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Literature review

Exercise-induced or exacerbated immune and allergic syndromes: what the exercise health professional needs to know?

Síndromes imunológicas e alérgicas induzidas ou exacerbadas por exercício: o que o profissional de saúde do exercício precisa saber?

Sérgio Dortas Duarte Júnior[1], Guilherme Gomes Azizi[1].

1. Universidade Federal do Rio de Janeiro, Rio de Janeiro, RJ, Brazil

ABSTRACT

Exercise-induced or exacerbated immunoallergic diseases are significantly important situations for both amateur and professional athletes. Asthma, bronchospasm, exercise-induced laryngospasm and anaphylaxis, chronic inducible urticaria, and hereditary angioedema are examples of these situations. This article aims to contribute to the knowledge of health professionals with guidance on the diagnosis and management of hypersensitivity disorders induced by exercise or triggered during sports practice, to allow their patients to safely perform activities related to exercise.

Keywords: asma; anafilaxia; angioedema; exercício; urticária.

RESUMO

As doenças imunoalérgicas induzidas ou exacerbadas pelo exercício são situações significativamente importantes tanto para atletas amadores quanto profissionais. Asma, broncoespasmo, laringoespasmo e anafilaxia induzidos pelo exercício, urticárias crônicas induzidas e angioedema hereditário são exemplos destas situações. O objetivo deste artigo é contribuir para o conhecimento de profissionais de saúde com orientação ao manejo de distúrbios de hipersensibilidade induzidos por exercícios ou desencadeados durante a prática esportiva, para permitir que seus pacientes realizem, com segurança, as atividades relacionadas ao exercício.

Palavras-chave: asthma; anaphylaxis; angioedema; exercise; urticaria.

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Correspondence: Guilherme Gomes Azizi, Rua Prof. Rodolpho Paulo Rocco, 255, 9°andar, Sala 9E10, Cidade Universitária da Universidade Federal do Rio de Janeiro 21941-617 Rio de Janeiro RJ. gazizi247@gmail.com

Introduction

Exercise-induced or exacerbated immune allergic diseases are significantly important situations for both amateur and professional athletes. Asthma, bronchospasm, exercise-induced laryngospasm and anaphylaxis, inducible urticaria, and hereditary angioedema are examples of these situations. This article aims to contribute to the knowledge of health professionals with guidance on the diagnosis and management of hypersensitivity disorders induced by exercise or triggered during sports practice, to allow their patients to safely perform activities related to exercise.

Exercise-induced asthma/bronchospasm

Exercise-Induced Bronchospasm (EIB), formerly called "Exercise-Induced Asthma", is defined as the transient narrowing of the airways in response to a wide variety of bronchoconstrictor stimuli related to intense physical exercise, presenting symptoms such as coughing, dyspnea, and wheezing. This condition occurs in a subgroup of individuals with asthma and in some non-asthmatics [1,2]. Thus, demonstrating a characteristic of intense airway hyperresponsiveness, EIB is more common in winter sports athletes and swimmers than in general population and athletes from other sports.

The prevalence in the Brazilian population was analyzed in 2 studies from different regions, Recife and São Paulo. Both demonstrated that children and adolescents with asthma have a prevalence of about 45% of EIB [4,5].

The intensity of ventilation, a fundamental factor for adequate oxygen supply during physical activity, can also be the "Achilles tendon" in individuals subject to EIB, as we can go from 6 L/min of respiratory volume to more than 200 L/min. In addition, breathing becomes progressively oral, from the moment the individual reaches 30 L/min.

Thus, mouth breathing does not have the range of mechanisms present during adequate nasal breathing, in which there is humidification and air heating, in addition, with greater flow, there is greater exposure to aeroallergens, irritants to the mucosa and particulate matter, which in the long term, can participate in the pathophysiology of respiratory diseases such as asthma and mixed rhinitis [6,7].

The pathophysiology of EIB is not yet fully described, however, studies indicate that there is possibly a correlation between airway cooling through inhaled air and subsequent rewarming of the airways after exercise [8]. Another proposed hypothesis is related to airway dehydration air, which through the intensity of ventilation, results in an increase in the osmolarity of the local fluid, increasing the periciliary movement and, consequently, increasing the water in the bronchial lumen [9]. Thus, it would release inflammatory mediators leading to bronchoconstriction through the contraction of smooth and edema [10]. Exercise immunology could explain the third hypothesis for this multivariate pathology, since high-performance athletes go

through periods of transient immunosuppression called "Open Window", in which they are more susceptible, especially which can exacerbate symptoms pre-existing conditions or cause isolated bronchoconstriction [11-13].

