 1980, the first series of patients with EIA was described, and the syndrome characterized (2). Systemic reactions to exercise or physical allergies occur in two clearly distinct forms: cholinergic urticaria and EIA. Symptoms of cholinergic urticaria are usually limited to the skin as presenting punctate wheals with prominent erythematous flare triggered by exercise and increased body temperature (3). In contrast, the patient with EIA may present with symptoms of an acute systemic allergic reaction, including pruritus, flushing, urticaria, angioedema, and in some cases, vascular collapse (4). As in other allergic syndromes, mast cells seem to play a prominent role, and most of the symptoms of EIA can be explained on the basis of release of mast cell mediators, including histamine, leukotrienes (LTC₄), and prostaglandins (PGD₂) (5). The incidence and natural history of EIA are incompletely understood, but the severity of the symptoms makes this condition an entity that all allergists and practicing physicians must recognize. More recently, an important subset of patients with EIA have been found to present food-triggered EIA (6), an entity that can be controlled by avoidance of food before exercise.

*Author to whom all correspondence and reprint requests should be addressed.

Clinical Presentation

The initial report of a study of 16 patients with EIA included 11 males and 5 females, with a median age of 24 yr (2). Those individuals were athletes who had been exercising for several years before EIA symptoms developed and in whom the symptoms had been noted for several years before diagnosis. Clinical criteria for the diagnosis of EIA were established based on these patients' symptoms. These included the presence of exertion-related onset of cutaneous pruritus and warmth, the development of generalized urticaria as the hallmark of the syndrome, and the appearance of additional manifestations, such as vascular collapse, gastrointestinal symptoms, including cramping, nausea, vomiting, and upper respiratory distress. Approximately 1000 cases have been subsequently identified. Initial epidemiological observations were published in 1989 with data from a questionnaire sent to 516 patients with exercise-related symptoms (7). Of respondents, 199 met clinical criteria for the diagnosis of EIA. There were 134 females and 65 males, with a mean age of 24.7 ± 10.8 yr at the onset of symptoms and a mean duration of symptoms of 7.9 ± 7.5 yr (Table 1). The average frequency of attacks was twice per week. The types of exercise associated with precipitation of attacks are noted in Table 2, and included jogging, aerobics, walking, dancing tennis, bicycling, racquetball, swimming, and skiing. Other types of exercise, including running, sprinting, and soccer, have been reported as triggers by other authors. Jogging is the activity most frequently reported, but the relative frequencies may reflect the rate at which a particular type of exercise is played in the general population.

From observations reported in the initial series and in subsequent literature, the clinical syndrome of EIA can be described. Premonitory symptoms include fatigue, diffuse warmth, pruritus, and erythema followed by typical urticarial lesions or angioedema. Affected areas most frequently include face, palms, and soles. A typical attack may start 10 min after exercise initiation, and can lead to vascular collapse if exercise is not promptly discontinued. With exercise discontinuation, the duration tends to span 30 min to 4 h. In some patients, vascular collapse and transient loss of consciousness may occur even after exercise discontinuation. Other symptoms (Table 3), including stridor, choking, gastrointestinal colic, nausea, and vomiting, are often present. A persistent (up to 72 h) and disabling headache is a common sequela of an attack. The attacks are not consistently elicited by the same type and level of exercise in a given patient suggesting a multifactorial nature of the triggers. In the initial demographic study, subjects evaluated other factors that seemed important in the precipitation of the attacks (Table 4).

Table 1
Clinical Characteristics in 199 Patients
with EIA (7)

	Range, yr
Age of onset	4–74
Duration of symptoms since first attack	0.5–41
Male/female ratio	1/2

Table 2
Type of Exercise Involved in 199 Patients
Experiencing EIA (7)

Jogging	69
Aerobics	35
Walking	30
Dancing	24
Tennis	21
Bicycling	19
Racquetball	16
Swimming	15
Crosscountry skiing	5
Downhill skiing	4

Table 3
Clinical Symptoms in 199 Individuals
with EIA (7)

