Curr Treat Options Allergy (2016) 3:181–188
DOI 10.1007/s40521-016-0083-3

Anaphylaxis (M Sánchez Borges, Section Editor)

Diagnostic and Therapeutic Approach in Patients with Exercise-Induced Anaphylaxis

Mario Geller, MD

Address
Division of Medicine, Academy of Medicine of Rio de Janeiro, Geller Allergy and Immunology Clinic, Rua Visconde de Piraja 303 Suite 603, Ipanema, Rio de Janeiro, RJ, 22410-001, Brazil
Email: drmariogeller@gmail.com

Published online: 5 April 2016

This article is part of the Topical Collection on *Anaphylaxis*

Keywords Exercise-induced anaphylaxis · Food-dependent · Food-independent · Drug-dependent · Triggers · Co-triggers

Opinion statement

The prevalence of exercise-induced anaphylaxis is estimated to be about 2.36-5 % of all cases of anaphylaxis. The clinical manifestations of exercise-induced anaphylaxis include flushing, increase warmth, diffuse pruritus, urticaria, angioedema, bronchospasm, gastrointestinal symptoms, hypotension, and laryngeal edema. The main differential diagnosis is with cholinergic urticaria. Exercise-induced anaphylaxis may display food-dependence, with or without specific IgE sensitivity. The most commonly implicated foods are wheat (omega-5 gliadin), shellfish (especially shrimps), celery, corn, cow's milk, mite-contaminated wheat flour, and peanuts. Interestingly, in these patients aerobic exercises alone, as well as the sole ingestion of the allergenic foods without associated exercises, do not cause anaphylaxis. The synergistic effect of both inducing factors is necessary for the occurrence of the anaphylactic manifestations. There may be drug-dependence in exercise-induced anaphylaxis. Implicated drugs and chemicals include NSAIDS, aspirin, antibiotics (cephalosporins), and the so-called anti-catabolic energizer supplements, such as beta-hydroxymethylbutyrate. Avoidance of eating the triggering foods is recommended when possible, and in temperate areas of the planet an additional preventive measure is not to exercise when there is high environmental exposure to pollens (then exercising indoors). It is also advisable to avoid exercising in extreme weather conditions (too hot, cold, or humid environments). Monoclonal anti-IgE (omalizumab) as a mast cell stabilizer with downregulation of the high affinity IgE receptors (FcεRI) can have a potential role preventing these anaphylactic episodes.

Key Points

1. Exercise-induced anaphylaxis may be food-dependent and independent and also drug-dependent.
2. For prevention, it is recommended to avoid exercising both 4-6 h after eating the specific food, as well as after the ingestion of aspirin and NSAIDS in drug affected patients.
3. Patients should stop exercising at the first onset of symptoms to avoid progression to the potentially fatal laryngeal edema and/or cardiocirculatory collapse.
4. Exercise always with a partner and two epinephrine auto-injectors immediately available.
5. Currently, there are no effective prophylactic medications.

Introduction

Exercise-induced anaphylaxis around the world is estimated to account for about 3 % of all cases of anaphylaxis. The clinical manifestations of exercise-induced anaphylaxis include flushing, increased warmth, weakness, diffuse pruritus, urticaria, angioedema, bronchospasm, nausea, vomiting, abdominal cramps, diarrhea, hypotension, and laryngeal edema, which is potentially fatal. The main differential diagnosis is with cholinergic urticaria. In exercise-induced anaphylaxis, the urticarial lesions are large, with diameters ranging from 10 to 15 mm, as opposed to the typically small 1 to 3 mm punctate wheals of cholinergic urticaria (generalized heat urticaria). The differential diagnosis of exercise-induced anaphylaxis also includes exercise-induced asthma, exercise-associated gastroesophageal reflux, indolent systemic mastocytosis, monoclonal mast cell activation syndrome, and cardiac conditions such as hypertrophic cardiomyopathy and arrhythmias.

