Exercise Testing And The Evaluation Of An Exercise Associated Allergic Syndrome

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Citation

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Abstract

Exercise induced anaphylaxis is a dramatic expression of physically induced mast cell stimulation (1). It may be difficult to distinguish from cholinergic urticaria, since both diseases may be associated with exercise. A young man with recurrent exercise associated allergic manifestation was studied with exercise challenge and serial plasma histamine measurements. The finding of exercise associated mediator elevation in the absence of signs or symptoms of anaphylaxis has implications for future management and studies of patients with exercise induced allergic disease.

CASE REPORT

A 36 year old Caucasian male presented 5/14/02 with recurrent episodes of facial swelling and shortness of breath during the preceding 8 years. The 4 most severe episodes of were associated with exertion during exercise. While playing soccer during the preceding week the patient developed swelling of his eyes, face, and lips, body hives, throat closing sensation, and difficulty breathing. He had been given a self-inject able epinephrine unit by a physician and administered it to himself and took a tablet of hydroxyzine. This improved his symptoms over then next 90 minutes. More recently, he developed hives and shortness of breath when he jogged. He had eaten food 5 hours prior to jogging. The patient denied a history of food allergy, allergic rhinitis, asthma, or prior allergy testing. There was no family history of allergic disease.

On physical examination, the patient was well developed, and had no wheezing, urticaria or angioedema. He had pet cat. The nasal mucosa and conjunctiva were normal appearing. He had a heart rate of 68, blood pressure of 130/90. A percutaneous skin test to cat dander showed a positive wheal and flare response. No responses to locally relevant pollen percutaneous tests were elicited. Pulmonary function tests performed using office spirometry, were within normal limits. The patient was given prescriptions for fexofenadine 180 mg/day, self-injectable epinephrine, and fluticasone/serevent fixed dose inhalation(100/50) to be taken twice daily. He was also asked to limit cat exposure and to refrain from soccer and other strenuous exercises.

Serologic tests revealed an IgE of 62 IU/mL, and negative Immunocap™ allergen specific IgE test to apple, cheddar, wheat, and various tree, grass, and ragweed pollens. A complete blood count showed no eosinophilia. The patient returned 2 weeks later claiming no problems when biking for 1 hour but he wanted to start playing soccer again. He also claimed to pressure or trauma provoked swelling on occasion. Famotidine 20 mg twice daily was additionally prescribed. The patient returned 1 month later after running out of fexofenadine. At that time he claimed that he was still getting facial swelling and shortness of breath with exercise. He attributed the symptoms to sweating. The patient was again given a prescription for fexofenadine 180 mg/day, and montelukast 10 mg/day was also prescribed. A 24 hour urinary histamine level was performed and was 11.1 ug/g creatinine(normal 5-29.5 ug/g creatinine). The patient was asked to undergo exercise testing using a treadmill.

While taking the medications prescribed, the patient underwent 2 exercise tests without having eaten during the prior 6 hours. The Bruce protocol($_2$) was utilized. The first exercise test was performed in an air-conditioned room with the patient wearing shorts and a T-shirt. A baseline plasma histamine level was obtained prior to testing. The patient exercised 10 minutes during which time his heart rate increased from 68 to 169 beats per minute. This maximum heart rate was 92% of the maximum predicted heart rate. The blood pressure rose from 130/90 to 170/90 during the exercise. Immediately after this first exercise test, another plasma histamine level was obtained. The patient denied any

pruritus or swelling at this time. No wheezing was heard. After a 10 minute rest, the patient underwent a second exercise test, but was instructed to wear a jacket and long pants at the time. Exercise testing was performed for 12 minutes and the heart rate increased from 80 to 191 beats per minute. The baseline blood pressure was 140/80 and during the exercise, the blood pressure was 144/70. The patient again denied pruritus or swelling either during or after the exercise test. No wheezing was observed. When the sphygmomanometer cuff was removed, some urticaria at the site was observed, consistent with a dermographic effect. No hives or angioedema were noted. Another plasma histamine level was obtained immediately after the exercise test.

