

Food dependent and food independent exercise-induced anaphylaxis

*Anafilaxia induzida por exercícios:
com e sem dependência alimentar*

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Abstract

Objective: To present and discuss the current classification of exercise-induced anaphylaxis based on clinical data and on related immunological and pathophysiological mechanisms. To describe clinical symptoms, triggers and co-triggers, different diagnostic tools, and also to discuss the different therapeutic approaches and the potential benefit of scaled physical desensitization.

Methods: The literature search was carried out using Medline (PubMed). Meta-analysis, case reports and reviews were evaluated. A description of the several modalities of physical allergies related to exercises was made. Tables with differential diagnosis are presented.

Results: Physical allergies are related to mast cell dysfunction with lowered threshold for the release of cytoplasmic vasoactive anaphylactic mediators, especially histamine, triggered by external physical factors including exercises.

Conclusions: Exercise-induced anaphylaxis may be food dependent and independent and also IgE dependent and independent. Drug dependent exercise-induced anaphylaxis is also another form of presentation of this important physical allergy. Treatment includes, after obtaining a precise and detailed diagnosis. It includes also the establishment of an operational plan for anaphylaxis, self-administration of epinephrin, the presence of a companion with training in assistance during all exercises, and the avoidance of eating 4-6 hours prior and after exercises. Preventive treatment with antihistamines is currently controversial. Physical desensitization is of potential benefit in exercise-induced anaphylaxis.

Rev. bras. alerg. imunopatol. 2008; 31(6):227-229 anaphylaxis, exercise, food, physical allergies, physical urticaria, cholinergic urticaria.

Resumo

Objetivo: Apresentar e discutir a atual classificação da anafilaxia induzida por exercícios baseada em sintomas clínicos e nos mecanismos imunopatológicos envolvidos. Descrever os diferentes quadros clínicos e os fatores precipitantes e agravantes, bem como os métodos diagnósticos empregados. Listar as opções terapêuticas e o benefício potencial da dessensibilização física escalonada e programada.

Métodos: A revisão da literatura empregou a base de dados do Medline (PubMed). Meta-análises, relato de casos, e revisões foram avaliadas. O diagnóstico diferencial das várias modalidades das alergias físicas relacionadas aos exercícios é apresentado e discutido.

Resultados: Nas alergias físicas há disfunção mastocitária com diminuição do limiar para a desgranulação citoplasmática dos mediadores de anafilaxia após estímulos físicos externos, sendo a histamina a principal substância vasoativa liberada. Esta desgranulação também ocorre na anafilaxia induzida por exercícios.

Conclusões: A anafilaxia induzida por exercícios pode ou não ter dependência alimentar, envolver ou não mecanismos imunológicos IgE mediados. A anafilaxia induzida por exercícios com dependência medicamentosa é uma modalidade também importante desta alergia física. O tratamento proposto, após o diagnóstico preciso, inclui a elaboração de um plano operacional para a eventualidade de anafilaxia. A auto-administração de epinefrina, a presença durante todos os exercícios de um companheiro com conhecimentos de assistência para os quadros anafiláticos potenciais, e também evitar-se a ingestão de alimentos por cerca de quatro a seis horas antes e após a prática de exercícios. A utilização de anti-histamínicos para a prevenção destes quadros anafiláticos é presentemente controversa. A dessensibilização física pode ser empregada, com cautela, na anafilaxia induzida por exercícios.

Rev. bras. alerg. imunopatol. 2008; 31(6):227-229 anafilaxia, exercícios, alimento, alergias físicas, urticária física, urticária colinérgica.

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Introduction

Physical allergies or urticarias consist in a group of skin disorders characterized by mast cell dysfunction due to a lower threshold for cytoplasmic degranulation of anaphylactic mediators, induced by environmental physical factors, not requiring, therefore, the presence of antigen-anti-

body complexes¹⁻². The triggering physical factors may be mechanical, thermal, related to exercise, to sun exposure or to water contact³. These disorders may be reproduced by changes in temperature or by direct skin stimuli, such as pressure, trauma, vibration, water or sunlight⁴.

