Exercise-induced anaphylaxis and antileukotriene montelukast

Sapna Gajbhiye, Rajendra Prasad Agrawal, Shubham Atal, Vikalp Tiwari, Pradeep Phadnis
Department of Pharmacology, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India

ABSTRACT

We report a rare case of exercise-induced anaphylaxis (EIA), occurring exclusively with exercise, without any other associated trigger, detected in the prodromal phase, and prevented from additional anaphylaxis episodes by treatment with cetirizine and 10 mg daily of antileukotriene montelukast to date. EIA is a syndrome in which patients experience a spectrum of the symptoms of anaphylaxis ranging from mild cutaneous signs to severe systemic manifestations such as hypotension, syncope, and even death after increased physical activity. Many people have triggers, such as, a variety of foods, various medications, alcohol, cold weather, humidity, and seasonal and hormonal changes along with exercise that cause the symptoms. Typically, either exercise or the specific trigger alone will rarely cause symptoms. It is differentiated from cholinergic urticaria by the absence of response to passive body warming and emotional stress.

Key words: Leukotriene, montelukast, cetirizine, exercise, anaphylaxis

INTRODUCTION

Anaphylaxis is a severe, potentially fatal, systemic allergic reaction. It can be idiopathic, caused by a specific allergen or exercise-induced (EIA).[1] Literature has shown only 1000 cases until 2001.[2] Although a rare condition, the incidences are increasing, as more people participate in physical activity and sport. The specific etiology is unclear; however, a lowering of the degranulation threshold of the mast-cell is detected in skin biopsies. It is often diagnosed on the basis of patient history and examination, but an exercise-challenge is confirmatory. The need for diagnostic certainty must be weighed against the risk of inducing anaphylaxis. To the best of our knowledge, we are reporting the first case wherein montelukast with cetirizine has been successful in preventing additional attacks of EIA.

CASE REPORT

A 26-year-old male presented with a three-year history of exercise-associated rash. Every time, almost 30 minutes after starting to exercise; he felt warm and developed pruritus, flushing, and angioedema of the eyelid. Soon pruritic skin lesions developed, which started on his face and quickly increased in both number and size and became generalized, with development of urticaria. He started having a headache simultaneously. The patient immediately discontinued physical exercise at the first sign of pruritus and malaise, and therefore, the symptoms did not progress, but persisted till he was medicated [Figure 1].
There were four such episodes in the last three years when the patient started exercising in the gymnasium, during the summer vacation. Each time he discontinued exercise as soon as he started feeling the discomfort. The symptoms subsided when the patient stopped the physical activity. He denied any associated chest pain, shortness of breath, abdominal pain, nausea, vomiting, diarrhea or wheezing, with his episodes.

His past medical history of nonspecific allergic rhinitis to dust was notable. Skin-prick tests (SPTs) performed on the patient were positive for mites and grasses, but negative for egg, milk, wheat, peanut, soy, fish, seafood, seeds and nuts, such as, cashew; fruits, including chestnut, lemon, lime, and mango; corn and maize; garlic, leek, and onion; legumes (chickpeas, beans, peas, lentils); and herbs like mint. There was no history of any specific food intake or medication before exercise. The skin prick test for wheat was negative. Specific Immunoglobulin E (IgE) was negative for wheat (<0.35 kU/l). The challenge test under supervision and after a six-hour fast (to exclude food-induced EIA) was not done. We were unable to test for basal tryptase as the patient was not a booked case and he came to our hospital after 12 hours of onset of the symptoms. He had no other history of skin rashes. His examination was equally unremarkable with no cutaneous lesions. There was no past history of such skin lesions after a hot shower bath. He did not exhibit dermatographism. Pulmonary spirometry tests were unremarkable at the examination. Hot and cold temperature provocation tests were negative after 20 minutes. A passive warming test was performed. A rise in core body temperature of 0.5°C to 1.5°C (0.9°F to 2.7°F) was achieved by immersing the patient in warm water in a controlled environment. This test did not produce urticaria or any other symptom in the patient. A plasma histamine level was not done. An exercise-challenge test was not performed, as we did not consider it ethical to reintroduce the patient to the known trigger, which precipitated the fatal anaphylaxis, for the confirmation of diagnosis. Also, the patient did not give his consent for the exercise-challenge test, as he was anxious about his condition. He was observant and very sure that from the last four years, every time he had the same episode after joining the gymnasium.