The most commonly implicated exercise modalities are those requiring running (jogging) and all aerobic exercises (brisk walking, bicycling, racquet sports, vigorous dancing, and even gardening).

Cytoplasmic mast cell degranulation with massive release of mediators of anaphylaxis, especially histamine, occur. Skin biopsies show degranulation of dermal mast cells following attacks. Mast cell clonality (twitchy mast cells) with C-kit mutations and consequent mast cell hyperresponsiveness may potentially be present, although more studies are required in order to prove this hypothesis. Family predisposition can occur, but is uncommon.

Exercise-induced anaphylaxis may display food-dependence, with or without specific IgE sensitivity. The most commonly implicated foods are wheat (gluten, with its main epitope being omega-5 gliadin), shellfish (especially shrimps), celery, bananas, corn, cow's milk, mite-contaminated wheat flour, and peanuts. Curiously, in these patients aerobic exercises alone, as well as the sole ingestion of the allergenic foods without associated exercises, do not cause this condition. The synergistic effect of both inducing factors is necessary for the delineation of the anaphylactic manifestations [1•].

There may be drug-dependence in exercise-induced anaphylaxis. The ingestion of classical NSAIDS, aspirin, antibiotics (cephalosporins), and the so-called anti-catabolic energizer supplements such as beta-hydroxymethylbutyrate have been associated with the induction of EIA. Sometimes only marked exercise-induced angioedema with no systemic manifestations occurs. In exercise-induced anaphylaxis there is a higher prevalence of personal and/or family atopic history. Syncope is seen in one third and laryngeal edema in two thirds of the cases of exercise-induced anaphylaxis. It is postprandial and non-specific in about 54 % and with drug-dependence in 13 % of all the reported cases.

Evolving concepts

The natural history of exercise-induced anaphylaxis shows a trend towards stabilizing. This improvement might be associated with adaptation in the practice of exercises, such as avoidance of eating for 4-6 h prior (more important), and also

after physical exertion, avoidance of eating the triggering foods, and in temperate areas of the planet avoidance of physical exercises when there is high environmental exposure to pollens (therefore, exercising indoors). It is also advisable to avoid exercising in extreme weather conditions (too hot, cold, or humid).

Patients perhaps should also not exercise after subcutaneous allergen immunotherapy and after taking cyclooxygenase-1 inhibitors (NSAIDS/aspirin). Monoclonal anti-IgE (omalizumab) as an effective mast cell stabilizer, which induces downregulation of the high affinity IgE receptors (FcεRI), can have a potential role preventing these anaphylactic episodes.

The diagnostic tests consist of programmed running or in standard treadmill exercises for about 30 min. A negative test nevertheless does not rule it out. The same is true for serum tryptase elevation that might not always occur. Therapeutic measures include prophylaxis, the possible use of oral anti-H1 antihistamines, preferably those with less or non-sedating properties, although there are conflicting data, and this approach is not yet recommended in the AAAAI practice parameters. The use of anti-H1 antihistamines might have the potential risk of precluding the recognition of anaphylaxis by masking the early dermatological symptoms and signs. Other preventive measures include the use of anti-leukotriene agents (montelukast) and the immediate availability of two epinephrine auto-injectors.

Anti-H2 antihistamines may also interfere with the normal digestion of food allergens, enhancing their intestinal absorption.

Individuals presenting this kind of physical urticaria should always be advised to be with a companion who is also familiar with the use of epinephrine auto-injectors when performing exercises, to carry a cell phone, to be near emergency medical facilities, and to wear some sort of medic alert identification (bracelet, for instance) informing of the problem. It is also very important immediately to stop exercising at the onset of symptoms to prevent the evolving anaphylaxis [2•, 3].