	Percentage, %
Pruritus	92
Urticaria	83
Angioedema	78
Flushing	75
Profuse sweating	43
Syncope	32
Headache	30
Gastrointestinal symptoms	30

Table 4
Cofactors Associated with Exercise in 199 Patients
with EIA (7)

	Percentage, %
Warm temperature	64
Cold temperature	23
High humidity	32
Food ingestion	54
Drug ingestion (aspirin and nonsteroidals)	13
Menstrual cycle	19
Hot shower	5

Associated or Cofactors for EIA

Food-Triggered EIA

The association of food ingestion prior to exercise was recognized in a patient with shellfish ingestion prior to exercise that presented with development of EIA (8). More than half of the individuals described in the epidemiological study reported the association of food ingestion 3–4 h before exercise, and some of them were able to identify specific food trigger (7). Specific foods included shellfish, celery, cabbage, and alcohol. Other reports have identified wheat in the form of bread, pasta, or cereal as a food frequently involved in food-triggered EIA (9). Eleven patients from Japan with EIA were identified, seven of whom described wheat as a trigger. Skin test was positive for wheat in all seven patients, and one of four patients open-challenged had a positive wheat-triggered EIA challenge with significant elevation of serum histamine (10). In a report of a single case of a 16-yr-old boy with severe EIA attacks with vascular collapse and epiglottis involvement (angioedema), wheat ingestion (pasta) preceded exercise. Wheat was identified by skin test and RAST test as a sensitizing allergen, and exercise challenge was done with and without wheat ingestion. Symptoms were induced only when wheat was ingested prior to exercise. The patient tolerated wheat without exercise, and a wheat flour avoidance diet induced permanent remission of symptoms (11). The true incidence of a clearly defined entity in which a specific food seems to be the primary factor involved in the induction of anaphylactic symptoms associated with exercise is still unknown. Some authors have suggested a battery of prick tests for foods in the population with EIA as a screening measure (12). A food diary is strongly recommended. In one study, skin tests for specific

Table 5
Foods Associated with EIA (7,2,10)

Grains: wheat, rye, barley, oats
Shellfish and seafood: shrimp, crab, oyster
Nuts: hazelnut
Legumes: peanut
Fruits: apple
Vegetables: celery, cabbage
Alcohol
Contaminated food with inhalant allergens: <i>D. farinae</i> , <i>Penicillium</i> (mold)

foods in 14 patients with the presumptive diagnosis of food-induced EIA were performed. After specific foods found to be positive on skin testing were eliminated from the diet, 12 patients became asymptomatic (13). Food-dependent EIA was triggered by challenge in 3 of 9 patients. Two patients had to eliminate all foods 4 h prior to exercise to become asymptomatic (12). Double-blind, placebo-controlled food exercise (DBPCFE) challenges have also been conducted to prove the association with EIA and help understand the physiopathology of the reaction. In one report of a 14-yr-old boy with severe EIA, penicillium-contaminated food was ingested prior to exercise. Food alone, penicillium alone, or exercise alone did not elicit symptoms. Challenge with a penicillium extract followed by exercise induced an attack of EIA (14). Table 5 lists foods commonly associated with food-dependent EIA. Apple (15), hazelnut (16), and peanut (10) have been shown to be associated with EIA. Patients sensitive to wheat and other cereals in the same family, such as rye, barley, and oats, but not rice, corn, millet, and buckwheat have been shown to have IgE against an ethanol fraction of those cereals. The fraction has been identified as gliadin by Western blotting using the patients' serum (17).

Medications

In early studies, at least 13% of the patients reported the ingestion of medication within a few hours of exercise (7). Aspirin and nonsteroidal anti-inflammatory agents have been the most frequently reported medications associated with EIA (18). Other medications, such as penicillin and cephalosporins, have also been reported.

Other Factors

Among females who have been surveyed for menstrual associations with EIA, at least 18% could identify a critical phase in the menstrual cycle with which EIA was associated (7).

