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Exercise-Induced Anaphylaxis: A Serious but Preventable Disorder

Christopher W.T. Miller, MD; Bhuvana Guha, MD; Guha Krishnaswamy, MD

Abstract: Described for the first time approximately 30 years ago, exercise-induced anaphylaxis is a rare disorder characterized by development of a severe allergic response occurring after mild-to-strenuous physical activity. This disorder is especially important to recognize with the recent increase in physical activity and health fitness fads. A number of predisposing factors (eg, prior ingestion of particular food groups) linked to exercise-induced anaphylaxis has been outlined over the years. Mechanisms governing the condition are still being unveiled, and it is likely that one mechanism involves mast cell degranulation and inflammatory mediator generation resulting from the biochemical effects of exercise, sometimes in the presence of an ingested allergen such that wheat or shell fish. Clinical manifestations usually occur after around 10 minutes of exercise, and follow a specific sequence, starting with pruritis and widespread urticarial lesions, evolving into a more typical anaphylactic picture with respiratory distress and vascular collapse. Fatality is exceedingly rare, with only one documented case in the literature. There is an overlap of symptoms with other syndromes (such as systemic mastocytosis and cholinergic urticaria), and these should be remembered when establishing a differential. Treatment of exercise-induced anaphylaxis consists of immediate stabilization geared toward the anaphylactic response with epinephrine and antihistamines. The patient needs to be educated on preventive measures and equipped with an epinephrine autoinjector in the event of an emergency. Exercise-induced anaphylaxis remains a potentially serious disorder, and the health care provider should be aware of its clinical features and effective management strategies.

Keywords: anaphylaxis; allergy; exercise; hypotension; urticaria; asthma

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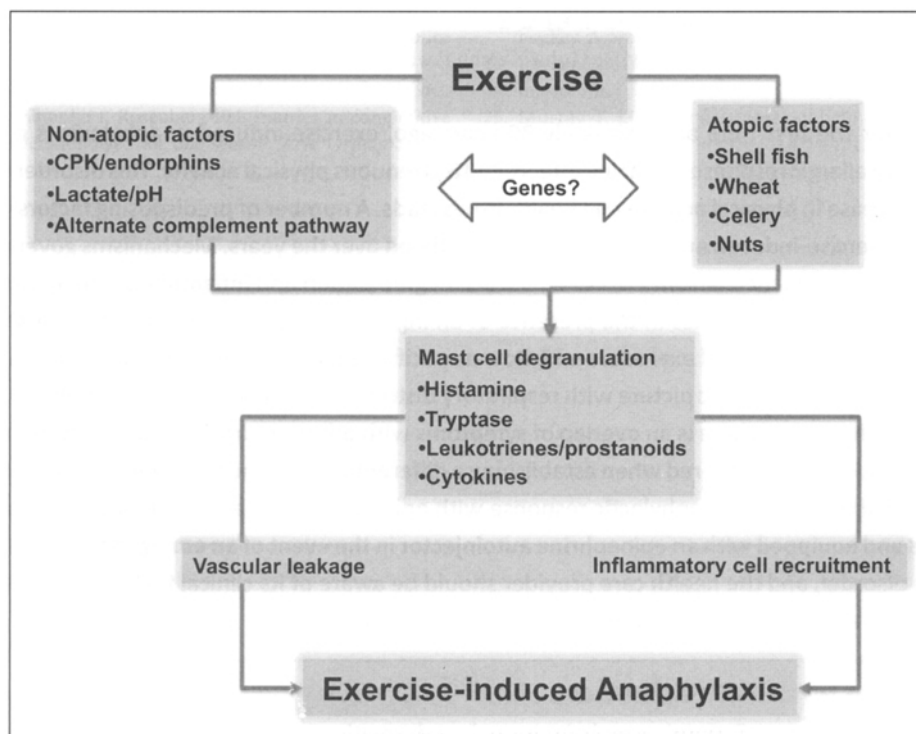
Introduction