The diagnosis of asthma can be made based on a history of characteristic symptoms (cough, wheezing, chest pain, and dyspnea) and documentation of variable airflow limitation, by means of spirometry with bronchodilator testing or bronchoprovocation tests, as the clinical diagnosis in the EIB can be complicated [14]. The diagnosis of EIB uses the variation in FEV1 before and in sequences of 5, 10, 15, and 30 minutes after the provocation tests, through vehicles such as treadmills or stationary bicycles. Forced expiration maneuvers should be performed in a standardized way, and the calculation of the variation should be performed in relation to the baseline value, with a reduction in FEV1 > 10% or 15%, which are observed in one or two moments of the assessment, depending on the literature [14]. To carry out the provocation test, the athlete should not practice any exercise in the previous 4 hours, as this could lead to a false-negative result, due to refractoriness in this period [1,16].

Differential diagnoses to EIB must always be considered, such as exercise-induced laryngospasm, poorly controlled rhinitis, gastroesophageal reflux, and hyperventilation syndrome. The goals of asthma treatment are to achieve and maintain asthma control, improve lung function, and prevent risk factors for acute events such as exacerbations. Specifically, in relation to the EIB, it will directly depend on the correlation with asthma or not [17,18].

Environmental measures and masks can help reduce the effects of exposure to cold air on winter sports athletes or the inhalation of air pollutant particles [19].

In addition to these, the pre-exercise warm-up can result in a reduction in bronchoconstriction by exercise in about 50% of individuals, which is performed for at least 10 to 15 minutes, reaching up to 60% of the maximum heart rate. Then, the athlete will enter a "refractory period" induced by the release of protective prostaglandins [20].

There are few randomized clinical trials for an adequate analysis of pharmacotherapy for the treatment of EIB. However, inhaled glucocorticoids are the mainstay of therapy for asthma, as this is basically a pathology with inflammatory characteristics [16], these agents, by inhalation, are allowed by sports authorities, such as the World Anti-doping Agency (WADA) and the Authority Brazilian Association of Doping Control (ABCD) [22,23].

The most commonly used strategy for athletes with or without asthma and who have EIB is treatment with inhaled glucocorticoids, inhaled β2-agonists before exercise (regular or if necessary) in association or not with β2 receptor antagonists leukotrienes (montelukast) [1,23].

Long-acting β-agonists are good options for athletes, as they have a bronchodilator action of up to 12 hours, unlike salbutamol, the main short-acting β-agonist with an action of up to 3 hours [18]. Formoterol and salmeterol (β-agonists of long-lasting) have no WADA restriction. The association with inhaled corticosteroids is

increasingly present, leaving the isolated prescription of β-agonists in the past, as this interaction minimizes tachyphylaxis and favors inflammation control [17].

Immunotherapy for aeroallergens has limited effectiveness in direct relation to EIB, as there are no large studies, however, immunotherapy is widely used in asthma or allergic origin, so this possibility should be analyzed together with the specialist, as in addition to being a modifying factor in the natural history of the disease, it is not a treatment characterized as doping [17,21,24].

Thus, we must emphasize that the health professional must act both for the health of the individual and for the well-being of the individual's work instrument, their body, since any reduction in physical capacity can be the line between victory and defeat.

Exercise-induced laryngospasm

Exercise-induced laryngospasm (EILs) are a group of conditions that cause laryngeal obstruction during exercise, among these are exercise-induced laryngomalacia (EIL, a supraglottic obstruction caused by arytenoid collapse) and exercise-induced vocal cord dysfunction (CVIE) [25,26].

EILs have symptoms similar to exercise-induced asthma and have a high prevalence among the population, however, it is still confused with EIA, which causes a misdiagnosis, however, many do not have associated asthma [27,28] from approximately 5% to 7% among adolescents and young adults [29].

The supraglottic obstruction appears to precede the inspiratory glottic narrowing, in greater proportion than during the expiratory period [20]. This and other anatomical-physiological factors provide some hypotheses that suggest that EIL has varied etiologies, these being the size of the larynx, which could contribute as a causal or facilitating factor, such as during puberty, when the laryngeal diameter of women begins its process of reaching a smaller diameter in relation to men, explaining the higher prevalence of adolescent women with a report of EIL [30,31].

