

CASE REPORT

# Wheat-dependent, Exercise-induced Anaphylaxis: A Successful Case of Prevention with Ketotifen

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Food-dependent, exercise-induced anaphylaxis (FDEIA) is the triggering of anaphylaxis after ingestion of certain foods when followed by physical exercise. Symptoms vary from the typical generalized urticaria to severe allergic reactions. We report the case of a 20-year-old woman who had a 7-year history of recurrent wheals and dyspnea after ingesting several kinds of food (wheat, pork, and beef) along with physical exercise. Based on a provocation test, she was diagnosed with wheat-dependent, exercise-induced anaphylaxis. She was instructed to take 2 mg of ketotifen 2 hours before ingestion of wheat to prevent the symptoms, and subsequently the provocation test did not elicit wheals. We therefore prescribed ketotifen (1 mg twice a day). She has not had recurrent wheals or dyspnea for 6 months. We herein report an interesting case of wheat-dependent, exercise-induced anaphylaxis with successful prevention by ketotifen. (**Ann Dermatol 21(2) 203~205, 2009**)

**-Keywords-**

Food-dependent, exercise-induced anaphylaxis (FDEIA), Ketotifen, Wheat

## INTRODUCTION

Food-dependent exercise-induced anaphylaxis (FDEIA) is a subtype of exercise-induced anaphylaxis (EIA), which is characterized by the onset of anaphylaxis during or soon

after exercise when preceded by the ingestion of a causal food allergen. FDEIA is divided into two types. In some cases, specific kinds of food cause anaphylaxis when exercise follows ingestion, but are tolerated if not followed by exercise (specific FDEIA). In the other cases, those affected suffer from EIA after any meal followed by exercise, regardless of the food eaten (non-specific FDEIA)<sup>1</sup>. We herein report an interesting case of food-dependent, exercise-induced anaphylaxis caused specifically by wheat.

## CASE REPORT

A 20-year-old female sought medical attention several times during the previous 7 years for itching and dyspnea accompanied by wheals, which appeared during physical exertion immediately following the ingestion of certain foods. In 2000, she was admitted to the hospital for treatment of anaphylaxis while walking after ingesting a hamburger. She experienced the symptoms specifically while walking or running after ingesting pork, beef, and wheat-based foods, such as breads, noodles, and instant noodles. Her past medical and family histories were non-contributory. The physical examination revealed an otherwise healthy woman with non-specific skin lesions. A CBC, blood chemistries, and urine analysis were within normal limits. The CAP-RAST 6-item test (milk, peanut, wheat, fish, pork, and meat) was negative. On the MAST 40-item test, *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* had high scores, and on prick testing, *D. farinae* and *D. pteronyssinus* were strongly positive.

Challenge tests to pork, beef, and wheat were performed with the patient's informed consent. At first, food challenge tests without exercise were performed. She ingested 200 g of each food type without food additives and had a rest with the least amount of movement possible for 2

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**Fig. 1.** 1×2 cm wheals on the face and anterior chest.

hours. She did not develop any symptoms from these three kinds of food. Thereafter, the food challenge tests followed by exercise were performed. She ingested each food type 30 min before exercise and ran for 20 min on a treadmill test. The heart rate, blood pressure, and electrocardiogram were monitored while she was running. She developed wheals and flares on her face and chest 10 min after the wheat challenge test with exercise (Fig. 1). Since she had an urticarial reaction only in response to wheat, but not pork and beef, she was diagnosed with wheat-dependent, exercise-induced anaphylaxis.

She took 2 mg of ketotifen 2 hours before ingesting wheat to prevent the symptoms, and a subsequent provocation test did not result in hives. She was initially prescribed a 2 mg, twice daily dose of ketotifen; however, due to severe drowsiness, she is now taking 1 mg of ketotifen 2 hours before meals and has not had recurrent wheals or dyspnea for 6 months, indicating the direct role of ketotifen in the successful prevention of wheat-dependent, exercise-induced anaphylaxis.