Systemic anaphylaxis can be a dramatic and disturbing syndrome that occasionally can be fatal.¹ While a variety of disorders such as drug, food, or venom sensitivity can result in anaphylaxis and have been recognized for many decades,² exercise-induced anaphylaxis was described only relatively recently. Individuals who suffer from this condition may suddenly develop systemic anaphylactic reactions while exercising, sometimes following ingestion of specific foods (food-dependent exercise-induced anaphylaxis [FDEIA]) or drugs (such as nonsteroidal anti-inflammatory drugs [NSAIDs]). In some cases, it may occur during the perimenstrual period of women, thereby falling partially within the hierarchy of the catamenial syndromes.³ The exact pathogenesis of exercise-induced anaphylaxis and FDEIA is unclear, but it is likely that circulating neuropeptides, muscle products, or allergens can influence mast cell degranulation, leading to a sequential process culminating in systemic anaphylaxis (Figure 1). The person experiencing exercise-induced anaphylaxis may first develop a prodrome of cutaneous warmth and pruritis, which may be rapidly followed by cardio-respiratory collapse and airway compromise. If exercise is stopped in the prodromal phase, the full evolution of the syndrome may be halted. Avoidance of specific triggers such as NSAIDs or food allergens prior to exertion is another way of averting this catastrophic event. Such individuals need to be educated about the pathophysiology of the syndrome, provided with a medical alert bracelet, and given prescriptions for injectable epinephrine and antihistamines for crisis management. This paper reviews a case of FDEIA and discusses the categories, pathophysiology, evaluation, diagnosis, and management of exercise-induced anaphylaxis and its variants.

Case Report

A 58-year-old white man was referred to the allergy/immunology clinic after being hospitalized on several occasions for loss of consciousness. These episodes would occur after the patient had performed moder-

Figure 1. This figure shows mechanisms leading to the development of exercise-induced anaphylaxis or food-dependent exercise-induced anaphylaxis (FDEIA). Mast cell degranulation can occur by atopic (food allergen absorption, probably modified by exercise) and nonatopic factors (such as CPK, lactate, pH, complement products, endorphins, and hormones generated by exercise) in the presence of an appropriate genetic background. This results in the release of mediators such as histamine, leukotrienes/prostanoids, cytokines, and proteases (such as tryptase). This results in vascular leakage, inflammatory cell recruitment, and the clinical manifestations of anaphylaxis (wheezing, hypotension, urticaria, and angioedema).



ate-to-strenuous exercise a few hours after lunch or dinner. The events would start sometimes with a prodrome of pruritis over the occipital region of his scalp, subsequently evolving rapidly into diaphoresis, flushing, and presyncope with or without subsequent syncope. He was hospitalized on a few occasions and extensive neurological and cardiological evaluations led to no unifying diagnosis. Records from his hospitalizations reported that the patient was diaphoretic, severely hypotensive, and bradycardic on arrival. The clinical picture would resolve after administering fluids and diphenhydramine. Due to the recurrent nature of his syncopal events, he underwent a cardiac work-up with a Holter monitor and cardiac catheterization, both reported as negative. The patient's medical history was significant for type 2 diabetes mellitus, hypercholesterolemia, and multiple food allergies (shell fish, wheat, Cajun peppers). Current medications included pravastatin and cimetidine. He was a former smoker and drank alcohol sporadically. A thorough immunological evaluation demonstrated elevated IgE and positive radioallergosorbent test (RAST) (Pharmacia

Diagnostics, Uppsala, Sweden) to barley (2+), wheat (5+), and gluten (6+). Due to the strict relationship of the syncopal events with exertion and prior food (especially wheat/gluten) intake, a diagnosis of FDEIA was established. The patient was told to avoid wheat and gluten products and start antihistamines. He was also educated on the use of the Epi-pen® (Dey, L.P., Napa, CA) autoinjector in the event of a severe allergic reaction. After these measures were implemented, the patient has not had an episode of anaphylaxis for the past 6 years, and has managed to stay physically active by lifting weights and walking on the treadmill. A recent reevaluation revealed loss of his IgE-mediated sensitivity to wheat and gluten, suggesting remission is possible with abstinence.

Epidemiology of Exercise-Induced Anaphylaxis

Exercise-induced anaphylaxis is a recently described phenomenon, with the first known case being reported by Maulitz et al in 1979. The authors described a late hypersensitivity reaction to shellfish ingestion brought on by strenuous exercise.⁴

More than 1000 cases have been documented over the past 30 years, with exercise-induced anaphylaxis accounting for about 7% to 9% of all anaphylaxis cases.⁵ There is a paucity of epidemiologic data in the United States, but large studies have been performed in Japan, revealing a prevalence of exercise-induced anaphylaxis of 0.031% among 76 000 high-school students.⁶ The prevalence is greatest among young adults (there is a 2:1 female predominance), with a mean age of 37.5 years.⁷ Patients usually have a significant background of atopic disorders (eg, asthma, rhinitis, eczema), which are observed in approximately 50% of patients and over half of their first-degree relatives.⁸ Among the different types of exercise, jogging seems to be the most common one associated with exercise-induced anaphylaxis.⁸