Another etiological hypothesis involves the pressure difference during the increase in intensity in a physical activity that normally requires accelerated breathing movements. Thus, it would be a partially passive phenomenon, in which increased effort and ventilation would increase the negative transmural pressure [32].

In addition, the anterior movement of the epiglottis puts tension on adjacent structures and would facilitate supraglottic closure, mainly due to the high tension of the aryepiglottic fold, pulling the arytenoid mucosa anteriorly, reducing the circumference of the larynx [33].

A third hypothesis would be hypersensitivity of the upper airways, in a physiological reflex of the glottic region to avoid aspiration, which could explain an inadequate local adduction [33].

In addition to these hypotheses, a fourth possibility was proposed for the origin of symptoms, which would be closely related to gastroesophageal reflux, as after

acid reflux reaching the laryngopharyngeal area, it would induce a state of hyperexcitability [34]. Thus, complementary diagnostic research is indicated and propose treatment with proton pump inhibitors. We must remember that the prevalence of reflux in the population varies between 10% and 60% [35]. Therefore, this would be a reasonably important hypothesis to be considered.

The management of the EIL is still under wide discussion and without a defined consensus, mainly due to the heterogeneity of the etiology and the possible phenotypes involved. Thus, a careful evaluation is indicated, in which predisposing and irritating factors that may develop the obstruction are excluded, in addition to the exclusion of differential diagnoses, including exercise-induced bronchospasm. Studies also associate psychological therapy as a complementary factor in treatment [36,37].

Some reports sought to identify possible therapies such as the use of inhaled ipratropium bromide before the activity, which would reduce vocal cord dysfunction [38]. In addition to the approaches described above, the possible surgical intervention should be evaluated together with the otolaryngologist surgeon.

Exercise-induced anaphylaxis

Anaphylaxis is derived from the Greek language ana ("inversion", "repeat") and phylaxis ("guard", "immunity"), having been adopted by Charles Robert Richet and Paul Portier in 1902 [38]. It is characterized by an intense and potentially hypersensitivity reaction fatal that results from a systemic release of inflammatory mast cell and basophilic mediators such as histamine, leukotrienes, tryptase, often correlated with a reaction involving immunoglobulin E (IgE) [38,39].

Anaphylactic reactions have an intense correlation with some allergens common in our environments, such as food, anti-inflammatory drugs, β-lactams, and insect venom (bees and wasps), due to previous sensitization (specific IgE) [40]. However, there are anaphylactic conditions in which the patient does not have sensitization to the causative agent, as indirect mast cell degranulation after MRGPRX2 receptor stimulation by drugs (quinolones, neuromuscular blockers, icatibant, opioids), mastoparan wasp venom, and substance P [41,42].

The clinical characterization of anaphylaxis is still not consensual. The clinical picture starts about 5-30 minutes after exposure to the allergen, however, symptoms can be observed within 6 hours.

Manifestations generally occur with skin involvement associated with one or more of the respiratory (70%), cardiovascular (10-45%), central nervous system (10-15%), and gastrointestinal tract (30-45%) systems. However, possible anaphylaxis should not be neglected if there is no skin involvement [42,43].

Chart 1 - Signs and symptoms

Cutaneous/subcutaneous/mucosal
Redness, pruritus, urticaria, angioedema, morbilliform rash, pillar erection
Lip, tongue and palate pruritus: palmoplantar and scalp pruritus
Edema of the lips, tongue and uvula
Periorbital pruritus, erythema and edema, conjunctival erythema, tearing
Pallor, sweating, lip and extremity cyanosis
Respiratory system
Laryngeal: itching and tightness in the throat, dysphagia, dysphonia, hoarseness, dry cough, stridor, itching sensation in the outer ear canal
Lungs: shortness of breath, dyspnea, chest tightness, wheezing
Nose: itching, congestion, runny nose, sneezing
Cardiovascular system
Hypotension, feeling of weakness, tachycardia, dizziness, syncope, altered mental status chest pain, arrhythmia
Gastrointestinal system
Nausea, cramping abdominal pain, vomiting, diarrhea
Others
Uterine contractions, convulsions, vision loss, tinnitus, feeling of impending death, loss of sphincter control, altered mental state

Modified of "Guia para manejo da anafilaxia-2012" – Grupo de Anafilaxia da ASBAI. Rev Bras Alerg Imunopatol 2012;35(2)

The differential diagnosis of anaphylaxis must be considered, however, disregarding possible anaphylaxis can lead to the patient's death. Thus, any affection that acts on the skin and mucous membranes can cause laryngotracheitis, bronchial obstruction, or an asthma exacerbation, as well as vasovagal syncope, pulmonary embolism, and other emergencies in other systems correlated with anaphylaxis [42].