Scaled and progressive supervised exercises may induce effective physical tolerance (physical desensitization), but definitely more studies are still needed in order to prove this concept. A personalized anaphylaxis emergency medical action plan should always be established for the affected individuals, and the recommended treatment is the usual for the other forms of anaphylaxis.

Clinical presentation and differential diagnosis

There are four forms of exercise-induced anaphylaxis (Table 1). Two are food-dependent, one is food-independent, and the other drug-dependent. In the food-independent presentation, the food ingestion is irrelevant since it is related exclusively to the practice of an aerobic exercise. Its cause is unknown, and it may not be reproducible all the time. In the drug-dependent form it is required that a medicine is taken prior to the exercise, usually 4-6 h ahead, and it is frequently associated with NSAIDS and aspirin. The mechanism is also not yet understood.

Food-dependent exercise-induced anaphylaxis can have or not specific IgE sensitization (documented in vivo or in vitro). The food-dependent exercise-induced anaphylaxis without specific IgE sensitization is basically a postprandial event, and it may occur rarely with a specific food or usually with any food ingested prior to the exercise. In the food-dependent exercise-induced anaphylaxis with specific IgE sensitization the concomitant ingestion of the food to which there is IgE sensitization and the practice of exercise are required. They are synergistic since

Table 1. Different forms of exercise-induced anaphylaxis

- Idiopathic/Primary (food-independent)
- With specific IgE food-dependence
- Without specific IgE food-dependence (postprandial)
- With drug-dependence

aerobic exercise alone without the food intake or its ingestion without exercise does not trigger anaphylaxis.

It has been proposed that increased gastrointestinal permeability, blood flow redistribution, and increased osmolality might contribute to the pathophysiology of this condition. Transglutaminase intestinal action could also play a role. Co-triggers might be too warm or cold environments, high humidity, seasonal pollen exposure in sensitive patients, alcoholic beverages, stress, infection, and menstruation.

This disease is considered primarily a mast cell-mediated disorder associated with a decreased threshold for the release of vasoactive agents present in the cytoplasmic granules. Skin biopsies have documented degranulation of dermal mast cells after the anaphylactic episodes. Histamine release and serum tryptase elevation have been reported [1•]. The widespread use of acid-suppressing medications (proton pump inhibitors) can increase the risk of developing food-dependent exercise-induced anaphylaxis [4].

Wheat-dependent exercise-induced anaphylaxis is becoming increasingly important worldwide, and it is not fully reproducible even in patients with a typical history of gluten allergy and the presence of its main epitope omega-5 gliadin-specific IgE. It has been originally reported that oral challenge tests with high doses of pure gluten-flour bread with or without additional co-trigger factors (aspirin plus alcohol), and even without physical exercise, can overcome the frequent nonresponsiveness to exercise challenges with wheat products. This is a practical difficulty in establishing the correct diagnosis. This study demonstrated for the first time that exercise is not an essential trigger for the onset of symptoms in patients with wheat-dependent exercise-induced anaphylaxis, and perhaps it can now be considered solely a co-trigger [5•]. The first case report of exercise-induced anaphylaxis after consumption of red meat related to specific IgE for galactose-alpha-1,3-galactose (alpha-gal) has been documented [6].

The diagnosis of exercise-induced anaphylaxis can be confirmed with a standard 30-min treadmill test, but it may not always be reproducible. The differential diagnosis includes cholinergic urticaria, cardiac taquiarrythmias, hypertrophic cardiomyopathy, exercise-induced asthma, exercise-induced gastroesophageal reflux, vocal cord dysfunction, indolent systemic mastocytosis, and monoclonal mast cell activation syndrome.

Management and treatment

The management of exercise-induced anaphylaxis must be individualized with a detailed medical history. It will depend on the severity of the symptomatology presented, the associated triggers and co-triggers, and on the desire to continue

exercising. A partner during exercises must be always present, and he or she must also know how to use the epinephrine auto-injectors. It is advisable to have always two epinephrine auto-injectors at hand.