Several variables have been suggested to contribute toward the development of exercise-induced anaphylaxis (Table 1), including medications (eg, aspirin or other nonsteroidal agents),⁹ airway infections, menstruation, exposure to pollen, fatigue, insect bites, and extremes in temperature. A large subset of patients will not develop anaphylactic symptoms with exercise unless they have ingested certain food groups a few hours before exertion. Food-dependent exercise-induced anaphylaxis has a prevalence of around 0.017%.⁶ Of note, the food groups most commonly implicated differ from those responsible for food allergy alone, and

include wheat products (responsible for around 60% of cases),¹⁰ soy, milk, eggs, peanuts, shellfish, corn, garlic, rice, celery, cheese, alcohol, tomato, peaches, and vegetables.¹¹⁻¹³ Patients who develop FDEIA will usually have a positive skin prick test and/or RAST, along with specific IgE antibodies formed against the food in question, as seen in the patient described in this report.^{14,15} It is important to point out that such patients may not develop a reaction with food ingestion or exercise alone, in the absence of the correct sequence.

There is a distinct subset of exercise-induced anaphylaxis in which food does not appear to play a significant role, but there are other factors with a clear influence on the development of anaphylaxis. Sayama et al described a patient with cold-dependent exercise-induced anaphylaxis, who rode his bicycle in a temperature of 2° to 6° C and would present symptoms of pruritis and wheals within 5 minutes of starting exercise.¹¹ Although this case only occurred in the specific setting of cold weather, several other cases of exercise-induced anaphylaxis seem to have cold as a significant cofactor, as avoidance of exercise in the winter has been reported to diminish incidence of exercise-induced anaphylaxis in a number of patients.¹³

Variants of Exercise-Induced Anaphylaxis

There are 2 additional subtypes of exercise-induced anaphylaxis that have been characterized. Variant-type exercise-induced anaphylaxis accounts for around 10% of all cases and is noted

Table 1. Variables Associated with the Development of Exercise-Induced Anaphylaxis

Syndrome	Diagnosis	Comments/Other
Familial	50% have family h/o atopy HLA-A3B8DR3	AD?
Sporadic		
Food-independent	Exercise alone	Cautious exercise
FDEIA: Food-dependent	Food followed by exercise	Challenge +/- food
Other variants		
DDEIA: NSAID	Use of aspirin or NSAID	History
Sex hormones	Perimenstrual exercise	History
Coincident syndromes		
Mastocytosis	Tryptase/c-kit mutation	Bone marrow
Insect sting	Positive tests for venom-IgE	
Idiopathic anaphylaxis	Prior history of IA	
Urticarial syndromes		
Autoimmune urticaria	Anti-FCεRI antibody+	ASST
Cold urticaria	History; cold immersion	Ice cube test
Cholinergic urticaria	Exercise; < 5 mm wheals	Methacholine ST

Abbreviations: AD, autosomal dominant; FDEIA, food-dependent exercise-induced anaphylaxis; ASST, autologous serum skin test; NSAID, nonsteroidal anti-inflammatory drug; DDEIA, drug-dependent exercise-induced anaphylaxis.

for a less intense skin reaction (with punctate skin lesions of 2–4 mm in diameter); although, systemic manifestations can still be very severe. This resembles cholinergic urticaria and may share pathogenetic mechanisms with the disorder.

Familial exercise-induced anaphylaxis (Table 1) was first described in a report about 2 siblings with exercise-induced anaphylaxis presenting with the HLA A3-B8-DR3 haplotype and a father with a history of atopy.¹⁶ Another report described respiratory and cutaneous findings after exercise in 7 men from 3 generations of a family, potentially suggesting an autosomal dominant inheritance, but this was never fully ascertained.¹⁷ One of the members had decreased C2 and C5, but further evaluation was not feasible to determine if complement deficiency could have been the culprit.

Exercise-induced anaphylaxis can sometimes complicate pre-existing disorders (Table 1) which may not be readily obvious at the onset of a reaction. These include mastocytosis, idiopathic anaphylaxis, venom sting during exercise, and the urticarial syndromes (such as autoimmune, cholinergic, or cold urticaria). Many of these conditions can be readily diagnosed with history and simple tests as listed in Table 1. Exercise-induced anaphylaxis may occur in extremes of temperature (for instance, in athletes with cholinergic urticaria who exercise in the heat, or in athletes with cold-induced urticaria who exercise in the cold). This is important when advising patients with the disorder on avoidance and lifestyle changes.

