

# Exercise-Induced Anaphylaxis, Pearls and Pitfalls: Medical Education

## Egzersize Bağlı Anafaksi

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**ABSTRACT** A case of exercise-induced anaphylaxis was briefly defined and the clinical characteristics, pathogenesis, diagnosis and management of the disease were discussed followed by clinical pearls and pitfalls for the practicing allergist. Exercise-induced anaphylaxis is described as a distinct form of physical allergy characterized by a variety of symptoms occurring during physical activity that range from cutaneous signs to systemic manifestations such as hypotension and even death. 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. The specific etiology of the disease is unclear. Recent studies suggest that food-induced reactions may occur frequently in exercise-induced anaphylaxis, which is a mast cell-dependent phenomenon. The diagnosis is principally based on a patient's history. A history of exercise-mediated cutaneous erythema and urticaria with the progression of symptoms to stridor due to laryngeal edema or syncope is highly suggestive of exercise-induced anaphylaxis. There is no specific diagnostic test and triggers are numerous. Systemic cholinergic urticaria should be ruled out to confirm the diagnosis. Serum tryptase, serotonin, plasma histamine and urinary 5-hydroxyindoleacetic acid (5-HIAA) levels are helpful to rule out flushing syndromes such as pheochromocytoma. Treatment depends on modifying activities, but long-term therapy may require avoiding exercise and precipitators, and prophylactic use of medications. Currently, antihistamines and cromolynes are known to be partially effective in prevention. Future treatment regimens may include use of leukotriene modifiers. The patient should be well educated on the use of epinephrine (adrenaline) auto-injectors or epinephrine ampouls in the event of new reactions.

**Key Words:** Anaphylaxis; exercise; food hypersensitivity

**ÖZET** Egzersize bağlı anafaksisi olan bir olgu kısaca sunuldu. Bu hastalığın klinik karakteristikleri, patogenezi, teşhis ve tedavisi, özellikle allerjistler açısından önemli ipuçları ve kaçınılması gereken hususlar belirtildi. Egzersize bağlı anafaksi fizik aktivite esnasında veya sonrasında ortaya çıkan hipotansiyon ve ölüm gibi sistemik bulgulardan sadece cilt bulgularına kadar çeşitli belirtiler ile seyredabilen, fiziksel allerjinin ayrı bir formu olarak tanımlanabilir. Hastaların semptomlarının her zaman aynı tip ve şiddette egzersiz ile ortaya çıkarılmaması bazı diğer ilişkili faktörlerin rolünü düşündürmektedir. Bu hastalığın spesifik etiyojisi belli değildir. Son yapılan çalışmalar egzersize bağlı anaflekside sık görülen gıdaya bağlı reaksiyonların mast hücreleri aracılığı ile ortaya çıktığını ortaya koymuştur. Teşhis esas olarak anamneze (hastanın hikayesine) dayanır. Hikayede egzersiz ile başlayan deride eritem veya ürtiker yanında laringeal ödeme bağlı stridor ve hipotansiyonu da içerebilen başka sistemik bulguların ortaya çıkması egzersize bağlı anafaksiyi düşündürmelidir. Spesifik bir diyagnostik test olmamakla birlikte serum triptaz düzeyi anafaksi tanısında yardımcı olabilir. Tetikleyici faktörler arasında bazı besinler ve ilaçlar da yer alabileceğinden şüpheli olgularda spesifik IgE incelemeleri ve/veya prick deri testleri kullanılabilir. Ayırıcı tanıda sistemik kolinerjik ürtiker ve feokromositoma gibi flushing sendromları ekarte edilmelidir. Bu açıdan, serum serotonin ve idrar 5-HIAA "5-hydroxyindoleacetic acid (5-HIAA)" düzeyleri yardımcı olabilir. Tedavi aktivitenin modifiye edilmesine bağlı olmakla beraber, uzun süreli tedavi egzersiz ve presipitan faktörlerden kaçınmak yanında profilaktik ilaç kullanımını gerektirebilir. Son zamanlarda, antihistaminlerin ve kromonların profilaksi açısından kısmen etkili oldukları görülmüştür. Hastalar yeni reaksiyonlar meydana geldiği takdirde epinefrin (adrenalin) otonejektörü veya temin edilemiyorsa adrenalin ampul kullanmak üzere eğitilmelidirler.