The baseline plasma histamine level was 0.54 ng/mL(normal range 1 ng/mL or less). After the first exercise test, the plasma histamine was 0.8 ng/mL. After the second exercise test, the plasma histamine level was 3.01 ng/mL(elevated).

Subsequently over the next 2 years, the patient stopped playing soccer, and discontinued fexofenadine, as he felt this did not prevent swelling episodes. He developed some spontaneous hives in the axillary areas when he stopped taking fexofenadine. He discontinued all other medication as well. He continued to have intermittent facial swelling episodes with certain types of exercise such as jogging and catching baseballs. He did not feel that heat was always associated with these episodes, and claimed that certain strenuous exercises such as mountain biking did not provoke swellings.

DISCUSSION

Exercise associated acute allergic syndromes primarily relate to 2 disease entities, exercise induced anaphylaxis and cholinergic urticaria. Although cholinergic urticaria does not typically manifest with anaphylaxis or angioedema, laboratory inductions of cholinergic urticaria (using maneuvers that raise body temperature) in patients with this disorder have resulted in systemic symptoms and mediator release. The case herein described showed a significant rise in histamine levels after an exercise test was performed with heavy clothing. Exercise challenge has been used to study patients with exercise induced allergic disease. Kaplan and colleagues ([3]) described a positive methacholine skin test result in a patient who had a positive exercise challenge, who was felt to thus have cholinergic urticaria. Casale and colleagues ([4]) showed that passively heating to raise core body temperature resulted in anaphylactic symptoms and plasma histamine elevations only in a patient felt to have cholinergic urticaria and not in a patient with exercise induced anaphylaxis. As both patients studied also had positive exercise challenges, the work by Casale and colleagues would suggest that a positive exercise challenge does not distinguish between cholinergic urticaria and exercise-induced anaphylaxis. Sheffer and colleagues ([5]) demonstrated that some but not all patients with exercise induced anaphylaxis had symptoms and histamine elevations when challenged with treadmill running with an occlusive suit for 5-17 minutes. These patients were deemed to have cholinergic urticaria. Lawrence and colleagues ([6]) challenged three patients with exercise after a hot bath who developed angioedema and urticaria as well as increased blood smooth muscle biological activity, measured using a bio-assay, which they deemed as evidence for cholinergic urticaria.

In the patient herein described, a threshold for mediator release was apparently achieved even in the absence of acute allergic symptoms or signs. The time course suggests that significant histamine release was not achieved until exercise was performed with insulating clothing. Thus the diagnosis of cholinergic urticaria was suggested. However, it is conceivable that mediator release began during the first exercise challenge and was potentiated by the exercise alone from the second challenge, and may not have related to the presence of insulating clothing. A sequential challenge with 2 exercise tests in the absence of insulating clothing would have been helpful in determining the relative role of heat as a provocative stimulus in the patient's condition. However, this was not performed. The treatment of exercise associated allergic disease is primarily supportive except in patients with food associated exercise induced anaphylaxis. This patient had mediator release with exercise despite having had no food for the prior 6 hours, and had no demonstrable IgE to relevant plant derived allergens tested. Mediator release occurred in the face of treatment with a leukotriene receptor blocking medication and combined H1 and H2 receptor blockade. Historically the patient's symptoms were not controlled by these medications. Kaplan and colleagues([3]) described a patient with exercise induced allergic disease who progressively increased daily exercise and was able to achieve less exercise associated symptoms and had less histamine release with this regimen.

This case demonstrates that exercise challenge can help document mediator release even in the absence of symptoms or signs of anaphylaxis. Thus in future cases, physicians could monitor improvement with treatment regimen(s) without having to provoke troubling symptoms for the

patient, using plasma histamine as a marker. Plasma histamine levels correlate better with acute allergic manifestations than serum tryptase levels ($_7$). However they require immediate separation of plasma to avoid contamination by spontaneously degranulating basophils in blood samples that have not had plasma separation.

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