Pathogenesis

Exercise can have various modulatory effects on the overall immune response, including the release of anti-inflammatory mediators to avoid development of a proinflammatory state.¹⁸ How these changes are related to anaphylaxis is not completely clear and the question needs further study.

The mechanism governing exercise-induced anaphylaxis is still conjectural. Even though exercise can have proinflammatory effects, not all degrees of exertion serve as triggers for exercise-induced anaphylaxis. Mast cell involvement has been implicated in the pathophysiology of exercise-induced anaphylaxis for over 2 decades. Using transmission electron microscopy, Sheffer et al demonstrated the morphologic changes occurring in mast cells after development of exercise-induced anaphylaxis, including loss of granule ultrastructure and elimination of their contents.¹⁹ Mast cells are multifunctional cells that respond to allergen-IgE and other stimuli by degranulating and immediate release of inflammatory media-

tors. The functions of mast cells in the allergic anaphylactic response have been summarized in the literature.^{2,20–23} It is hypothesized that exercise can precipitate mast cell degranulation directly and indirectly (through release of endorphins and gastrin) as demonstrated by a peak in serum histamine levels after 5 to 10 minutes of exertion.^{7,19,24,25} A role for creatinine phosphokinase (CPK), blood lactate, and the alternate pathway of complement activation has been proposed (Figure 1). The decrease in serum pH seen with exercise may be paramount for degranulation to occur, supported by 2 studies showing that pretreatment with sodium bicarbonate precluded development of symptoms upon exercising.^{26,27} In one of these patients, elevation in plasma histamine levels and decrease in pH were also blunted. The influence of serum pH may indeed factor into the lack of anaphylactic manifestations in these patients, as Saeki et al have reported that mast cell degranulation will occur optimally at a pH of 7.0.²⁸ Another manner by which exercise may directly contribute to a reaction has been outlined in a recent study by Barg et al who hypothesized that basophils may be hypersensitive to the transient serum hyperosmolarity induced by physical exertion, triggering an increase in histamine release.²⁹ The presumed mechanisms governing exercise-induced anaphylaxis evolution are shown in Figure 1.

There is a much greater deal of insight into the pathophysiology behind FDEIA. Normal uptake of food proteins can occur through 2 routes: transcellular and paracellular. Transcellular absorption occurs via endocytosis by intestinal epithelia, after which the protein is degraded in lysosomes. The paracellular route is restricted by the presence of tight junctions. In food-allergic patients, there will be an increased expression of low-affinity IgE receptors (FcεRII/CD23) on the surface of gut epithelial cells, facilitating a bidirectional transcytosis of IgE.³⁰ The complex formed between IgE and the food allergen will then be transported to activate gut mast cells by IgE cross-linking. After this occurs, tight junctions undergo disruption and facilitate paracellular transport of incompletely digested food proteins (including allergens), further enhanced by the increase in local blood flow induced by exercise.^{12,31} Increased allergen absorption has been observed with alcohol and aspirin as well.³¹ A second mechanism has been proposed by Cooper et al. They suggested that lymphocytes and macrophages within the gut can be presensitized due to their exposure to food allergens, and redistribution of blood flow induced by exercise would release these cells into the systemic circulation and create the potential for an anaphylactic response after reacting with mast cells and basophils.³² In the specific case

of wheat-induced FDEIA, omega-5 gliadin has already been identified as the precipitating allergen.³³ Upon exercising, transglutaminase will be activated, an enzyme with enterocyte activity which generates high-molecular-weight complexes of omega-5 gliadin. As this gliadin is the only one possessing IgE-binding epitopes, it participates directly in cross-linking and induction of mast cell activation and degranulation.

A role for aspirin in the frequency and severity of FDEIA has already been well documented. Apart from increasing absorption of allergens from the gastrointestinal tract, aspirin may possess a role in directly activating mast cells and serve as a primer to enhance sensitization of immune cells.⁹ Pretreatment with aspirin increases reactivity of skin prick tests, and in some cases an anaphylactic reaction may not occur if the patient did not take aspirin before eating.⁹ An additional mechanism may involve inhibition of prostaglandin synthesis by blocking cyclo-oxygenase, as prostaglandins have been shown to inhibit mast cell release.⁷