**Anahtar Kelimeler:** Anafaksi; egzersiz; gıda allerjisi

## QUESTION

A 19-year-old male was referred to our hospital since he had experienced five different anaphylactic episodes within the last several months during physical activities. He has been followed by a private allergist for the last 2 years with a diagnosis of recurrent hives and idiopathic anaphylaxis and was taking cetirizine 10 mg and Doxepin 50 mg. He reported that he had had a syncope during a basketball game 15 months ago for the first time and in the previous year, he had a couple of similar episodes. The attack frequency had started to increase a few months ago. Although ranitidine was added to the treatment, attacks did not decrease and he was referred to our department. Episodes were mostly associated with basketball play or physical activity. He experienced large hives progressing to confluence and angioedema on his eyes at the onset of an episode and thereafter, breathing difficulty, hypotension, and eventually loss of consciousness accompanied. Although these episodes were occasionally preceded by meals several hours before activity, no clear relationship was identified for a specific food. He did not have a history of any symptoms during a shower or a bath. His past medical and family history was noncontributory.

The examination revealed a well-developed/nourished male who was plotted at the 50th percentile for weight and height with normal pulmonary, cardiac and neurological systems. Laboratory evaluations showed normal complete blood count (CBC), erythrocyte sedimentation rate (ESR), blood chemistry, thyroid profile and C1 esterase inhibitor levels. Anti-thyroglobulin and anti-nuclear antibody (ANA) autoantibodies were negative. Skin prick tests and serum specific IgE levels (ImmunoCAP) were negative for foods including wheat and celery and indoor and outdoor inhalant allergens. Heat challenge test and methacholine skin test were also negative. No anaphylactic responses occurred after a provocation test of wheat bread intake. A graded exercise stress test was carried out on a treadmill and confirmed the diagnosis by cutaneous erythema, giant hives with the progression of symptoms to stri-

dor and hypotension. Desloratadine 5 mg once a day was added to the treatment regimen and he was advised to avoid exercise. He has been doing pretty well since then. Which of the following statements are correct?

- A. This is a classical case of exercise-induced anaphylaxis (EIA) with no associated trigger.
- B. Some postprandial EIA attacks are known to occur without being elicited by any foods.
- C. IgE-mediated hypersensitivity to certain foods or aeroallergens mostly causes an episode.
- D. Aspirin or nonsteroidal anti-inflammatory drug (NSAID) intake is also described as a precipitator of attacks.
- E. The patients may have a higher incidence of personal and/or family history of atopy.

## INTRODUCTION

EIA is a distinct form of physical allergy that is increasingly reported recently.<sup>1-4</sup> Although the majority of reports are described in trained athletes, it is not clear whether the magnitude or frequency of exercise are independent risk factors. Jogging was reported by 78% of subjects in a cohort to provoke an episode besides brisk walking and bicycling.<sup>5</sup> Even labor-delivery may trigger an attack.<sup>5</sup> The gender distribution is equal and a family history is common. At least half of the patients are atopic and although some have symptoms only after ingesting specific foods, a definite co-precipitating factor can be identified only infrequently.<sup>5</sup> Moreover, EIA linked to a food contaminant and multiple food intake were also reported.<sup>6</sup> There is no specific diagnostic test, triggers are numerous and possibly non-immunologic anaphylaxis can occur after a postprandial exercise.

## CLINICAL CHARACTERISTICS AND PATHOPHYSIOLOGY

Typical premonitory symptoms may include diffuse warming, itching, erythema and large conventional ( $\geq 2$ -3 mm) urticaria, resulting in usually progression to confluence and often angioedema during exercise. Cutaneous manifestations may be followed by gastrointestinal symptoms, laryngeal

edema, and/or vascular collapse. Symptoms tend to occur variably with exposure to exercise and do not typically occur with passive warming. Besides, they can persist for 30 minutes to hours. Transient loss of consciousness occurs in about a third of patients because of vascular collapse, whereas symptoms of upper respiratory tract obstruction occur in almost two thirds of patients. Although some pregnant patients who continued exercising reported worsening of symptoms, some improved during their second or third pregnancies.<sup>5</sup>