Atopy

Almost 50% of the patients with EIA are atopic as defined by a history of eczema, asthma, or allergic symptoms in relation to inhalants or animal dander exposure. This percentage is higher than that of the general population. First-degree relatives of patients with EIA are also atopic in high proportion (7). The majority of the patients who present EIA before the age of 20 are atopic or have first-degree relatives with atopy. In contrast, patients who develop EIA symptoms after the age of 30 do not have a strong personal or family history of atopy (10).

Pathophysiology

Histochemical studies have implicated mast cell mediator release in the events leading to the clinical manifestation of the disease (19). Five patients who had experienced exercise-associated pruritus, urticaria, and collapse on continued exertion were challenged in the hospital setting wearing a plastic occlusive suit to reduce loss of body heat. The exercise consisted of running during 10 min and induced pruritus and erythema. Blood samples for histamine demonstrated a significant elevation in four of five patients (2.1–4.4 ng/mL) not seen in control patients. Other mediators implicated in anaphylaxis, such as PGD₂ or LTC₄, have not been studied. Similar elevations of histamine levels in blood have been consistently found in other studies with exercise challenges in which the patient experienced generalized urticaria and/or pruritus (10). Tryptase, the major mast cell protease, which is stored in high amounts in dermal mast cells (35 pg/cell), has also been found to be elevated in serum postexercise (20). Skin biopsies taken after exercise demonstrated ultrastructural evidence of mast cell degranulation. These changes are similar to those seen *in vitro* in dispersed pulmonary activated mast cells after crosslinking of the high-affinity IgE receptor FcεRI (21), or those seen *in vivo* in dermal mast cells after intradermal injection of ragweed in a sensitized individual. Findings included a loss of granule structure with fusion of perinuclear membranes and apparent discharge of granule contents. None of those changes were observed in the biopsies taken before exercise challenge or in control subjects (19). No histochemical studies have defined the type of mast cell that participates in EIA. Dermal mast cells are over 90% of the TC type according to histochemical studies using monoclonal antibodies (MAbs) against tryptase and polyclonal antibody against chymase TC mast cells, and are characterized at the ultrastructural level by the quasiabsence of scrolls and the presence of lattice/grating crystalline pattern (22). The mast cells described as degranulated in the individuals after EIA can be identified by their ultrastructural pattern as TC mast cells (19).

Differential Diagnosis

Cholinergic urticaria is a syndrome characterized by generalized flushing and erythematous generalized small (2–4 mm) pruritic wheals in response to changes in body temperature that can be induced actively by exercise or that can occur passively after a hot bath, or with fever and emotional stress (23). Angioedema, bronchospasm, and hypotension with vascular collapse are rarely seen. Lacrimation, salivation, and diarrhea occur rarely. Onset of symptoms typically occur from ages 10 to 30, and can persist for years. The lesions of cholinergic urticaria occur within minutes of exercise, start on the upper part of the thorax and neck, and can become generalized within minutes, involving face, back, and extremities. Symptoms are limited to the skin in the majority of cases and resolve without systemic involvement. Symptoms can be reproduced by increasing the body temperature. A study (24) of seven patients with cholinergic urticaria were challenged on a treadmill wearing occlusive suits and showed an elevation of histamine in the serum of all patients. All patients had typical small generalized wheals of cholinergic urticaria, and six had associated dyspnea and wheezing with a significant reduction in FEV1. The increase in histamine was found as early as 6 min, with a peak at 20 min and returning to baseline at 40 min. Chemotactic activity for neutrophils and eosinophils was detected at 6 min and returned to baseline at 20–30 min. No changes in complement levels were found. Several other studies in which patients have been challenged to induce not only skin symptoms, but also systemic involvement have clearly shown the association between histamine increase and cholinergic urticaria, implicating mast cells and/or basophils in its pathogenesis since only those two cells can store histamine in their granules and release it on activation. Tryptase has not been found elevated in five patients with reproducible symptoms and increased peak histamine levels (25). Sampling was reported only up to 50 min, which is insufficient since the kinetics of tryptase release require at least a 2-h period for optimal detection (26). The pathophysiology of cholinergic urticaria is not well defined nor is the cellular basis clearly implicated in the symptoms, although histamine is believed to be the principal mediator. Partial or differential mast cell and/or basophil activation with only histamine release cannot be excluded.

