EXERCISE-INDUCED ANAPHYLAXIS

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ABSTRACT

Exercise-induced anaphylaxis (EIA) is a unique physical allergy characterised 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. Although EIA is a rare condition, it is becoming increasingly recognised, as more people participate in physical activity and sport. The specific aetiology of EIA is unclear; however results from skin biopsies reveal a lowering of the mast-cell degranulation threshold, which causes the release of histamine and other mediators. Five types of EIA can be distinguished and have been described in the literature. Because of the fact that there are specific precipitating factors in EIA, physicians in collaboration with their patients should develop individual long-term management strategies for controlling EIA. Management of acute episodes of EIA typically includes cessation of exercise, administration of epinephrine and antihistamines, vascular support and airway maintenance.

INTRODUCTION

The USA National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network defines anaphylaxis as a 'severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance'.[1] Anaphylaxis can be idiopathic, triggered by a specific allergen, or exercise-induced.[2] Exercise-induced anaphylaxis (EIA) is a syndrome in which patients experience the symptoms of anaphylaxis, which occur only after increased physical activity.[3] Thus, EIA is a unique medical emergency since it derives from a physical allergy.[4] EIA has become increasingly recognised as more people participate in physical activity.[5] Since the original case description during the 1970s, more than 1000 cases have been described in the literature up until 2001.[6]

The focus of this review is to investigate exercise as a cause of anaphylaxis. The results of investigations at this point indicate that research and related material on EIA is very limited. Furthermore, the vast majority of available literature or research material currently appears to focus on a specific subset of EIA, namely food-dependent EIA. Therefore more research on this potentially fatal and increasingly recognised condition is warranted.

CATEGORIES OF CLINICAL PRESENTATION

EIA has been categorised in a variety of formats in the literature. More recently, the most comprehensive categorisation has distinguished five types of EIA, namely, classic, variant-type, familial, food (specific and non-specific) and medication-dependent EIA. Classic EIA is the most common type. Urticaria or angio-oedema with upper respiratory obstruction and hypotension precipitated by exercise are described as the classic EIA presentation. The variant form of EIA is the least common form, which is similar to classic EIA, except the typical hives are not observed. In their place small punctate skin lesions are described. The variant type of EIA accounts for approximately 10% of cases. Familial EIA has been described involving patients with a family history of EIA. However, further research is required to establish the inheritance pattern.

Two forms of food-dependent EIA have been described, noting that food or exercise alone does not produce symptoms. Specific-food EIA occurs when a particular type of food is known to be the offending allergen. Numerous foods have been implicated, including wheat, raw celery, shellfish, cabbage, peaches, grapes, chicken, hazel nuts and apples. Most events occur within 2-3 hours of ingestion. In non-specific food EIA no particular type of food is identified, but eating any food prior to exercise causes symptoms of EIA. The last type, described as medication-dependent or drug-dependent EIA, occurs in patients who develop the syndrome only after ingesting a specific medication and then participating in physical exercise. Offending medications that have been reported include aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), cold remedies and antibiotics. [3,5-12]

EIA has been reported in children as young as 4 years old, and into adulthood, and there does not appear to be an overwhelming difference between genders or races.[3]

PATHOPHYSIOLOGY

The specific aetiology of EIA is unclear; however results from skin biopsies reveal that skin mast-cell degranulation occurs during symptomatic attacks.[8,13] It is likely that vasoactive mediators released by mast cells are responsible for the symptoms.[6] Other products of mast-cell degranulation (tryptase and leukotrienes) have also been shown to be present at increased levels in symptomatic patients.[4] The mechanism by which exercise lowers the mast-cell degranulation threshold is unknown.[3] However, it has been theorised that increased sympathetic nervous activity stimulates cholinergic fibres innervating eccrine sweat glands to release acetylcholine, leading to mast-cell degranulation and liberation of vasoactive substances.[6] In food-dependent EIA, the process is influenced by immunoglobulin E (IgE) mast-cell sensitisation by a known or unknown food.[3]

PRECIPITATING FACTORS

EIA may be triggered by any physical activity but most commonly jogging, brisk walking, dancing and aerobic sports are the triggers. Even mild activities have been shown to induce an attack.[14] Most of the available literature cites aerobic-type activities as the trigger for EIA attacks; however, anaerobic activities such as sprinting

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have also been noted.[3] Other factors that have been associated with EIA include menstruation and exercising in warm, humid or cold environments.[5,15]

DIAGNOSIS

EIA is unpredictable and difficult to diagnose.[16] Symptoms vary greatly. In a study conducted by Shaddick *et al.*,[14] comprising 279 EIA patients, the most frequently occurring symptoms at the time of an EIA attack were generalised pruritus and urticaria, flushing and angio-oedema. However, symptoms suggesting vascular compromise, including tachycardia and loss of consciousness, headache, gastrointestinal colic and nausea, upper respiratory obstruction and even dysphagia, were also described (Table I).[14]