The affected individual should exercise close to medical facilities for a potential efficacious anaphylaxis treatment and should also carry a cell phone. The use of a medic alert such as a bracelet should be encouraged so that in case the patient faints, they are not mistaken as an alcoholic, drug addict, or a diabetic with hypoglycemia.

Avoidance of factors and co-factors (foods, drugs, and extreme weather conditions, for example) should be stressed in advance. Patient education is fundamental, e.g. not eating 4-6 h prior to exercising.

After the occurrence of the first dermatologic signs and symptoms (warming, flushing, itching, urticaria, and angioedema) it is imperative to stop exercising immediately. Pretreatment with anti-histamines is still controversial and should not be relied upon. Ketotifen, a mast cell stabilizer, may have potential benefits, but it is not universally accepted. The same is true for oral cromolyn. No effective preventive pharmacologic approach exists.

Omalizumab is a promising therapeutic agent [7] and has been successfully documented in a case of exercise-induced anaphylaxis [8]. Exercise-induced anaphylaxis should be vigorously treated as any other form of anaphylaxis [9, 10]. With more information available to the medical community more cases are going to be diagnosed, treated, and properly managed. There are still many important unanswered questions (Table 2).

Current directions

Exercise-induced anaphylaxis is a form of physical urticaria. Patients with exercise-induced anaphylaxis should be advised not to exercise for at least 4 to 6 h after the ingestion of known triggers such as a specific food or drug. It rarely has been reported to occur 24 h after eating [22].

It is very important to distinguish exercise-induced anaphylaxis from cholinergic urticaria. Cholinergic urticaria is a common form of physical urticaria associated with an increase in core body temperature, usually less than 1 °C. In cholinergic urticaria there are 1-3 mm puntiform hives surrounded by large erythematous flares with a fried egg look, whereas in exercise-induced anaphylaxis large 10-15 mm hives are present. Common triggers for cholinergic urticaria are exercise, hot baths or showers, stress, and the ingestion of spicy foods. A positive methacholine intradermal challenge is elicited in one third of the cholinergic urticaria patients. They may also have a positive mecholil bronchial provocation challenge in the absence of asthma. Immersion in a hot water bathtub is another useful diagnostic test for this physical urticaria. Although exercise challenge in a controlled environment can be positive in both conditions, passive heating is a trigger solely for cholinergic urticaria.

Patients with exercise-induced urticaria and anaphylaxis should always practice aerobic efforts and sports with a partner aware and knowledgeable about this entity. They should carry at least two auto-injector epinephrine devices, and definitely a medical alert such as a bracelet should be worn. Aerobic exercises on very cold, warm, or humid days, and also when there is a high atmospheric pollen count should be avoided.

Concomitant use of aspirin and NSAIDS and alcohol intake should be discouraged. They should stop exercising immediately when the early skin manifestations of anaphylaxis such as flushing, itching, urticaria, and angioedema develop. Exercising close to emergency medical facilities is crucial. Treatment of a severe episode is similar to the management of any form of anaphylaxis and may require the intramuscular administration of epinephrine, intravenous fluids, oxygen, anti-H1 and anti-H2 antihistamines, corticosteroids, endotracheal intubation, and all the usual resuscitative measures. Exercising constantly is not only pleasant, but very healthy and should always be encouraged.