Variant type of EIA: Exercise induces a small urticarial rash in these 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 in contrast to cholinergic urticaria. This type is uncommon and probably accounted for 10% of patients with EIA in the initial series (2). Other overlap

syndromes have been described in which patients may present with symptoms in association with increases in body temperature. These syndromes may represent severe cholinergic urticaria (27).

An increase in histamine levels has been found in patients with variant EIA similar to the elevations found in cholinergic urticaria, peaking along peak clinical symptoms (20).

Familial EIA

A heritable predisposition to EIA has been suggested by the presence of several affected members in certain families. Two reports have identified two families with several affected siblings (28,29). 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.

Exercise-Induced Asthma (30)

Patients with asthma typically respond to exercise by increasing airway resistance and by bronchospasm without skin lesions or vascular collapse. Exercise-induced asthma is usually controlled with the use of inhaled bronchodilators prior to the exercise or sodium cromolyn. Recent studies have indicated that LTC₄ receptor antagonists, in particular montelukast, might be of benefit in blocking exercise-induced asthma.

Idiopathic Anaphylaxis (31)

Urticaria, angioedema, bronchospasm, and vascular collapse can occur without the association of exercise during acute attacks of idiopathic anaphylaxis. This entity is one of the most severe of allergic conditions and results from uncontrolled release of mediators from mast cells and/or basophils without a known trigger. Anaphylactic manifestations do not differ from those seen in EIA. The true incidence of idiopathic anaphylaxis is unknown, and most patients require daily medication with systemic steroids and antihistamines. Since 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, particularly in association with food ingestion.

Systemic Mastocytosis (32)

Systemic mastocytosis is a rare disease characterized by skin manifestations, such as urticaria pigmentosa and hyperplasia of mast

cells in bone marrow, liver, spleen, bones, and lymph nodes. Because of the systemic increase in mast cells of the TC type (containing tryptase and chymase), patients can present with acute anaphylactic episodes that can be initially categorized as idiopathic. Since 90% of the systemic mastocytosis are indolent (type I), patients have a normal life-span, and morbidity is associated with the uncontrolled release of mast cell mediators that can occur spontaneously or be triggered by nonspecific stimuli. Exercise is not a common trigger of acute mediator release in patients with systemic mastocytosis. α -Tryptase reflects mast cell numbers and is elevated in patients with systemic mastocytosis, whereas β -tryptase reflects mast cell activation and is acutely elevated within few hours of systemic anaphylaxis (27).

Treatment

Acute

The emergency management of EIA is identical to that of anaphylaxis of any cause. The single agent that will best treat symptoms is epinephrine, which can be self-administered subcutaneously (33). To be fully effective, epinephrine needs to be administered promptly by the patient or a companion, before seeking medical help and within minutes of a severe attack. Antihistamines are helpful in blunting the severity of the attack, but alone will not reverse systemic symptoms, such as vascular collapse. Once epinephrine has been self-administered, the patient requires immediate attention in a medical facility. The need for iv volume repletion, oxygen therapy, and repeated epinephrine treatments can be evaluated. Careful treatment of compromised airway will include inhaled bronchodilators and/or endotracheal intubation or tracheostomy for severe angioedema. Severe bronchospasm may require continued inhaled bronchodilator therapy and aminophylline. Late-phase reactions in EIA have not clearly been documented, but individuals need to be observed for at least 6 h after a severe attack. Corticosteroids are not part of the treatment of acute attacks of EIA, but severe episodes that require resuscitation and/or intubation will require corticosteroids, such as in any anaphylactic event.

Prevention

The recognition of the exercise-associated nature of the event is critical to avoid recurrent attacks. No one single laboratory test will define EIA by itself. The most important tool is a complete and exhaustive clinical history. A close historical review of the present episode and past events may suggest a pattern consistent with a

reproducible event. Since the same level of exercise may not trigger the same symptoms, associated conditions must be considered. Minimal exercise levels, such as walking briskly, may be sometimes overlooked. Environmental factors, such as ambient temperature and humidity, at the time of the attack should be considered. Of paramount importance is the association with food and medication. The use of aspirin and nonsteroidals may not be considered relevant medication by some athletes, since their use is so common, but they need to be carefully investigated. The ingestion of foods, including wheat, which is emerging as a major allergen in the precipitation of EIA attacks, require special attention.

