

CASE REPORT

Food-dependent exercise-induced anaphylaxis with a high level of plasma noradrenaline

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ABSTRACT

Ingesting certain foods sometimes triggers anaphylaxis when followed by exercise (food-dependent exercise-induced anaphylaxis, FDEIA). Specific food-induced mucocutaneous urticaria may also progress to anaphylaxis (oral allergy syndrome, OAS). A positive skin test and/or radioallergosorbent test (RAST) to the foods suggest involvement of immunoglobulin (Ig)E-anaphylaxis in both disorders. The triggering foods and initial target organs are usually different in each case. In the present study, a 32-year-old male reported dyspnea accompanied by wheals, and symptoms of low blood pressure while walking after eating Chinese noodles and donuts. He also reported uncomfortable sensations in his mouth and throat after ingesting melon. Exercise challenge tests were administered. Serum histamine, plasma adrenaline, noradrenaline and dopamine were measured pre- and post-test. No symptoms were induced by exercise or by the ingestion of any single food item before exercise. However, numerous wheals appeared when exercise followed the combined ingestion of foods. Likewise, the sequence of eating pancakes and then exercising resulted in numerous wheals and anaphylaxis. Olopatadine hydrochloride and ketotifen fumarate completely inhibited this anaphylaxis. The skin prick tests resulted in fruit-induced erythema and wheals. The results of these tests with wheat, butter and sugar were negative, and no symptoms were induced by the exercise test after ingestion of watermelon, melon or apple. The anaphylactoid symptoms were accompanied by a significant increase of plasma noradrenaline. In this case, not only wheat, but sugar and butter may induce the onset of FDEIA. There was no significant correlation between the intensity of the symptoms and the serum histamine levels in the present case. Noradrenaline may be involved in the onset of FDEIA, since noradrenaline may selectively inhibit T-helper (Th)1 functions while favoring Th2 responses. The tests showed no cross-reactivity between the causative foods of OAS and FDEIA, indicating that the mechanisms of onset are different between them.

Key words: catecholamines, food-dependent exercise-induced anaphylaxis, histamine, oral allergy syndrome.

INTRODUCTION

In certain individuals, exercising after ingesting certain foods sometimes triggers anaphylaxis (food-dependent exercise-induced anaphylaxis, FDEIA). Specific food-induced mucocutaneous urticaria may also progress to anaphylaxis (oral allergy syndrome, OAS). A positive skin test and/or radioallergosorbent test (RAST) to the foods suggest

involvement of immunoglobulin (Ig)E-anaphylaxis in both disorders. However, the triggering foods are usually different in each, and FDEIA requires physical exertion, whereas OAS does not. The initial target organs are also different in each disorder: FDEIA first manifests in the skin while OAS appears in the oral mucosa.

The mechanism underlying FDEIA has been studied recently. It has been reported that ω -5 gliadin is a

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major allergen involved in wheat-dependent, exercise-induced anaphylaxis (WDEIA).¹ Further, ω -5 gliadin is reported to have IgE-binding ability.² In this study, we report a case of FDEIA in which the symptoms were provoked not only by wheat but also by wheat and butter and/or sugar after exercise and the anaphylactoid symptoms resulted in increased plasma noradrenaline levels.

CASE REPORT

A 32-year-old male had sought medical attention several times during the previous 3 years for dyspnea accompanied by wheals, which appeared during physical exertion immediately following the ingestion of certain foods. In April 2001, the patient appeared at the emergency outpatient clinic for treatment after reporting similar symptoms while walking after ingesting Chinese noodles and donuts. His blood pressure was low. The patient also reported feeling uncomfortable sensations in his mouth and throat during the previous 5 years whenever he ingested melon and watermelon. The patient did not have any severe symptoms like those of anaphylaxis. The patient's serum IgE level is shown in Table 1.

Challenge tests were performed with the patient's informed consent. Exercise challenge was administered using the standard Bruce protocol.³ Heart rate, blood pressure and electrocardiogram were monitored. Food was ingested 30 min before exercise and antihistamines were administered 3 h pre-test, as needed. The intensity of the symptoms was rated as follows: (–) no symptom; (+) wheal; and

(2+) wheal and anaphylactoid symptoms (e.g. dyspnea and falling of blood pressure). The amount of wheat, sugar and butter was 200 g, 50 g and 100 g respectively, roughly equivalent to the quantities in a serving of pancakes.

A venous line was maintained before and during the test. The patient stayed quiet 30 min after taking the food and then started the physical exertion. Blood was collected 10 min before and after physical exertion. The serum histamine was analyzed by radioimmunoassay (RIA).⁴ Plasma adrenaline, noradrenaline and dopamine were measured pre- and post-test using high-performance liquid chromatography (HPLC).⁵

No symptoms were induced by exercise or wheat, sugar or butter alone, followed by exercise. However, numerous wheals appeared when exercise followed the combined ingestion of wheat and sugar, wheat and butter, and wheat, sugar and butter (intensity of the symptoms, +). Eating a pancake, consisting of wheat, sugar and butter alone, induced no symptoms, but the sequence of eating the pancake first, then exercising, resulted in numerous wheals and anaphylaxis just after exercise (intensity of the symptoms, 2+). Olopatadine hydrochloride and ketotifen fumarate completely inhibited the anaphylaxis. Cetirizine hydrochloride and fexofenadine hydrochloride only partially inhibited the symptoms, while epinastine hydrochloride had zero inhibitory effect (Table 2).

