

Clinical Management of Exercise-Induced Anaphylaxis and Cholinergic Urticaria



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Date of Original Release: July 1, 2020. Credit may be obtained for these courses until June 30, 2021.

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List of Design Committee Members: Mario Geller, MD (author); Robert S. Zeiger, MD, PhD (editor)

Learning objectives

1. To classify the 4 different categories of exercise-induced anaphylaxis (EIA) and distinguish them from cholinergic urticaria (ChoIU).
2. To establish both preventive and action plans for patients with exercise-related adverse reactions.
3. To reassure patients that EIA and ChoIU can be prevented and be successfully managed.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Relevant Financial Relationships with Commercial Interests: The author declares that he has no relevant conflicts of interest. R. S. Zeiger declares no relevant conflicts of interest.

Exercising is both pleasant and healthy. In some individuals, it can trigger adverse reactions. Examples of these reactions include exercise-induced anaphylaxis (EIA) and cholinergic urticaria (ChoIU). EIA presents as food-associated and non-food-associated conditions. Strenuous exertion may provoke both EIA and ChoIU, but with exercise the passive warming will induce solely ChoIU and not EIA. The morphologic size of the urticarial wheals can help distinguish between these 2 types of conditions. Small punctate wheals are present in ChoIU and large ones in EIA. Wheat is the most common food associated with food-dependent exercise-induced anaphylaxis and gluten is its most important antigen. Omega-5-gliadin is the major epitope of gluten. The most common medicines associated with drug-dependent exercise-induced anaphylaxis are the nonsteroidal anti-inflammatory drugs including aspirin. © 2020 American

Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2020;8:2209-14)

Key words: Exercise; Anaphylaxis; Inducible urticarias; Cholinergic urticaria; Physical tolerance; Triggers; Cotriggers; Food-dependence; Food-independence; Drug-dependence

Allergists are in the front line of educating, diagnosing, and treating mast cell-related events using precision medicine.¹

Exercises can trigger events such as exercise-induced anaphylaxis (EIA) and cholinergic urticaria (ChoIU). These conditions are relevant concerns because of the widespread promotion of exercising.

EIA prevalence is estimated to be approximately 2.36% to 5% of all the cases of anaphylaxis.² The most commonly implicated exercise modalities are those requiring running (eg, jogging), brisk walking, biking, racquet sports, vigorous dancing, and intense gardening.² Even enthusiastic and vigorous sexual intercours can precipitate EIA.³ The natural history of EIA shows over time a trend toward stabilization.^{2,4} In EIA, there is massive release of mediators of anaphylaxis, especially histamine. There are 4 types of EIA that will be herein discussed: food-independent exercise-induced anaphylaxis (FIEIA), food-dependent exercise-induced anaphylaxis with IgE sensitivity (FDEIA with IgE sensitivity), food-dependent exercise-induced anaphylaxis without IgE sensitivity (FDEIA without IgE sensitivity), and drug-dependent exercise-induced anaphylaxis (DDEIA) (Tables I and II).

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No funding was received for this work.

Conflicts of interest: The author declares that he has no relevant conflicts of interest.
Received for publication September 10, 2019; revised January 3, 2020; accepted for publication January 17, 2020.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2020.01.025>

Abbreviations used

ChoIU- Cholinergic urticaria
CIndU- Chronic inducible urticarias
DDEIA- Drug-dependent exercise-induced anaphylaxis
EIA- Exercise-induced anaphylaxis
FDEIA- Food-dependent exercise-induced anaphylaxis
FIEIA- Food-independent exercise-induced anaphylaxis
NSAID- Nonsteroidal anti-inflammatory drug
WDEIA- Wheat-dependent exercise-induced anaphylaxis

FDEIA is a disorder in which an episode of anaphylaxis develops during exercise within 4 to 6 hours of ingesting a specific food, and usually there is IgE-mediated allergy.⁴ In wheat-dependent exercise-induced anaphylaxis (WDEIA), it was demonstrated that exercising is not essential for the development of symptoms and that if enough gluten is ingested, often with additional cofactors such as alcohol and aspirin, symptoms can be induced at rest. In this particular situation, gluten is the trigger and exercise might be considered only a cotrigger. It is therefore an atypical form of food allergy.⁵

ChoIU is an example of chronic inducible urticarias (CIndU). The prevalence of CIndU is estimated to be 0.5% of the general population, and the incidence of ChoIU is 6% to 13% in adults and 19% in children presenting with CIndU.⁶ Small 1- to 3-mm punctate urticarial wheals are typically present in ChoIU. These small wheals may later converge into larger ones.⁶ Anaphylaxis with ChoIU has been described but has not been documented elsewhere.⁷