In some patients EIA will only occur after ingestion of a specific food, designated food-dependent exercise-induced anaphylaxis (FDEIA) or medication such as ASA or NSAIDs, for example naphylpropion acid, named drug-dependent EIA.<sup>6-8</sup> Ingestion of those medications before exercise was reported by 13% of affected individuals.<sup>5</sup> Thirty-seven per cent reported that there were one or more food triggers that contributed to an attack.<sup>5</sup> EIA in the postprandial state, without identification of a specific food, occurred in 54% of the respondents in the same survey.<sup>5</sup> While multiple food and dual food intake were also reported to induce attacks wheat, hen's egg, celery, onion, pistachio, sea foods (crustaceans), fruits (such as apple and orange) and alcohol were mostly singled out. Recently, dust mite ingestion-associated EIA has been described.<sup>9</sup> Wheat-dependent EIA is the best known among FDEIAs.<sup>10</sup> In contrast to data from Europe and Japan, wheat products were identified by only 5% of affected individuals in a US cohort.<sup>5</sup> Wheat omega-5 gliadin and high molecular weight glutenin subunit are major allergens in wheat-dependent EIA.<sup>11</sup> Thus, within the EIA syndromes there are five different clinical forms including classic, food-

or drug-dependent or familial and even a variant form, more uncommon and with manifestations similar to cholinergic urticaria. Characteristics of different EIA syndromes are shown in Table 1.

Although the etiology is still uncertain, antigen-IgE antibody-mediated mast cell degranulation may sometimes be present. During attacks or provocations, mast cell degranulation and increase in serum histamine suggesting "mast cell sensitization" were shown.<sup>12</sup> Exercise and aspirin intake may enhance histamine release from mast cells. However, eosinophile-derived proteins and the complement system are also blamed in FDEIA.<sup>13</sup> In addition to specific IgE/IgA antibodies, decreased IL-10 expression is held responsible in the development of gliadin-specific T cell responses in the pathogenesis of wheat-dependent EIA.<sup>11</sup> Moreover, changes in stomach pH and enzymatic function as well as gastrointestinal permeability induced by the autonomic nervous system abnormalities are suggested as etiologic factors. These changes may yield new epitope formation and increased allergen absorption.<sup>14</sup>

## DIAGNOSIS

A detailed history of symptoms associated with the first episode, as well as previous attacks, should be obtained.<sup>1-5</sup> The history should include details concerning activities and any foods that might precipitate an episode.<sup>1-5</sup> Particular attention should be given to the antecedent use of aspirin or NSAIDs, as well as any seasonality of the attacks.

Although the suspected foods generally produce positive skin test reactions, their role must be confirmed by open-challenge. Simultaneous detection of specific IgE to epitope sequences of both

**TABLE 1:** Characteristics of exercise-induced syndromes.

Type	Precipitator	Wheal Size	Systemic Collapse	Pulmonary Symptoms	Reproduced Symptoms	Altered Symptom threshold by exercise
Cholinergic Urticaria	Heat, stress, exercise	Punctate	Rare	Bronchospasm	+	+
C EIA	Exercise only	Large	Yes	Laryngeal edema	±	-
V EIA	Exercise only	Punctate	Yes	Laryngeal edema	±	-
FD EIA	Food+Exercise	Large	Yes	Laryngeal edema	±	-
DD EIA	Drug+Exercise	Large	Yes	Laryngeal edema	±	-
Familial EIA	Exercise only	Large	Yes	Laryngeal edema	±	-

Abbreviations: EIA= Exercise-induced anaphylaxis; C EIA= Classic EIA; V EIA= Variant EIA; FD EIA= Food dependent EIA; DD EIA= Drug dependent EIA.

omega-5 gliadin and high molecular weight glutenin was suggested to achieve higher sensitivity and specificity compared with the in vitro serum food-specific IgE assays currently used for diagnosis of wheat-dependent EIA.<sup>11</sup>

An asymptomatic food allergy manifested through physical effort should be considered although in many occasions it is not possible to find a responsible allergen. EIA with or without the ingestion of a meal or of a single food should be reproduced by an exercise challenge. This challenge reaction can also be reproduced by pretreatment with oral aspirin or NSAIDs.<sup>7,8</sup>

EIA should be distinguished from other exercise-associated medical conditions (Table 2).<sup>15</sup> Arrhythmias or other isolated cardiovascular events related to exercise may first present with vascular collapse but are not associated with urticaria-angioedema or upper respiratory obstruction. A minority of patients with variant EIA may have cutaneous lesions consistent with cholinergic urticaria. However, unlike cholinergic urticaria, simply increasing the core body temperature does not necessarily produce EIA symptoms. Differential diagnosis of EIA was shown in Table 2.