As per the history given by the patient and after his examination, other causes of EIA were excluded. He did not consume alcohol. There was no co-administration of nonsteroidal anti-inflammatory drugs (NSAID), muscle relaxants, any antibiotic, H2-receptor antagonists and proton pump inhibitors (PPI), cardiovascular drugs or concomitant infectious diseases documented. He was not following any medical treatment at all. As the patient presented late with a complaint of erythema, pruritus, and urticaria and no chest pain, shortness of breath, abdominal pain, nausea, vomiting, diarrhea, or wheezing, he was prescribed Cetirizine (Alerid) 10 mg, twice a day, which provided significant improvement. Montelukast (Montair) 10 mg, once a day, was also added, which provided complete resolution in 12 weeks, although the patient started exercising from the eighth week with no symptoms. He became stable on the regimen, and was able to exercise with no outbreaks to date.

**DISCUSSION**

Five types of EIA, namely, classic, variant-type (approximately 10% of the cases), familial, food (specific and nonspecific), and medication-dependent EIA are known. Sheffer and Austen[9] have described four phases of anaphylaxis attack — prodromal, early, fully established, and late, in a case series of 16 patients with EIA, of age 12–54 years. Any physical activity, even mild can trigger EIA, but jogging, brisk walking, dancing, and aerobic sports are the most common triggers. Menstruation, humid or cold environments, and exercising in a warm environment are other associated factors.

Release of vasoactive mediators along with tryptase and leukotrienes on mast cell degranulation is probably responsible for the symptoms. The mechanism by which exercise lowers the degranulation threshold of the mast cells is unknown.[9] Theories state that the increased activity of the sympathetic nervous system stimulates the cholinergic fibers innervating the eccrine sweat glands to release acetylcholine, leading to mast-cell degranulation and liberation of vasoactive substances.

There is great variability of symptoms in EIA, hence, it is unpredictable and difficult to diagnose.[6] Shaddick et al.[7] conducted a study on 279 EIA patients, which showed that generalized pruritus and urticaria, flushing, and angioedema were the most frequently occurring symptoms at the time of an attack. However, symptoms suggesting vascular compromise, headache (28%), gastrointestinal colic and nausea, upper respiratory obstruction, and even dysphagia, were also
described.[7] EIA was often diagnosed on the basis of patient history. A history of exercise-induced warmth, erythema, and pruritus, with or without urticaria, was highly suggestive of exercise-induced urticaria or anaphylaxis. Progression of symptoms to dysphagia, dyspnea, wheezing, dizziness or syncope was also consistent with EIA. Symptoms typically lasted from 30 minutes to four hours after the cessation of exercise. In a majority of individuals, the frequency of attacks tended to decrease or remain the same over time.

The need for diagnostic confirmation must be weighed against the risk of inducing anaphylaxis.[8] In suspected cases of EIA, an exercise-challenge test can be conducted, after getting informed consent from the patient. Supervision during exercise testing is mandatory. At set time points or when the patient is symptomatic, pulmonary function testing is also typically performed. It is not possible that the reproducibility of symptoms in EIA is variable; although a positive test confirms the diagnosis, a negative test does not rule out the diagnosis. Other tests including Specific Immunoglobulin Ethylene Oxide (EtO) allergens (foods, aeroallergens), allergy skin testing, food-challenge testing, exercise food-challenge testing, and methacholine-challenge testing can also be performed. The cholinergic urticaria must be differentiated from exercise-induced anaphylaxis, as in the latter, no passive heating (e.g., from hot baths or saunas) is involved, as in our patient. Food- or drug-related exercise-induced anaphylaxis is another differential diagnosis.

Physical exercise should be discontinued at the first sign of cutaneous erythema, pruritus, urticaria or malaise, to prevent worsening of the EIA. The treatment of an acute attack consists of subcutaneously administered epinephrine, intravenously administered fluids, oxygen, antihistamines, airway maintenance, and corticosteroids.

The management typically consists of modification of exercise, relative to intensity, duration, and weather conditions, and abstaining from food before exercise. Patients should be advised to exercise with an emergency epinephrine kit and a partner who is able to administer basic life support and epinephrine.

Recent advances in treatment regimens include mast-cell stabilizer and leukotriene-modifying agents such as montelukast; however, their effectiveness remains to be determined.[9]

**CONCLUSION**

This case report provides us with valuable data, which show that once an acute attack of EIA settles down, the patient’s quality of life can be improved by preventing additional attacks of EIA by maintaining him/her on cetirizine and montelukast. However, mechanisms related to its suitability should be clarified in the investigations.

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