Dissociation between history and challenge in patients with CIndU is estimated to be 38%.⁸ ChoIU is common, usually affects young individuals, and may lead to great discomfort and a decrease in their quality of life.⁶

EXERCISE-INDUCED ANAPHYLAXIS

Definition and clinical features

EIA is a disorder in which anaphylaxis occurs exclusively in association with physical exertion of significant intensity.^{9,10} EIA may begin at any stage of the exercise and rarely occurs afterward.¹¹ EIA has a prevalence of approximately 3% of all cases of anaphylaxis.² In Japanese teenagers, EIA is rare.^{12,13} Signs and symptoms of EIA include flushing, increased warmth, malaise, diffuse itching, urticaria, angioedema, gastrointestinal symptoms (nausea, vomiting, abdominal cramps, and diarrhea), hypotension, syncope, laryngeal edema, and rarely asthma. In EIA, wheals are large and may converge.^{2,14} Anaphylaxis quite often is present in EIA.⁹ A fatality in a teenager with FDEIA has been reported. This patient has exercised after eating peanuts to which he was allergic.¹⁵ It is very important to immediately stop exercising at the onset of the dermatological signs of flushing, pruritus, urticaria, and angioedema, because progression to life-threatening laryngeal edema and/or severe hypotension might occur.¹⁶

The natural history of EIA shows that about half of the patients improve within a 10-year follow-up: decrease in 47%, becoming stable in 46%, and remaining inactive in the last year of observation in 41%.¹⁷

There are 4 types of EIA: FIEIA, FDEIA with IgE sensitivity, FDEIA without IgE sensitivity, and DDEIA (Table 1).

In FIEIA, the sole trigger of anaphylaxis is exercise unaffected by food ingestion.

TABLE 1. Exercise-induced anaphylaxis

- Food-independent
- With IgE food-dependence
- Without IgE food-dependence
- With drug-dependence

FDEIA with IgE sensitivity requires both the ingestion of the allergenic food and the aerobic exercise, usually within 4 to 6 hours. They are synergistic because exercise alone without the allergenic food intake or its ingestion without exercise does not trigger anaphylaxis. Both events are therefore required. Many times patients are unaware that they have IgE-mediated food allergy.

In FDEIA without IgE sensitivity to any particular food, the oral food intake in combination with exercise can trigger anaphylaxis. It is basically a postprandial event, and it is also very rare. These patients should exercise only after 4 to 6 hours of eating.²

In DDEIA, often nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, are involved, and again, the drug intake alone or exercise alone does not cause anaphylaxis. The combination of both triggers anaphylaxis. It has also been described with cephalosporins. The underlying causes of all types of EIA are still unknown.^{2,18,19}

Triggers and cotriggers

Wheat is the most commonly reported allergen in FDEIA with IgE sensitivity. Omega-5-gliadin, a major protein component of gluten, is the most important allergen in this disorder.²⁰ In WDEIA, establishing the diagnosis is still difficult because provocation tests are only positive in approximately 60% of patients, and in only 30% of patients tested with commercially available wheat extracts.^{5,21-25} In WDEIA, exercise is not absolutely necessary to induce anaphylaxis, and it may be solely a cotrigger (augmenting factor) instead of a trigger. In these patients, aspirin and alcohol, also as cotriggers, may elicit symptoms if large amounts of gluten are ingested.^{2,5,26} Aspirin and alcohol might then be considered important augmenting cofactors in these individuals with WDEIA. Exercise lowers the threshold and increases the severity of WDEIA, but anaphylaxis in these patients can be elicited at rest without exercise.²⁷ Omega-5-gliadin allergy can be associated with severe WDEIA, and this diagnosis is frequently delayed because physicians are usually unaware of this condition. In suspected cases, serum omega-5-gliadin-specific IgE should be tested. A gluten-free diet or a wheat-free one will prevent these episodes of anaphylaxis. An epinephrine autoinjector must always be prescribed in addition to dietary advice.²⁸

Dust mite ingestion-associated EIA has been described.²⁹ In Southeast Asia and in Latin America, shellfish is the most common food associated with FDEIA.² Other examples of foods implicated in FDEIA with IgE sensitivity have recently been reported: tomato,³⁰ corn,³¹ almond,³² soybean,³³ rye,³⁴ and bee pollen.³⁵ Prick to prick allergy skin testing may be applied when routine allergy skin testing with commercial extracts is negative, as for instance using a prick of a wheat flour paste.⁴ FDEIA with IgE sensitivity to cow's milk can also provoke significant angioedema.³⁶