## MANAGEMENT

The management mainly consists of nonpharmacologic, pharmacologic and emergency management.

TABLE 2: Differential diagnosis of EIA.	
<b>Exercise-induced asthma</b>	
Cholinergic urticaria	Exercise-induced cholinergic urticaria
<b>Other physical urticarias</b>	Cold, heat, solar etc.
<b>Increased endogenous histamine</b>	Systemic mastocytosis
<b>Aeroallergen and food-mediated anaphylaxis</b>	Pollens, molds, wheat, fish, peanut
<b>Drug- or chemical-dependent anaphylaxis</b>	Penicillin, latex
<b>Drug-dependent anaphylactoid reactions</b>	Niacin, aspirin, vancomycin
<b>Idiopathic anaphylaxis</b>	Psychogenic
	Panic attacks, somatoform anaphylaxis

In addition to intensive search for any triggering factor, nonpharmacologic treatment is preventive and includes modification and avoidance of food at least 8 hours before exercise. Those patients for whom a specific food trigger is identified should avoid that food for at least 12 hours. Also, avoidance of exercise in humid conditions and during periods with high levels of seasonal aeroallergens and ambient temperature extremes was preventive in some patients.<sup>5</sup> Early recognition of the prodromal manifestations of EIA is extremely important and affected individuals should discontinue exercise at the earliest symptom e.g. cutaneous warmth. Such individuals should be accompanied during exercise by a companion aware of their condition and capable of providing emergency assistance. The patients should carry epinephrine and emergency warning information and be well educated on the use of intramuscular epinephrine ampoules and epinephrine auto-injectors. Information on EIA should be provided especially for athletes and schoolteachers.

Pharmacologic management is not always useful in preventing EIA. Prophylaxis with H1-H2 antihistamines, mast cell stabilizers (cromones and ketotifen) and others (bicarbonate) can be used but  $\beta$ -agonists and xanthines offer little clinical benefit.<sup>10,16,17</sup> Emergency management of EIA is identical to that of anaphylaxis of other causes and early administration of epinephrine is essential.

## ANSWERS TO THE QUESTIONS

- A. Correct.
- B. Correct.
- C. False.
- D. Correct.
- E. Correct.

## PEARLS

- A detailed history of symptoms and triggering factors such as foods and/or medications associated with the attacks is essential for diagnosis.
- Wheezing and bronchospasm more often go along with cholinergic urticaria, whereas laryngeal edema with stridor is seen with EIA.

■ While patients with exercise-induced bronchospasm only have symptoms related to lower respiratory tract, EIA patients have wheezing with other symptoms of anaphylaxis.

■ Cholinergic urticaria elicited during exercise is associated with an increased core body temperature and punctuate wheals but it does not cause vascular collapse.

■ Ingestion of medications e.g. aspirin before exercise was reported by 13% of affected individuals.<sup>5</sup>

■ EIA without identification of a specific food may occur up to 54% of the patients.<sup>5</sup>

■ Serum serotonin and urinary 5-HIAA levels are helpful to rule out flushing syndromes e.g. pheochromocytoma.

## PITFALLS

■ There is no specific diagnostic test and triggers are numerous.

■ Since symptoms may vary greatly many persons are unaware of their condition and similarly it often goes undiagnosed because of being a relatively rare condition.

■ Systemic cholinergic urticaria should be ruled out to confirm the diagnosis.

■ Currently, there are no entirely effective preventive measures or medications.

■ Although long-term management may require exercise abstinence, there is controversy as to whether all patients should similarly be advised not to exercise postprandially.

■ Bearing in mind avoiding exertion is not practical; the patients should always carry an epinephrine auto-injection kit.

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