Exercise-induced anaphylaxis (EIA) is a condition initially reported by Maulitz et al. [44] in 1979, which described a picture of hypersensitivity occurring in vigorous physical activity preceded by ingestion of shellfish (shrimp and oysters) between 5 and 24 hours before.

It is estimated that EIA may have an incidence between 7 and 9% within the epidemiology of anaphylaxis [45], and may occur at any intensity of physical activity, however, studies have shown that sports with lower cardiovascular demand have fewer reports [46].

Foods with the greatest involvement in exercise-induced anaphylaxis with IgE-mediated food dependence are wheat (correlated with 5-omega-gliadin), shellfish, peanuts, corn, cow's milk, soy, mite-contaminated flours, and fruits from Rosaceae family (peach, loquat, plum, apricot, cherry, and others) [44,47]. The symptoms can start during or after exercise, however, most occur about 30 minutes after stopping the activity [44].

EIA may also have medications as triggers, mainly non-steroidal anti-inflammatory drugs and antibiotics (cephalosporins), requiring the interaction between medication and physical activity [44].

Several hypotheses have been suggested to explain this disease. The most accepted hypothesis would be the correlation of physical activity with increased gastrointestinal permeability [44]. This pathophysiology would be related to the increase in low-affinity IgE receptors in the intestinal mucosa cells, which, in patients with food allergy, could stimulate the cascade inflammatory potentiated by increased blood flow to physical exercise. Studies have shown that exercise and ASA enhance the absorption of allergens, especially the omega-5-gliadin present in wheat. Thus, if a food challenge with exercise or AAS occurs or is purposely performed, it could induce the anaphylactic manifestation [44,47].

Transglutaminase could alter the absorption of food allergens, which in association with exercise could accelerate the process of allergen distribution. Other triggers described in the literature would be environments of high or low temperature, high humidity, exposure to seasonal pollen, especially in northern hemisphere countries, alcoholic beverages, stress, infection, and menstrual period [48].

The diagnosis is entirely related to a good anamnesis. However, serum tryptase measurement after the suspected or confirmed condition of exercise-induced anaphylaxis could confirm this, as well as in anaphylaxis, enabling subsequent preventive intervention regarding the allergen triggering the reaction. Thus, the investigation of allergic sensitization to foods. However, if the history and the search for sensitization (specific IgE) are not clear, the challenge test will be an important tool.

There is no standardized challenge test exclusively for EIA. However, the Bruce protocol is a maximal exercise test that uses a treadmill, and encourages an increase in speed and incline every 3 minutes, so, due to its easy reproduction, this test is widely used in association with the previous intake of said food causing the reaction. We must remember that the environment must be controlled, vital signs must be monitored continuously and the test must be performed under medical supervision. The patient should be asked to discontinue antihistamines and leukotriene antagonists for at least 3 days before the challenge test [49-51].

After the diagnostic hypothesis is proposed, the necessary support must be offered for the well-being of the athlete or practitioner of physical activity. All patients should be prescribed and trained to manage self-injecting epinephrine. In addition, the patient must be educated about the characteristic symptoms of anaphylaxis, its possible triggers (avoid food between 4-6h prior to exercise, avoid aspirin and/or NSAIDs between 24 and 48h prior to activity) involved in each case, and recommends the performance of physical activities always accompanied. H1 antihistamines can and should be used according to the symptoms, on a regular basis or before physical activity, if the specialist deems it necessary [41,44].

Chronic inducible urticaria

According to current guidelines, urticaria is defined as a condition determined by the onset of urticaria, angioedema, or both. Wheals is characterized by a le-

sion with central edema of variable size, almost always surrounded by erythema, a sensation of itching or burning, and fleeting nature, with the skin returning to its normal appearance between 30 minutes and 24 hours. Angioedema, in turn, presents as sudden and pronounced edema of the lower dermis and subcutaneous tissue, or mucous membranes, with a sensation of pain at the site, and slower resolution than wheals, which may last up to 72 hours [52].