TABLE II. Description of the concepts of EIA and ChoIU

Characteristics	EIA	ChoIU
Symptoms and signs	Flushing, increase warmth, malaise, diffuse itching, urticaria, angioedema, gastrointestinal symptoms (nausea, vomiting, abdominal cramps, and diarrhea), hypotension, syncope, laryngeal edema, anaphylaxis, and rarely asthma. In EIA, wheals are large and may converge	Wheals are typically small, punctate, with a surrounding flare reaction, and may converge, involving mainly the trunk and extremities, precipitated by exercise and passive warming with core body temperature elevation (usually less than 1°C). ChoIU may be induced by hot baths and showers, wearing heavy clothes, eating spicy foods, and with underlying emotional stress
Risk of anaphylaxis	Common	Extremely rare
Provocation tests	Standard treadmill exercises for approximately 30 min after specific food or drug intake	Standard treadmill exercises for approximately 30 min and then passive warming with core body temperature elevation
Management	Rule out associated food allergies. Check a baseline serum tryptase. Always exercise with a companion. Medic alert bracelet. No exercise for 4-6 h after eating or taking NSAIDs. It is very important to immediately stop exercising at the onset of symptoms. Omalizumab usually controls refractory cases	Symptomatic treatment with nonsedating second-generation H1-antihistamines. Updosing to 4-fold the licensed dose of antihistamines in initial nonresponders may be effective. Omalizumab usually controls refractory cases
Need for an epinephrine autoinjector prescription	Yes	No
Long-term prognosis	Good	Good

ChoIU, Cholinergic urticaria; *EIA*, exercise-induced anaphylaxis; *NSAID*, nonsteroidal anti-inflammatory drug.

Patients with systemic mastocytosis can present with elevation in histamine and tryptase after exercise, and therefore it is an important differential diagnosis with EIA.³⁷ The differential diagnosis of EIA includes ChoIU, indolent systemic mastocytosis, mast cell activation syndromes, cardiac arrhythmias, hypertrophic cardiomyopathy, vocal cord dysfunction, laryngomalacia, exercise-associated gastroesophageal reflux, exercise-induced asthma, and idiopathic anaphylaxis.^{2,4}

Pathogenesis

The underlying mechanisms behind EIA have not been elucidated. Exercise may modify enzyme and cytokine expression, resulting in altered processing and enhanced immunogenicity of different food allergens. NSAIDs, including aspirin, can increase intestinal permeability and therefore promote food antigen absorption in FDEIA. The same may happen with oral anti-H2-antihistamines, which might interfere with gastric food digestion. Exercises may divert blood flow from the intra-abdominal mesenteric region to muscles and skin, and this might increase plasma osmolality and cause pH changes, and consequently favor food allergen absorption. Transglutaminases might also contribute to enhancing food intestinal antigen transportation.^{2,4,21,38}

Management

The preventive measures of EIA include the following: educate patients on how to deal with anaphylaxis when it occurs; make an epinephrine autoinjector readily available as well for the companion; check a baseline serum tryptase; evaluate for possible food allergies; do not exercise 4 to 6 hours after eating and sometimes before it; avoid eating the pertinent allergenic foods; stop exercising at the onset of symptoms; H1-antihistamines are unreliable and may dangerously mask the prodromal dermatological signs and symptoms of anaphylaxis (lack of effectiveness);

always exercise with a companion; wear medic alert identification; and when pollen and mold counts are high, prefer exercising indoors; always carry a cell phone; stay close to emergency facilities; avoid alcohol and NSAIDs before exercise, including aspirin; and skip exercising when it is too cold, hot, or humid (extreme weather conditions) because they can be potential cotriggers.^{2,4}

RECOMMENDED APPROACH ON EXERCISE-INDUCED ANAPHYLAXIS

Signs and symptoms

EIA is estimated to be approximately 3% of all cases of anaphylaxis.² The clinical signs of EIA include flushing, increased warmth, fatigue, diffuse pruritus, urticaria, angioedema, bronchospasm, gastrointestinal symptoms, hypotension, and laryngeal edema that is potentially fatal.

Differential diagnosis

The main differential diagnosis is with ChoIU. In EIA, 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 ChoIU. The differential diagnosis of EIA 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 tachyarrhythmias. The most commonly implicated exercise modalities are those requiring running (eg, jogging), brisk walking, biking, racquet sports, enthusiastic dancing, intense gardening, and vigorous sexual intercourse. Cytoplasmic mast cell degranulation occurs with massive release of mediators of anaphylaxis, especially histamine. Skin biopsies show degranulation of dermal mast cells after attacks. Family predisposition in EIA is uncommon.