The diagnosis of EIA can often be made on the basis of the patient history. A history of exercise-induced warmth, erythema and pruritus with or without urticaria is highly suggestive of exercise-induced urticaria or anaphylaxis. Progression of symptoms to dysphagia, dyspnoea, wheezing, dizziness or syncope is also consistent with EIA. Symptoms typically last from 30 minutes to 4 hours after the cessation of exercise. Frequency of attacks may vary considerably, from a single episode to several episodes annually.[6] It appears that in the majority of individuals the frequency of EIA attacks tends to decrease or remain the same over time.[14]

Table I. Frequency of EIA symptoms in 279 subjects

Symptom	%
Pruritus	92
Urticaria	86
Angio-oedema	72
Flushing	70
Shortness of breath	51
Dysphagia	34
Chest tightness	33
Loss of consciousness	32
Diaphoresis	28
Headache	28
Nausea/diarrhoea/colic	28
Choking/throat constriction/hoarseness	25

Table created from data provided in Shaddick *et al.*[14]

The need for diagnostic certainty must be weighed against the risk of inducing anaphylaxis.[17] If a patient is suspected of having EIA, 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. This should be done under controlled conditions in which resuscitation equipment and skilled personnel are readily available. During the challenge test, mediator measurements such as histamine and tryptase are typically obtained though an intravenously placed catheter, at predetermined time points before, during, and after exercise. At set time points or when the patient is symptomatic, pulmonary function testing is also typically performed. It is important to bear in mind that the reproducibility of symptoms in EIA is variable; a negative test does not rule out the diagnosis. A positive test, however, helps confirm diagnosis. [3,5,6,18]

Other tests that can be performed to obtain valuable information about a patient's suspected EIA include radioallergosorbent testing (RAST), allergy skin testing, food-challenge testing, exercise food-challenge testing, and metacholine-challenge testing.[3,9]

MANAGEMENT

Physical exercise should be discontinued at the first sign of cutaneous erythema, pruritus, urticaria or malaise, to prevent worsening the EIA.[3] The treatment of an acute attack of EIA is the same as that for anaphylaxis of any cause and consists of subcutaneously administered epinephrine, intravenously administered fluids, oxygen, antihistamines and airway maintenance. Corticosteroids such as methylprednisolone or prednisone are used in anaphylaxis primarily to decrease the incidence and severity of a delayed (biphasic) reaction. Corticosteroids may not influence the acute cause of the disease; therefore they have a lower priority than epinephrine and antihistamines.[2] Prevention of future episodes is difficult but remains the mainstay of treatment for patients with EIA. Thus, modification of activities and behaviours are essential, and include the following:

- adaptation of the exercise prescription in respect of intensity and duration of exercise to below threshold that induces symptoms
- avoidance of exercise in extreme climatic conditions
- avoidance of exercise 4-6 hours after eating
- avoidance of specific medications before exercising
- refraining from exercise around the time of menses.[5,6,15,19]

The course of EIA during pregnancy has not been well studied. It is however recommended that postpartum patients with EIA consider resuming exercise gradually.[14]

Partial benefits have been demonstrated by administering antihistamines in an attempt to prevent EIA. Furthermore, the use of cromolyn, a mast-cell stabiliser has shown variable results. Future treatment regimens may include the use of leukotriene-modifying agents; however their effectiveness remains to be determined.[6,15] Because patients with EIA might be competitive athletes, physicians should take care to avoid medications that are banned by sport-governing bodies and the World Anti-Doping Agency (WADA) and make use of the Therapeutic Use Exemption (TUE) guidelines if such pharmacological agents are used.[6] A list of medications requiring TUE and guidelines for application can be found at www.wada-ama.org.

Patient education should also form an important part of treatment. Patients must understand the emergent nature of EIA and should be advised to exercise with an emergency epinephrine pen-syringe available and a partner who is able to administer basic life support and epinephrine.[3,6]

CONCLUSION

Anaphylaxis is the most urgent and potentially the most significant condition evaluated and managed by allergists.[20,21] EIA is a chronic, episodic condition in which patients experience the symptoms of anaphylaxis only after increased physical activity.[2,6] EIA has been recognised with increasing frequency since its original description.[22] The symptoms of EIA may range from mild urticaria with warmth and flushing to life-threatening laryngeal oedema and vascular collapse.[5] Activities requiring more cardiovascular demand appear to be more likely to provoke an attack than less strenuous activities.[14] Because symptoms vary greatly, many persons with EIA are unaware of their condition, and therefore it often goes undiagnosed. For patients with EIA management typically consists of modification of exercise relative to intensity, duration and weather conditions and abstaining from food before exercise. Patients should also be advised to always carry an epinephrine kit and exercise with a partner.[5,6,14,20,23,24,25]

Declaration of conflict of interest

The authors declare no conflict of interest.

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