Urticaria is classified according to the duration of clinical manifestations as acute when signs and symptoms persist for less than 6 weeks, or chronic in cases where it manifests daily or almost daily for 6 or more weeks. Chronic urticaria (UC), in turn, can occur spontaneously or be induced by specific stimuli such as cold, heat, pressure, increase in body temperature (cholinergic urticaria), etc. [52].

Cholinergic urticaria and cold urticaria are important situations to be considered in the context of sports practice [53]. Cholinergic urticaria is characterized by the appearance of micropapular lesions, related to an increase in body temperature, from physical exercise or local application of heat; in addition to emotional stress, spicy foods or hot drinks. The lesions are approximately between 1 and 3 mm, located on the trunk and upper limbs. Lesions tend to last 15 to 60 minutes and may be associated with local angioedema. If cholinergic urticaria is suspected, it is important to differentiate it from exercise-induced anaphylaxis, aquagenic urticaria, adrenergic urticaria, and cold-induced cholinergic urticarial [54,55].

The provocation test to confirm cholinergic urticaria also aims to rule out exercise-induced anaphylaxis. A standardized protocol for diagnosing and measuring cholinergic urticaria thresholds using heart rate monitoring exercise testing has been proposed. The test is performed by ergometry with heart rate control, so the patient positions himself on the ergometric bicycle and starts pedaling, being instructed so that the heart rate rises by 15 beats per minute every 5 minutes, reaching 90 beats per minute above the basal level after 30 minutes. The time for the onset of urticaria is inversely proportional to the intensity of the disease (image 1), that is, the shorter the time for the onset of lesions, the more severe the cholinergic urticaria is [54].

Image 1 - Lesions compatible with cholinergic urticaria after provocation test. HUCFF-UFRJ Immunology Service Courtesy

The therapy of the first choice consists of non-sedating antihistamines. However, there are alternatives for refractory cases such as Omalizumab, an anti-IgE monoclonal antibody.

Cold urticaria is defined by the appearance of wheals after exposure to cold, whether by solid objects, air, or cold liquids. Lesions are usually limited to the site of contact with cold (wheals and angioedema), but they can be generalized and accompanied by systemic manifestations, including progression to acute respiratory failure and anaphylaxis. These mainly occur in situations such as carrying refrigerated objects, swimming in ice water, staying, or entering a refrigerated environment, which can put swimmers and skiers at high risk [52,56].

Challenge methods for cold urticaria include the classic "ice cube test" (picture 2 and 2.1) and the TempTest® (picture 3 and 3.1).54 Management of cold urticaria includes: avoiding cold exposure, drinking or cold foods; non-sedating antihistamines in recommended doses or even quadrupled; in selected cases the use of omalizumab. In severe cases, with cold anaphylaxis, an emergency plan must be instituted, including the prescription of epinephrine autoinjectors, which is the gold standard medication in severe conditions involving inflammatory mediators, such as histamine [54].