Conclusions

Table 2. Unanswered questions in exercise-induced anaphylaxis

- Why do patients develop exercise-induced anaphylaxis?
- What is the real mast cell dysfunction in this physical urticaria?
- Are there any mutations?
- Why the pathophysiology of food-dependent and independent exercise-induced anaphylaxis differ?
- Why, in some families, is there a genetic predisposition and in others not?
- Why is it rare in children?
- What is the role for atopy predisposition, since patients usually report a personal or family history for atopy?
- There is only one fatality reported [11]. What is the real morbidity and mortality?
- Is this entity underdiagnosed or misdiagnosed?
- How safe is the practice of exercise after immunotherapy?
- How safe is the intake of cyclooxigenase inhibitors (aspirin and NSAIDS) prior to aerobic exercises?
- Why is it not always reproducible even in the same conditions?
- Why does serum tryptase elevation not always occur?
- Why do about half of the patients become less symptomatic or asymptomatic in a 10-year period [12]?
- Why can climatic extremes (too cold, warm, or humid) be co-triggers [13]?
- How can the pollen season in pollen-allergic patients become a co-factor?
- Why can menstruation and alcoholic intake play a role as co-triggers?
- Why might wheat-dependent exercise-induced anaphylaxis not require exercise as a trigger if there is a high gluten ingestion with or without aspirin and alcohol intake (co-triggers)?
- How effective are disodium cromoglycate and ketotifen (mast cell stabilizers) as pretreatment preventive strategies [14, 15]?
- What are the risks of anti-H1 antihistamine pretreatment masking the prodromal dermatological signs and symptoms of this physical urticaria anaphylaxis [16, 17]?
- Why does anaphylaxis not occur with the sole food ingestion without a concomitant aerobic exercise in food-dependent exercise-induced anaphylaxis with specific IgE sensitization [18, 19]?
- Could cholinergic urticaria with exercise-induced anaphylaxis be considered a variant of the classical exercise-induced anaphylaxis [20]?
- Is there any future role for biological intervention to prevent anaphylaxis [21]?

Exercise-induced anaphylaxis is a modality of physical urticaria. Patients and the medical community should become aware of this potentially fatal condition. Mast cell cytoplasmic degranulation has an important role in its pathogenesis. It can be food-independent and food-dependent with or without IgE sensitization. There is also a variant form called drug-dependent exercise-induced anaphylaxis. The majority of patients require both the ingestion of the food for which there is IgE sensitivity and the subsequent practice, within 4-6 h, of an aerobic exercise. The most commonly implicated foods are wheat (gluten), shellfish, peanuts, milk, bananas, corn, celery, and mite-contaminated flours. Cyclooxigenase-1 inhibitors (aspirin and NSAIDS) are the most frequent drug culprits. When dermatologic symptoms and signs occur exercise should be promptly ceased to prevent the dangerous progression towards the full blown anaphylaxis.

Patients should have an exercise companion and carry at least two auto-injector epinephrine devices. They should also abstain from eating 4 to 6 h prior to exercising. They should always exercise near medical facilities, carry a cell phone, and avoid exercising when the weather is too cold, warm, and humid and when the atmospheric pollen count is very high for the sensitive atopic individuals. They should wear a medic alert such as a bracelet. Changing exercise habits usually benefit these patients.

Pre-exercise use of anti-H1 antihistamines and anti-leukotrienes (montelukast) has not been shown to be helpful for prevention. More research into the role of mast cell stability and the possible use of cromolyn, ketotifen, and omalizumab is definitely needed. There are, therefore, no efficacious prophylactic drugs for EIA. Physical desensitization with progressive and slowly more intense exercises is also a promising avenue of achieving a complete remission.

Compliance with Ethical Standards

Conflict of Interest
Dr. Mario Geller declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1.• Lieberman P, Nicklas RA, Randolph C, Oppenheimer J, Bernstein D, Bernstein J, et al. Anaphylaxis-a practice parameter update 2015. Ann Allergy Asthma Immunol. 2015;115(5):341–84.
Excellent review updating pertinent information of the different modalities, clinical presentations, management and treatment of exercise-induced anaphylaxis and the differential diagnosis with the other forms of anaphylaxis.

2.• Bernstein JA, Lang DM, Khan DA. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133:1270–7.

Complete and comprehensive update of the diagnosis, management and current treatment of both acute and chronic urticaria.