The prophylactic use of antihistamines before exercise has not been universally successful at blocking attacks of EIA, in particular, severe attacks. Each patient needs to be evaluated individually for the benefits of prophylactic antihistamines. Anticholinergic, β -adrenergic, and phosphodiesterase inhibitors have not provided apparent benefit prophylactically (27). A few cases have been reported in which the use of oral (400 mg to 2.4 g/d) or inhaled cromoglycate has partially blocked EIA (34). In one patient, sodium bicarbonate was helpful in preventing wheat triggered EIA (35).

Recognition of the prodromal manifestations of EIA is important in order to discontinue exercise at the earliest warning signs. Modification of exercise programs by reducing the intensity or the duration may be required. Avoiding outdoor exercise in warm and humid days and deferring heavy exercise 4–6 h postprandially must be considered a general rule for patients with EIA. In patients with clearly recognized medication-induced EIA, aspirin and nonsteroidals need to be avoided at least 4–6 h before exercise and if at all possible at all times. In patients with clearly recognized foods that have been implicated as a precipitant factor, avoidance of those foods 4–6 h before exercise may be the most therapeutic approach. Ideally patients affected with EIA need to exercise with a companion who is aware of the condition and able to provide emergency treatment. Self-injectable epinephrine needs to be carried at all times when patients are exercising, and a medical identification bracelet is the best way to protect patients.

Mortality

About 1000 cases of EIA have been reported, and only one fatality has occurred (26). Since the true incidence of EIA is not known, deaths owing to EIA may be underestimated. Tryptase level drawn at the time of death is a useful screening test for the presence of pre-mortem anaphylaxis and should be drawn in each patient that dies of possible EIA. Elevations of β -tryptase are associated with anaphylaxis

induced by insect stings and have been shown to correlate with the severity of the symptoms. Patients with vascular collapse are found to have elevated tryptase levels, whereas patients with only skin manifestations may lack such elevation (27).

Summary

EIA is a unique physical allergy with increasing incidence as the exercising population increases. Clinical features are indistinguishable from IgE-mediated anaphylaxis in which the offending allergens are known (food or insect stings). Recognition of the association with exercise is crucial. A wide variety of exercises can induce the symptoms, including brisk walking. Symptoms may not be always reproduced by the same amount and type of exercise in a given patient suggesting that associated factors are also needed. Food is an associated factor recognized with increasing frequency, and in the last 5 yr, wheat has been the most frequently associated. Avoidance of the known associated factors, such as food or nonsteroidals, induces a long-lasting remission of EIA. Treatment does not differ from that of anaphylaxis of any other cause. General recommendations for patients with EIA include avoidance of exercise 4–6 h after eating, avoidance of aspirin and nonsteroidals before exercise, and avoidance of all associated conditions known to trigger attacks in each particular patient. Discontinuation of exercise at the earliest warning symptom is critical.