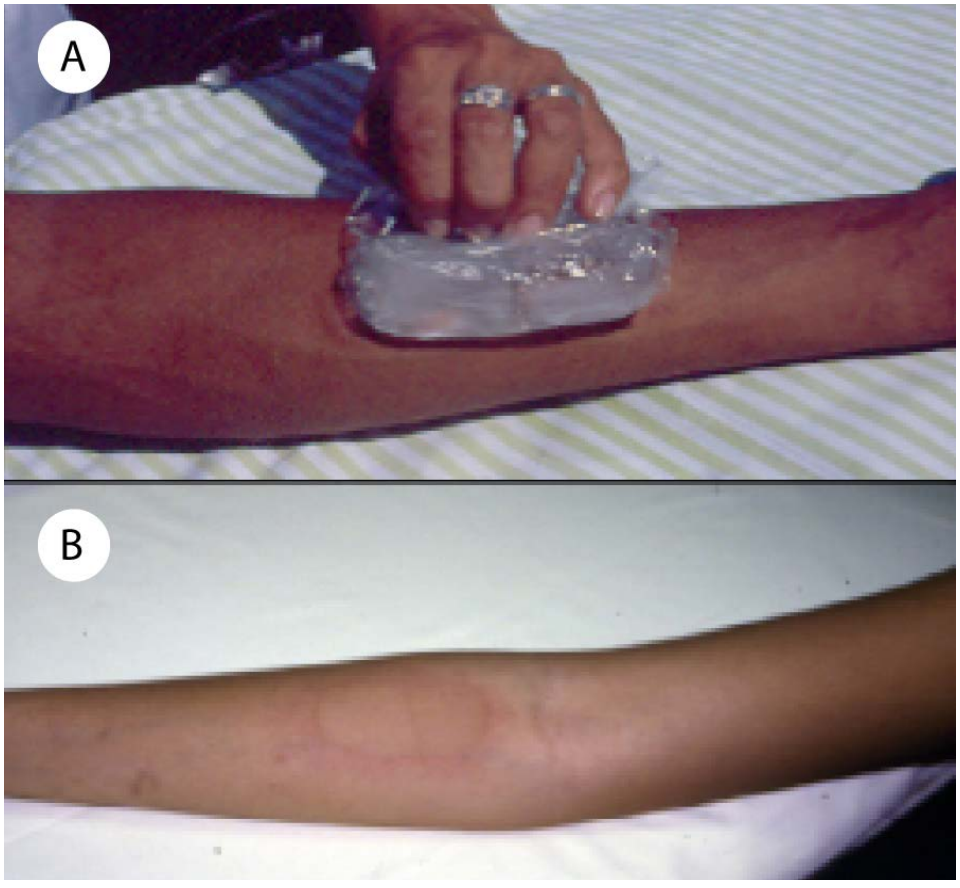

Image 2 - (A) Image 2 - Ice cube provocation test (Ice cube test) for diagnosis of cold urticaria; (B) - Positive "ice cube" challenge test for cold urticaria. HUCFF--UFRJ Immunology Service Courtesy

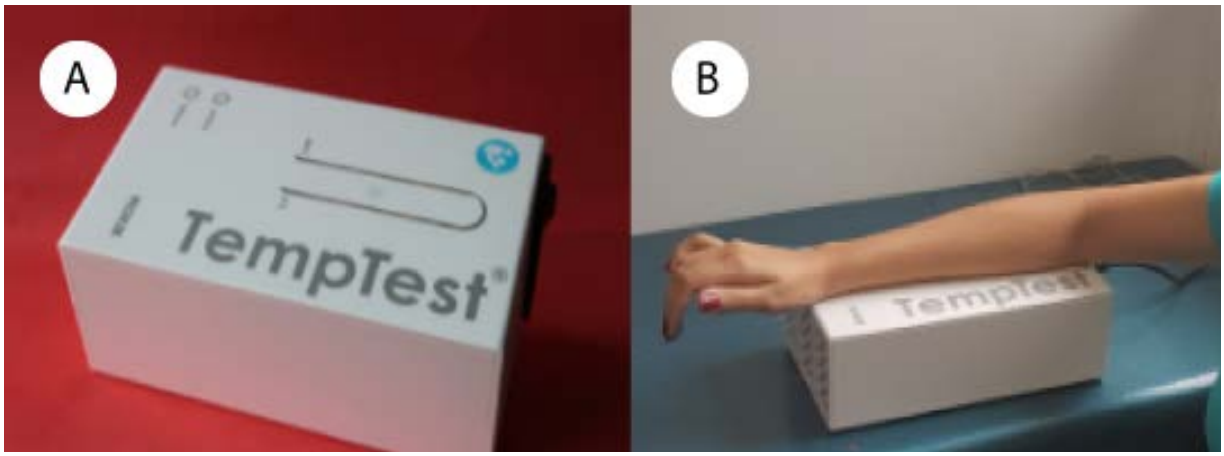

Image 3 – (A) Temp Test® -Instrument aimed at provocation testing in cold urticaria and heat urticaria; **(B) Carrying out the specific provocation test for cold urticaria through TempTest®. HUCFF-UFRJ Immunology Service Courtesy**

Delayed Pressure Urticaria (DPU) is a condition in which deep tissue swelling occurs several hours after a sustained pressure stimulus, for example, wearing a mouthguard, prolonged adherence to sports equipment, on the soles of the feet after running, or on the buttocks after long-distance cycling or rowing. The therapeutic response is variable to antihistamines and the use of quadrupled doses is often necessary. Omalizumab, dapsone, sulfasalazine, anti-TNF, and theophylline have also been used to control DPU symptoms [54,57,58].