3. Lang DM, Hsieh FH, Bernstein JA. Contemporary approaches to the diagnosis and management of physical urticaria. Ann Allergy Asthma Immunol. 2013;111:235–41.
4. Chen JY, Quirt J, Lee KJ. Proposed new mechanism for food and exercise induced anaphylaxis based on case studies. Allergy, Asthma Clin Immunol. 2013;9:11.
5.• Brockow K, Kneissl D, Valentini L, Zelger O, Grosber M, Kugler C, et al. Using a gluten oral food challenge protocol to improve diagnosis of wheat-dependent exercise-induced anaphylaxis. J Allergy Clin Immunol. 2015;135:977–84.

An important new vision on wheat-dependent exercise-induced anaphylaxis showing that exercise could be considered a co-trigger and not a classical trigger of this condition.

6. Knight ME, Wyatt K, James HC. Exercise-induced anaphylaxis after consumption of red meat in a patient with IgE antibodies specific for galactose-alpha-1,3-galactose. J Allergy Clin Immunol Pract. 2015;3(5):801–2.
7. Stokes JR, Casale TB. The use of anti-IgE therapy beyond allergic asthma. J Allergy Clin Immunol Pract. 2015;3:162–6.
8. Bray SM, Fajt ML, Petrov AA. Successful treatment of exercise-induced anaphylaxis with omalizumab. Ann Allergy Asthma Immunol. 2012;109(4):281–2.
9. Simons FER, Ebisawa M, Sanchez-Borges M, Thong BY, Worm M, Tanno LK, et al. 2015 update of the evidence base: World Allergy Organization anaphylaxis guidelines. World Allergy Organ J. 2015;8:32.
10. Campbell RL, Li JTC, Nicklas RA, Sadosty AT. Emergency department diagnosis and treatment of anaphylaxis; a practice parameter. Ann Allergy Asthma Immunol. 2014;113:599–608.
11. Ausdenmoore R. Fatality in teenager secondary to exercise-induced anaphylaxis. Pediatr Allergy Immunol. 1991;5:21.
12. Shadick NA, Liang MH, Partridge AJ, et al. The natural history of exercise-induced anaphylaxis: survey results from a 10-year follow-up study. J Allergy Clin Immunol. 1999;104:123–7.
13. Sheffer AL, Austen KF. Exercise-induced anaphylaxis. J Allergy Clin Immunol. 1980;66:106–11.
14. Juji F, Suko M. Effectiveness of disodium cromoglycate in food-dependent, exercise-induced anaphylaxis: a case report. Ann Allergy. 1994;72:452–4.
15. Choi JH, Lee HB, Ahn IS, et al. Wheat-dependent, exercise-induced anaphylaxis: a successful case of prevention with ketotifen. Ann Dermatol. 2009;21:203–5.
16. Geller M. The multiple faces of anaphylaxis: exercise-induced anaphylaxis and idiopathic anaphylaxis. Braz J Allergy Immunol. 2013;1(1):8–13.
17. Geller M. Anaphylaxis and physical urticarias. Braz J Allergy Immunol. 2013;1(4):195–201.
18. Geller M. Physical urticarias: mast cell dysfunction. Preventive, diagnostic and therapeutical approach. Einstein. 2007;5(3):273–80.
19. Geller M. Exercise-induced anaphylaxis with food dependence without specific IgE. Braz J Allergy Immunol. 2013;1(4):236.
20. Magerl M, Borzova E, Giménez-Arnau A, et al. The definition and diagnostic testing of physical and cholinergic urticarias-EAACI/GA2LEN/EDF/UNEV consensus panel recommendations. Allergy. 2009;64:1715–21.
21. Wolff PG, Geller M. Recent advances in the use of biologicals in allergic diseases. Braz J Allergy Immunol. 2014;2(4):132–8.
22. Maulitz RM, Pratt DS, Schocket AL. Exercise-induced anphylactic reaction to shellfish. J Allergy Clin Immunol. 1979;63:433–4.