Categories of EIA

EIA may display food dependence, with or without specific IgE sensitivity. The most commonly implicated foods are gluten antigen from wheat (the major epitope of gluten is omega-5 gliadin), shellfish (crustacea), especially shrimp, celery, corn, cow's milk, mite contaminated wheat flour, and peanuts. Curiously, in these patients, 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 occurrence of anaphylaxis. In WDEIA, a high gluten intake without exercising, and with aspirin and alcohol as cofactors, may cause anaphylaxis.

There may be DDEIA with the following: NSAIDs, including aspirin, antibiotics (cephalosporins), and the so-called anticatabolic energizer supplements, such as beta-hydroxymethylbutyrate (Table 1). Sometimes only exercise-induced angioedema, usually facial, with no systemic manifestations occurs.

In EIA, there is a higher prevalence of personal and/or family respiratory atopy. There is no genetic transmission in EIA.

Syncope occurs in one-third and laryngeal edema in two-thirds of the cases. It is postprandial in 54% and with drug dependence in 13% of the episodes.²

Prognosis and diagnosis

The natural history of EIA shows a trend toward stabilization. This improvement might be associated with adaptation in the practice of exercises, such as avoidance of eating for 4 to 6 hours before (more important) and after physical exertion, avoidance of eating the triggering foods, and in temperate areas of the planet avoidance of exercise when there is high environmental exposure to pollens and/or molds (then exercising indoors). It is also advisable to avoid exercising in extreme weather conditions (too hot, cold, or humid). Patients perhaps should also not exercise for at least 4 hours after allergen immunotherapy and after taking NSAIDs, including aspirin. Anti-IgE (omalizumab) as a mast cell stabilizer, with downregulation of high-affinity IgE receptors (FcεRI), can have a potential role in preventing these episodes.

The diagnostic tests consist in programmed running or in standard treadmill exercises for approximately 30 minutes. A negative test nevertheless does not rule it out. The same is true for serum tryptase elevation that might not always occur.

Treatment

Therapeutic measures include the following: prophylaxis; the possible use of oral anti-H1-antihistamines, preferably those with less or nonsedating properties, with conflicting data and yet no established proof according to the American Academy of Allergy, Asthma, and Immunology practice parameters, and also potentially precluding the recognition of anaphylaxis by masking the early dermatological symptoms and signs; and patients should always have the immediate availability of an epinephrine autoinjector. Anti-H2 antihistamines may also interfere with normal digestion of food allergens and enhance their intestinal absorption.² Individuals presenting this condition should always be advised to be with someone when exercising, who is also familiar with the use of an epinephrine autoinjector, to carry a cell phone, to be near emergency medical facilities, and to wear some sort of medic alert identification (bracelet for instance) informing the problem. It is very important to immediately stop exercising at the onset of symptoms.

Scaled and supervised increase exercises may induce effective physical tolerance, but more studies are still needed. A personalized anaphylaxis emergency medical action plan should always be established for the affected individuals.^{2,4}

Prophylactic pharmacotherapy to prevent FDEIA in adults might include oral cromolyn sodium (200 mg, 3 times daily taken 20 minutes before meals),^{4,39} misoprostol,⁴⁰ and ketotifen.⁴¹ In difficult to control and refractory cases of EIA, omalizumab might be tried, and successful cases have been reported.^{42,43}

CHOLINERGIC URTICARIA

Definition and prevalence

ChoIU is part of a group of dermatosis called CIndU. These CIndU are triggered by different stimuli, including cold, heat, physical pressure, vibration, sunlight, water, and exercise. Angioedema might also be present. They can occur alone or be present in individuals who already have chronic spontaneous urticaria. Their exact pathogenesis is unknown. The diagnosis of CIndU is suspected by clinical history and physical examination, and can be confirmed by specific provocation testing. The goal on these dermatologic disorders is to adequately control symptoms and to prevent the specific provocative triggers.⁴⁴

ChoIU is common, accounting for 5% of all cases of chronic spontaneous urticaria and approximately 30% of all cases of CIndU,⁴⁵ and affecting equally young adults of both sexes.⁴⁶