Physical allergies

Physical allergies usually appear minutes after exposure to the inducing factors and tend to disappear within one to two hours, unless there are typical delayed manifestations, such as delayed urticaria and/or angioedema. Histopathology is different from that of idiopathic chronic urticaria. In physical urticarias, there is dilatation of the superficial vas-

cular plexus associated to the separation of collagen fibers by edema, with no mononuclear inflammatory infiltrate in the dermis, except in delayed pressure urticaria and angioedema. Several types of physical urticarias may coexist in the same patient⁵. Physical urticarias comprise a subgroup of chronic urticarias, representing about 17% of the total². They are more frequent in young adults, may be localized or diffuse, classical or atypical, acquired or familial, with or without IgE involvement, with variable duration; they may worsen with stress and even disappear spontaneously⁶. The treatment of these skin diseases consists in preventing the triggering physical factors and using antihistamines, or effective and safe anti-inflammatory drugs, steroidal or not. There are situations in which graded and scaled physical tolerance (desensitization) may be induced with great therapeutic and preventive success⁷, improving the quality of life of these patients. The current classification of physical allergies is complex and dynamic, encompassing the understanding of the pathogenetic mechanisms involved. Present treatments utilize the added potential of several novel medications⁷⁻⁸. In physical urticarias, it is essential to make a precise diagnosis, identify the clinical expression, triggering and aggravating factors, choose a tailored pharmacotherapy combined with a prevention plan, and when possible, with a well succeeded induction of physical tolerance.

Cholinergic urticaria

Cholinergic urticaria affects young adults, aged 10 to 30 years, and it is also called generalized heat-induced urticaria. The urticarial lesions are small, 1 to 3 mm in diameter, surrounded by an erythematous eruption, which causes the "fried egg" look. They can further coalesce and systemic manifestations may be associated⁹⁻¹⁰. In this type of physical urticaria, lesions appear when the body temperature increases, usually by less than 1°C, and they may be actively induced by exercise or passively, by hot baths, heavy and thick clothing, spicy foods and by stress as well. For unknown reasons, fever (endogenous pyrogens) usually does not cause cholinergic urticaria. Patients with anhidrosis may have it, demonstrating that sweat, on its own, does not cause it. In this physical urticaria there is cytoplasmic mast cell degranulation with histamine release. It is believed that acetylcholine release in peripheral nerves also occurs, since the anesthetic neural block prevents the appearance of cholinergic urticaria. The intradermal test with 0.01mg of methacholine chloride diluted in 0.1ml of saline solution is positive in one third of cases, when the appearance of a central urticarial lesion surrounded by smaller peripheral satellite lesions is observed. Exercising in warm environment for 10 to 15 minutes is a usual trigger for this type of physical urticaria. The same happens when the patient is passively immersed in the Hubbard physiotherapy bathtub, with water at 40°C. Cholinergic urticaria was recently classified into two types: a non-follicular, showing highly positive intradermal autologous sweat test and negative autologous serum test, and a follicular type, with weakly positive intradermal autologous sweat test but with a very positive autologous serum test¹¹. The treatment of choice for cholinergic urticaria is hydroxyzine, 100 to 200mg daily in adults. When cold-induced urticaria coexists, cyproheptadine may be successfully added.

Exercise-induced anaphylaxis

The clinical manifestations of exercise-induced anaphylaxis (Table I) include flushing, diffuse pruritus, urticaria, angioedema, bronchospasm, hypotension and rarely laryngeal edema which is potentially fatal in athletes¹². It could be the cause of sudden death tragically occurring