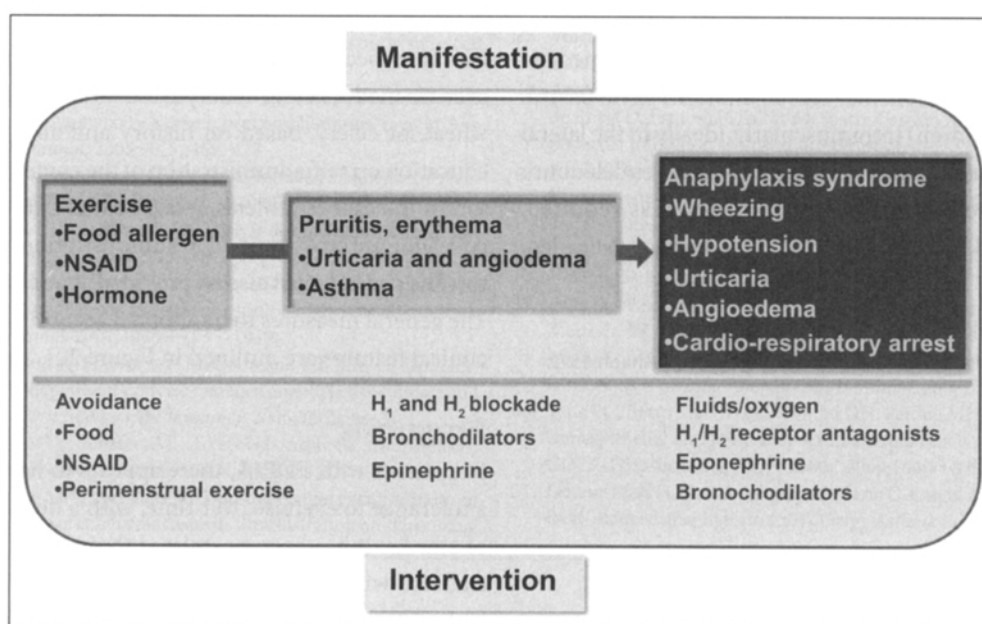
In summary, mast cell degranulation by atopic (food allergen absorption, probably modified by exercise) and nonatopic factors (such as CPK, lactate, pH, complement products, endorphins, and hormones) results in the release

of mediators such as histamine, leukotrienes/prostanoids, cytokines, and proteases (such as tryptase). This results in vascular leakage, inflammatory cell recruitment, and the clinical manifestations of exercise-induced anaphylaxis (Figure 1).

Clinical Manifestations

In essence, the clinical features of exercise-induced anaphylaxis resemble those of a traditional anaphylactic reaction in which IgE-sensitized mast cells are activated by exposure to an offending agent (Figure 2). Perkins described a sequence of 4 clinical phases in exercise-induced anaphylaxis:³⁴ 1) the prodromal phase, in which the patient will start to experience fatigue, generalized warmth, flushing, erythema, and pruritis after approximately 10 minutes of exercise; 2) the early phase, characterized by confluent urticarial lesions (in both exercise-induced anaphylaxis and FDEIA, the wheals average 10–15 mm in diameter) and angioedema involving the palms, soles, and face; 3) the complete phase, with a mucocutaneous (urticaria and angioedema), gastrointestinal (nausea, vomiting, abdominal pain), cardiovascular (vascular collapse with hypotension), pulmonary (bronchospasm, laryngeal edema due to upper- and lower-airway mucosal edema), and neurological (loss of

Figure 2. This figure shows general treatment measures to be adopted according to the clinical manifestations in exercise-induced anaphylaxis. The specific contributory factors should be properly assessed in each patient and a concerted effort made to avoid these triggers. Upon development of allergic manifestations culminating in anaphylaxis, aggressive supportive measures need to be promptly employed to avoid rapid and potentially fatal deterioration. These include fluid resuscitation and administration of epinephrine, histamine receptor antagonists, and bronchodilators.



consciousness, reported in 30%–75% of patients) sequelae;^{12,35} and 4) the late phase, during which the patient can manifest a persistent headache for approximately 24 to 72 hours.