References

1. Matthews, K. P. and Pan, P. M. (1970), *Ann. Intern. Med.* **72**, 241–249.
2. Sheffer, A. L. and Austen, K. F. (1980), *J. Allergy Clin. Immunol.* **66**, 106–111.
3. Hirschmann, J. V., Lawlor, F., English, J. S., Louback, J. B., Winkelmann, R. K., and Greaves, M. W. (1987), *Arch Dermatol.* **123**, 462–467.
4. Sheffer, A. L. and Austen, K. F. (1984), *J. Allergy Clin. Immunol.* **73**, 699.
5. Bochner, B. S. and Lichtenstein, L. M. (1993), *N. Engl. J. Med.* **324**, 1786–1790.
6. Kidd, J. M., Cohen, S. H., Sosman, A., and Fink, J. N. (1983), *J. Allergy Clin. Immunol.* **71**, 311–316.
7. Wade, J. P., Liang, M. H., and Sheffer, A. L. (1989), *Prog. Clin. Biol. Res.* **297**, 175.
8. Maulitz, R. M., Pratt, D. S., and Schocket, A. L. (1979), *J. Allergy Clin. Immunol.* **63**, 433–434.
9. Buchbinder, E. M., Bloch, K. J., Moss, J., et al. (1983), *JAMA* **250**, 2973.
10. Dohi, M., Suko, M., Sugiyama, H., et al. (1991), *J. Allergy Clin. Immunol.* **87**, 34.
11. Armentia, A., Martin-Santos, J. M., Blanco, M., et al. (1990), *Ann. Allergy* **65**, 149.
12. Guinneapolis, M. T., Elort, C., Raffard, M., et al. (1996), *Ann. Allergy Asthma Immunol.* **77**, 491–619.
13. Romano, A., DiFonis, M., et al. (1995), *Allergy* **50**, 817–824.
14. Fiocchi, A., Mirri, G. P., Santini, I., et al. (1997), *J. Allergy Clin. Immunol.* **100**, 424, 425.
15. Anibarro, B., Dominguez, C., Diaz, J. M., Martin, M. F., Garcia-Ara, M. C., Boyano, M. T., et al. (1994), *Allergy* **49**, 481–482.

16. Martin Munoz, F., Lopez Cazana, J. M., Villas, F., Contreras, J. F., Diaz, J. M., and Ojeda, J. A. (1994), *Allergy* **49**, 314–316.
17. Vasjonen, E., Vainio, E., and Kalimo, K. (1997), *Clin. Exp. Allergy* **27**, 162–166.
18. Dohi, M., Suko, M., Sugiyama, H., et al. (1990), *Arerugi* **39**, 1598.
19. Sheffer, A. L., Tong, A. K., Murphy, G. F., Lewis, R. A., McFadden, E. R., Jr., and Austen, K. F. (1985), *J. Allergy Clin. Immunol.* **75**, 479–484.
20. Schwartz, H. J. (1995), *J. Allergy Clin. Immunol.* **95**, 917–919.
21. Holgate, S. T., Benyon, R. C., Lowman, M. A., et al. (1989), *Prog. Clin. Res.* **297**, 103.
22. Craig, S. C. and Schwartz, L. B. (1989), *Immunol. Res.* **8**, 130–148.
23. Moore-Robinson, M. and Warin, R. P. (1968), *Br. J. Dermatol.* **80**, 794–799.
24. Soter, N. A., Wasserman, S. I., Austen, K. F., and McFadden, E. R., Jr. (1980), *N. Engl. J. Med.* **302**, 604–608.
25. Volcheck, G. W., Beck, K. C., Mottram, C. D., and Hunt, L. W. (1996), *Ann. Allergy Asthma Immunol.* **76**, 76.
26. Volcheck, G. W. and Li, J. T. C. (1997), *Mayo Clin. Proc.* **72**, 140–147.
27. Schwartz, L. B. (1994), *J. Clin. Immunol.* **11361**, 25,956–25,957.
28. Grant, J. A., Farnam, J., Lord, R. A., Thueson, D. O., Lett-Brown, M. A., Wallfisch, H., et al. (1985), *Ann. Allergy* **54**, 35–38.
29. Longley, S. and Panush, R. S. (1987), *Ann. Allergy* **58**, 257–259.
30. McFadden, Er, Jr. and Gilbert, I. A. (1996), *New Engl. J. Med.* **330**, 1362.
31. Wiggins, C. A., Dykewicz, M. S., and Patterson, R. (1988), *J. Allergy Clin. Immunol.* **82**, 839–855.
32. Austen, K. F. (1992), *New Engl. J. Med.* **326**, 639–640.
33. Horan, R. F. and Sheffer, A. L. (1992), *Immunol. Allergy Clin. North Am.* **12**, 559.
34. Juji, F. and Suko, M. (1994), *Ann. Allergy* **72**, 452–454.
35. Katsunuma, T., Iikura, Y., Akasawa, A., Iwasaki, A., Hashimoto, K., and Aki-moto, K. (1992), *Ann. Allergy* **68**, 184–188.