Pathogenesis

It is believed that in ChoIU there is an increased secretion or hypersensitivity to acetylcholine. Impaired cholinesterase activity, hypohidrosis, and antigen-antibody immune complex reactions have also been postulated.^{44,47-50} In ChoIU, provocative intradermal injection of methacholine chloride 0.01 mg in saline 0.1 mL can induce the formation of satellite wheals surrounding a central one. This positive response occurs in one-third of the cases, and may confirm but does not rule out the diagnosis of ChoIU (poor negative predictive value).⁴⁷ Bronchial hyper-responsiveness has been documented in patients with ChoIU using a methacholine bronchial challenge test.⁵¹

Clinical presentation

In ChoIU, the wheals are typically small, punctate, with a surrounding flare reaction, and may converge, involving mainly the trunk and extremities, precipitated by exercise and passive warming with core body temperature elevation (usually less than 1°C) (Figure 1). ChoIU with exercise may be induced after hot baths and showers, or even for wearing heavy clothes, eating spicy foods, and with underlying emotional stress.⁶ ChoIU must be differentiated from EIA that is an anaphylaxis induced by physical activity only, and presenting distinctively with large wheals.⁵² Angioedema frequently occurs in ChoIU and sometimes is more pronounced than the associated urticaria.⁵³ There is an atypical and very rare form of cold urticaria associated with ChoIU called cryocholinergic urticaria, where ChoIU is precipitated by exercising in cold environments or swimming in contact with cold waters.⁵⁴ Two distinct subtypes of ChoIU have been classified based on the responsiveness to intradermal autologous sweat and serum: follicular with positive reactions to intradermal autologous serum and weak reactions to autologous sweat, and nonfollicular that shows strong positive reactions to autologous sweat and negative reactions to autologous serum.⁵⁵ The pathogenic role of sweating in ChoIU is still unclear.²

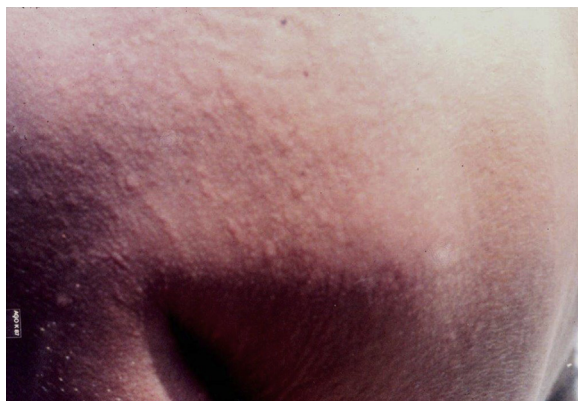


FIGURE 1. Punctate wheals of cholinergic urticaria.

Anaphylaxis due to cholinergic triggers has been reported.⁷ This has not been confirmed in the literature. Provocation testing may be performed to confirm ChoIU and to rule out EIA. A standardized protocol for diagnosing and measuring trigger thresholds using pulse-controlled ergometry has been proposed.^{6,56}

Treatment

Symptomatic treatment with nonsedating second-generation H1-antihistamines is the first choice for ChoIU. Updosing to 4-fold the licensed dose in initial nonresponders may be effective.^{57,58} Physical desensitization may also work with progressive efforts to increase body temperature.⁵⁹ The efficacy and safety of omalizumab treatment, administered for several weeks, in ChoIU have been demonstrated in patients who were unresponsive to high doses of H1-antihistamines.⁶⁰⁻⁶² Omalizumab is therefore an alternative treatment for CIndU.⁶³ With proper care ChoIU can be well controlled, leading to great improvement in quality of life.

CONCLUSIONS

In susceptible individuals exercising can trigger adverse effects: EIA and ChoIU. Each must be distinguished from the other. There are 4 types of EIA: FIEIA, FDEIA with IgE sensitivity, FDEIA without IgE sensitivity, and DDEIA. ChoIU is associated with exercises and passive warming (body temperature elevation, usually less than 1°C). In EIA, the urticarial wheals are large, whereas in ChoIU, they are typically small. In FDEIA, wheat (gluten with omega-5-gliadin allergy) and, to a lesser degree, shellfish (crustacea) are usually the most implicated foods. In FDEIA with IgE sensitivity, the association of eating the allergenic food and then exercising within 4 to 6 hours is imperative. In DDEIA, NSAIDs, including aspirin, are the most common triggers. Nonsedating second-generation H1-antihistamines should be prescribed in ChoIU. Omalizumab can be successfully used in refractory cases of both EIA and ChoIU. The description of the concepts of EIA and ChoIU is summarized in Table II. A well-defined action plan should be presented to these patients through a detailed education program.

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