during exercising and sports, especially in previously healthy young individuals. 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, opposed to the typically small lesions of cholinergic urticaria. The passive increase of body temperature, not exercise related, is not able to cause exercise-induced anaphylaxis. The differential diagnosis of exercise-induced anaphylaxis also includes exercise-induced asthma and cardiac conditions like hypertrophic cardiomyopathies and arrhythmias. The most commonly implicated exercise types are those requiring running. Cytoplasmic mast cell degranulation and massive release of mediators of anaphylaxis, especially histamine, occur. Family predisposition is uncommon. Exercise induced anaphylaxis may display food dependence, with or without specific IgE mediation (Table II). The most commonly implicated foods are celery, shellfish, especially shrimps, wheat, corn, mite contaminated flour and mustard. Curiously, in these patients, aerobic exercise alone, as well as the ingestion of the allergenic foods without associated exercise, does not cause this syndrome. The synergistic effect of both inducing factors is necessary for the occurrence of the anaphylactic manifestations¹³. There may be drug dependence in exercise-induced anaphylaxis: antibiotics (cephalosporins), nuphypropionic acid/NSAIDs, aspirin, and the so-called "antimetabolic supplements", such as beta-hydroxymethyl-beta-butyrate (Table III). Sometimes only marked exercise-induced angioedema with no systemic manifestations occurs. In exercise-induced anaphylaxis there is a higher prevalence of personal and/or familial atopy. Syncope is seen in 1/3 and laryngeal edema in 2/3 of the cases. It is post prandial, non specific, in 54% and with drug dependence in 13% of the cases.

Table I - Types of exercise-induced anaphylaxis

<ul style="list-style-type: none"> • Classical exercise-induced anaphylaxis • Exercise-induced angioedema • Cholinergic urticaria
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Table II - Exercise-induced anaphylaxis

<ul style="list-style-type: none"> • Idiopathic / Primary (food independent) • With IgE food dependence • Without IgE food dependence (post prandial) • Drug dependence

Table III - Modalities of exercise-induced anaphylaxis food dependence

<ul style="list-style-type: none"> • With specific IgE (wheat/omega-5 gliadin, celery, shellfish, corn, mustard, cows milk, soy, nuts, peanut, pea, coulliflower, banana, mite contaminated flour, etc...) • Without specific IgE (post prandial) <p>Drug dependence (antibiotics, aspirin, NSAIDs)</p>
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The natural history of exercise induced anaphylaxis shows a trend towards stabilizing with less intense symptoms than previously. This improvement might be associated with adaptation in the practice of these exercises, such as avoidance of eating for 4-6 hours prior and after physical exertion, avoidance of eating the triggering foods and, in some temperate areas of the planet, avoidance of physical exercise when there is high environmental exposure to pollens. It is also advisable to avoid exercising in extreme weather conditions (hot or cold) and in polluted environments. Patients also should not exercise after allergen immunotherapy. The diagnostic tests consist in programmed running or in standard treadmill exercises for about 30 minutes. A negative test nevertheless does not rule it out. There might be medical legal aspects ordering these tests in these individuals. Therapeutic measures include prophylaxis, already mentioned, the possible use of oral antihistamines, conflicting data with yet no established proof, preferably those with less or non sedating properties, and the immediate availability of self-injecting epinephrine (Epi-Pen). Individuals presenting this kind of physical allergy should always be advised to be with someone else when performing exercises that is also familiar with the use of self-injecting epinephrin, and to wear some sort of medical alert identification (bracelet for instance) informing about the problem, aiming at greater supervision and safety (Table IV). Scaled and supervised exercises may induce effective physical tolerance but more studies are needed¹⁴. Oral mite (pancake syndrome) exercise-induced anaphylaxis has also been reported¹⁵. Management requires diagnostic and therapeutic expertise¹⁶⁻¹⁷. In Japan wheat is reported to be the food antigen with the highest frequency of food dependent exercise-induced anaphylaxis and omega-5 gliadin and high molecular weight glutenin are its major allergens¹⁸⁻¹⁹. Aspirin consumption, even at low doses, is a potential risk for food-dependent exercise-induced anaphylaxis²⁰. Food-dependent exercise-induced anaphylaxis is an uncommon allergic condition in childhood and a safe return to normality is usually achieved when the ingestion of the causal food allergen and exercise are separated from each other²¹.

Table IV - Management of exercise-induced anaphylaxis

- No exercises 4-6 hours in the pre and post prandial periods
- Preventive anti-H1 is unreliable and may mask the initial symptoms of anaphylaxis
- Exercises always with a companion
- Epi-pen readily available
- Medical alert

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