Symptoms typically begin between 5 and 50 minutes after the start of exercise,⁷ lasting approximately 30 minutes to 4 hours after its cessation.³⁴ In the case of FDEIA, more than 50% of patients describe having ingested food 3 to 4 hours prior to exercising,⁷ although variations from 30 minutes to 24 hours have been described.^{4,7,15} It is recommended to patients that events can be prevented by exercising after at least 4 to 6 hours have elapsed since ingestion of causative foods.¹⁵ Death is exceedingly rare, with only 1 reported case to the authors' knowledge.³⁶ As there may be significant overlap with other syndromes, it is possible that the mortality figures are greatly underestimated. The important differential diagnoses to be considered when presented with exercise-induced anaphylaxis-like syndrome are shown in Table 2. These include vasovagal responses, arrhythmia, cardiovascular disease, pulmonary embolism, cholinergic urticaria, idiopathic anaphylaxis, and exercise-induced asthma and/or vocal cord dysfunction. These conditions can be readily differentiated by a proper history, detailed physical examination, and a few simple investigations (such as electrocardiograms, computerized tomography, laryngoscopy and pulmonary function testing).

Management

The management of exercise-induced anaphylaxis and FDEIA is summarized in Table 3. Immediate care includes general measures such as assessment of airway, breathing and circulation, and prompt resuscitation.³⁷ This could include the immediate administration of epinephrine (1:1000 dilution) 0.3 to 0.5 mL (0.01 mL/kg in children) intramuscularly, ideally in the lateral thigh. The patient needs to be placed in the Trendelenburg position and fluids and oxygen administered as required. Military antishock trousers (MAST) could be used if needed.

Table 2. Differential Diagnosis of Exercise-Induced Anaphylaxis

Vasovagal episode
Arrhythmia
Cardiovascular disease
Pulmonary embolism
Cholinergic urticaria
Idiopathic anaphylaxis
Exercise-induced asthma and/or vocal cord dysfunction
Mastocytosis

Table 3. Management of Exercise-Induced Anaphylaxis and FDEIA

Acute Management

- Trendelenburg position
- IV fluids
- Oxygen
- Epinephrine 0.3–0.5 mg IM
- Benadryl® 25 mg IM/IV

Prevention

- Avoid eating (especially wheat, shrimp) at least 6 hours prior to exercise
- Always have epinephrine autoinjector available
- Train coach and colleague in use of autoinjector
- Stop exertion at the onset of premonitory symptoms

Others

- Medic alert bracelet
- Epinephrine autoinjector: training/instruction

Abbreviations: FDEIA, food-dependent exercise-induced anaphylaxis.

Pressors may be required for hypotension. Diphenhydramine 25 to 50 mg can be administered either orally or parenterally (5 mg/kg/24 hours in children). In some situations, the administration of H₂-receptor antagonists (such as cimetidine) can reverse hypotension. Corticosteroids, though not beneficial acutely, are often administered in the hope of preventing delayed or late reactions. If bronchospasm is manifest, a nebulized β_2 -agonist can be administered. Patients on beta-adrenergic antagonists (such as propranolol) may require the administration of glucagon (either as intravenous bolus or as an infusion), as epinephrine may be ineffective.

In the case of exercise-induced anaphylaxis and FDEIA, the more specific measures would include education regarding exercise modification, dietary avoidance (foods such as shrimp, wheat, or celery, based on history and allergy testing), and education on self-administration of the epinephrine autoinjector. In the case of athletes, it is essential that the coach and a colleague are cross-trained in administration of the autoinjector. The patient must also be provided a medical alert bracelet. The general measures to be adopted according to the patient's clinical features are outlined in Figure 2.

Prognosis

In patients with FDEIA, there appears to be development of a tolerance to exercise over time, with a decreased frequency of attacks. It has been postulated that, over a period of time, exercise will lead to a lessened inflammatory response of leukocytes and proinflammatory cytokine release, as well as a

downregulation of toll-like receptor 4 expression on the surface of immune cells, thus diminishing the overall immune response to exercise.³⁸ In fact, one 10-year study showed either stabilization or regression of episode severity in 93% of patients.¹³ Even so, many patients find themselves restricting their activity due to fear of causing a reaction. This requires proper education and reassurance by the physician-consultant.

Conclusion

Exercise-induced anaphylaxis and FDEIA are part of a group of exercise-induced allergic disorders which can have disastrous consequences if not recognized or treated effectively. Due to overlap with other syndromes (eg, mastocytosis and cholinergic urticaria), attention should be given to the chronology of events and potential influencing factors to avoid misdiagnosis. Once the diagnosis is established, avoidance of exercise within a few hours of a meal, avoidance of ingesting specific allergenic foods, and education about self-administration of epinephrine are all uniformly effective in influencing the natural history of these disorders. Due to the potentially fatal nature of the disease, clinicians should be aware of its clinical features and should be knowledgeable of appropriate management of anaphylactic reactions in order to promptly stabilize the patient and decrease morbidity and mortality.

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