Solar urticaria occurs in individuals shortly after exposure to the sun. Management includes barrier protection, use of sunscreens, and antihistamines before sun exposure. Different therapeutic modalities were described, according to the intensity of the symptoms: sunscreen, oral antihistamines, cyclosporine, desensitization with different types of phototherapy, omalizumab, plasmapheresis, Intravenous Immunoglobulin (IgIV), afamelanotide, among others. Although therapeutic recommendations have been proposed in the context of chronic urticarias, there are no consensus-based guidelines that define the specific approach for solar urticarial [54,57].

Aquagenic urticaria is uncommon and represents a body's reaction to water; this is independent of temperature. H1 antihistamines and UV therapy are used to treat this disease with variable response [54,57].

Hereditary angioedema

Hereditary angioedema (HAE) is a rare, potentially fatal disease characterized by attacks of cutaneous edema, submucosal and not correlated with wheals (image 5). Patients with HAE have a quantitative or qualitative defect in the C1 inhibitor (C1-INH), an enzyme from the SERPINA superfamily that acts as a serine protease. Later a new group of HAE patients with normal C1-INH has been defined [58].

Three types of HAE are defined: 1) HAE with quantitative C1-INH deficiency (formerly designated as HAE C1-INH Type I); 2) HAE with C1-INH dysfunction (formerly designated as HAE C1-INH of Type II); and AEH with normal C1-INH (formerly referred to as AEH Type III) [58-60].

Image 4 - Large angioedema in a patient with Hereditary Angioedema. HUCFF-UFRJ Immunology Service Courtesy

The main mediator of angioedema in patients with HAE-1/2 is bradykinin through the binding of this mediator to its B2 receptor, which is constitutively expressed in endothelial cells and interferes with endothelial junctions, increasing vascular permeability [61].

Patients with HAE suffer from recurrent angioedema episodes involving the skin and submucosa of various organs. The most commonly affected sites are the face, extremities, genitalia, oropharynx, larynx, and digestive system. However, rare clinical manifestations such as severe headache, urinary retention, and acute pancreatitis can also occur [61].

Although many of the crises occur spontaneously, several triggering factors have been identified: trauma (even if mild), stress, infection, menstruation, pregnancy, alcohol consumption, extreme temperature changes, exercise, use of ACE inhibitors, and use of estrogen (contraceptives and hormone replacement therapy). In adolescence, there may be a substantial increase in disease activity, particularly in young females, due to menstrual cycles and the use of oral contraceptives containing estrogen. As trauma is among the main triggering causes of crises, impact/combat physical activities should be discouraged for these patients [61].

HAE can present with non-anaphylactic edema of the upper airways, which can cause suffocation and death in athletes, as reported in an undiagnosed patient who practiced martial arts as well as his family members [61]. Pharmacological treatment for anaphylaxis is ineffective and airway management should not be delayed. If not diagnosed, mortality can reach 33% [62,63].

All patients with suspected AEH-1/2 (ie, recurrent angioedema in the absence of a known cause) should be evaluated for blood levels of C4, C1INH, and C1INH function; and these tests, if abnormally low, should be repeated to confirm the diagnosis.

Education and guidance are the most important initial actions to avoid serious consequences of HAE and to improve the quality of life of patients and their families. Patients should receive written information that is relevant about the HAE, including preventive measures and an action plan for crisis management [59].

Identifying and eliminating triggers such as stress and trauma can reduce the risk of seizures. High-impact sports and hobbies that are at risk of trauma are contraindicated, as are medications that can induce or prolong an HAE crisis, such as ACE inhibitors, Angiotensin II receptor blockers (ARB), estrogen-containing medications, and gliptins. Patients who need contraception should only receive progestins. Vaccination against hepatitis A and B is recommended, as blood products can be used in the treatment of HAE, although there is no record of infection by these viruses in patients who used the drugs currently available [59].

HAE pharmacotherapy is divided into three modalities: long-term prophylaxis, short-term prophylaxis, and treatment of crises. As this article is a bibliography for sports emergencies, we took a moment to discuss the treatment of angioedema crises in these patients.

Conclusion

Physical activities can trigger different illnesses (asthma, rhinitis, anaphylaxis, urticaria, and hereditary angioedema) that impair performance. The early diagnosis of immunoallergic disorders in athletes is important in order to implement effective preventive measures and rescue strategies, allowing the full performance of physical activities.

Potential conflict of interest
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