In the skin prick tests, watermelon, melon, apple, kiwi fruit, peach, tomato, avocado and banana (as is) induced symptoms that were 3+, 2+, 2+, 2+, 2+, 2+, 3+ and 2+ in intensity, respectively, compared with 10 mg/mL histamine. The results of these tests with wheat, butter and sugar were negative, and no symptom was induced by the exercise test after ingestion of watermelon, melon or apple.

The intensity of the symptoms in the provocation tests was compared among the three groups. The combination of cake and exercise following administration of epinastine hydrochloride resulted in a 50-fold increase in histamine. However, histamine levels failed to show a similar increase in the combination of cake and exercise, as indicated in Table 2. Plasma noradrenaline levels increased drastically together with the appearance of severe clinical symptoms, wheals and anaphylaxis (intensity of the

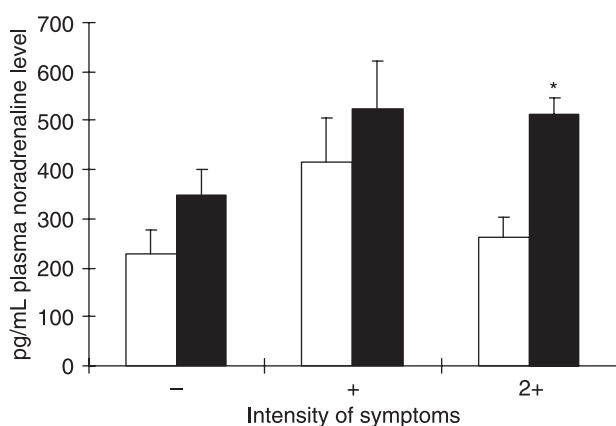
Table 1. Serum immunoglobulin (Ig)E level

Antigen	Ag-specific IgE (UA/mL)	Class
Orchard grass	0.85	2
Ragweed	0.35	1
Ceder	7.18	3
<i>Dermatophadoides pteronyssinus</i>	<0.34	0
<i>Dermatophadoides farinae</i>	<0.34	0
Mugwort	<0.34	0
Tomato	<0.34	0
Melon	<0.34	0
Gluten	<0.34	0

Total IgE (IU/mL), 50.

Table 2. Serum histamine level and intensity of symptoms before and after provocation test

Test groups	Histamine nmol/L		Intensity of symptoms
	Before test	After test	
Exercise alone	1.9	2.5	–
Olopatadine hydrochloride + pancakes + exercise	2.6	2.1	–
Ketotifen + pancakes + exercise	2.3	1.5	–
Wheat + butter + exercise	2.9	3.2	+
Cetirizine hydrochloride + pancakes + exercise	1.9	2.2	+
Fexofenadine + pancakes + exercise	3	9.3	+
Pancakes + exercise	1.4	2.6	2+
Epinastine hydrochloride + pancakes + exercise	0.6	31	2+

**Figure 1.** Mean $\pm$ SE of the plasma level of noradrenaline measured by high-performance liquid chromatography (HPLC) 10 min before (□) and after (■) tests; * $P < 0.05$ significant increase from before test.

symptoms, 2+). However, there was no significant increase in plasma noradrenaline levels in the absence of symptoms (intensity of the symptoms, –) or the presence of wheals (intensity of the symptoms, +) (Fig. 1). The other catecholamines examined, adrenaline and dopamine, showed no evidence of involvement (data not shown).

DISCUSSION

Exercise load is essential to WDEIA onset because exercise increases blood gliadin levels in WDEIA,² which, in turn, enhances the binding of antigens with their specific IgE antibodies on mast cells, or lowering the mast cell degranulation threshold. In this case, not only wheat but sugar and/or butter

may have induced the onset of FDEIA. Aihara *et al.* have reported a case in which anaphylaxis was induced by the combination of exercise and the ingestion of wheat and Japanese plum.⁶ In the present case, the wheat antigen might have been modified by the simultaneous ingestion of other foods to cause the onset of FDEIA.

There was no significant correlation between the intensity of the symptoms and the serum histamine levels in the present case. However, plasma noradrenaline levels increased significantly only when anaphylactoid symptoms were induced. Plasma adrenaline levels are known to increase during both anaphylactoid reactions⁷ and exercise. Noradrenaline may be involved in the onset of FDEIA, because noradrenaline selectively inhibits T-helper (Th)1 functions while favoring Th2 responses and humoral responses or acts directly on the cellular components of both cellular and humoral immunity.⁸

Blood was drawn 10 min before and after exercise. Because the full-blown wheals and anaphylactoid symptoms were already apparent when the blood samples were taken, the levels of serum histamine and plasma noradrenaline can be said to reflect the symptoms of FDEIA. This observation is of some importance, considering that the half-life of these substances is a few minutes and that the fixed 10 min periods pre- and post-exercise could show a fluctuation in their levels.

Food-dependent exercise-induced anaphylaxis and OAS are considered type I allergic reactions, but the tests showed no cross-reactivity between the causative foods of OAS and FDEIA, indicating that the mechanisms of onset are different between them.

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