## DISCUSSION

Maulitz et al<sup>2</sup> first reported a case of EIA in 1979 as a previously uninvestigated late allergic reaction to shellfish induced by exercise. Data for the incidence of FDEIA is limited. According to a large study in Japan, the incidence among students was estimated to be 0.012%<sup>3</sup>. FDEIA is most likely to appear between the 25 and 35 years of age<sup>4</sup>. These anaphylactic symptoms are usually induced by physical exercise after food ingestion, and most cases display these symptoms within 2 hours. The typical symptoms include skin manifestations, respiratory symptoms, abdominal pain, fatigue, and loss of consciousness. The skin manifestations include urticaria, erythema, and an-

gioedema<sup>5</sup>.

EIA has presented following all levels of physical exercise and during various physical activities. In susceptible persons, ingestion of certain foods or medications before physical activity may be a predisposing factor. Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) have been the most frequently involved medications for FDEIA, and only these drugs induced anaphylactic symptoms without physical activity<sup>6,7</sup>. Numerous foods, such as shellfish, shrimp, alcohol, tomatoes, cheese, celery, wheat, strawberries, peaches, and milk, have been noted as frequent causes of FDEIA<sup>1</sup>. Wheat and shrimp are the most common allergenic foods in Japan. In contrast, tomatoes are the most frequent cause in European countries<sup>7-9</sup>.

The mechanism of FDEIA is unknown, but it has been suspected that exercise triggers allergic reactions in patients who have low-grade type I allergies specific for certain foods<sup>1</sup>. Exercise enhances the degranulation of mast cells and the absorption of allergens from the gastrointestinal tract, so the plasma histamine level rises in patients with exercise-induced anaphylaxis<sup>10-12</sup>. Recently, there were some reports that omega-5 gliadin and high-molecular weight (HMW) glutenin, which are the proteins consisting of wheat, are the most common allergens involved in wheat-dependent, exercise-induced anaphylaxis (WDEIA)<sup>5,13-15</sup>.

A correct diagnosis of FDEIA is made on the basis of a careful and detailed history, especially regarding total food intake. A history of symptoms and observation of skin lesions with a passive warming test, such as a hot shower or a hot bath, help differentiate cholinergic urticaria, and an exercise provocation test on an empty stomach helps differentiate EIA. Skin prick tests and *in vitro* serum food-specific IgE assays provide some information on causative foods; however, a positive reaction on the skin prick test or positive values on *in vitro* serum food-specific

IgE assays do not necessarily indicate the causative foods<sup>1</sup>. In cases of FDEIA, a low level of IgE-mediated hyper-reactivity is most often detected. However, the skin prick test and the in vitro serum food-specific IgE assay could be all negative, as in this case. Therefore, a food challenge test followed by exercise is required for the confirmation of the diagnosis for FDEIA. Since some patients sometimes fail to develop clinical symptoms in the provocation test, a repeat provocation test may be necessary. In this case, we observed a positive reaction only in the challenge test to wheat, and we subsequently ruled out pork and beef as the causative allergen by repeat challenge tests.

The best method of treatment for FDEIA is avoidance. In specific FDEIA, patients should avoid the ingestion of the causative foods before exercising, and in non-specific FDEIA, patients should avoid exercise 1~6 hr after ingestion of common foods and avoid medications, such as NSAIDs and aspirin before exercising. Also, patients should carry an emergency kit, including antihistamines, corticosteroids, and epinephrine, especially when exercising. Antihistamines may be helpful in the treatment of FDEIA and may be useful in the prevention of urticaria or angioedema<sup>5</sup>. Ketotifen is an orally active tricyclic benzocyclo-heptathiophene derivative and thus may be a useful medication in the treatment and prevention of allergic responses<sup>16</sup>. Ketotifen is a potent H1 receptor antagonist which has properties of mast cell stabilization and anti-inflammatory capabilities. Ketotifen also has other anti-inflammatory properties, which include reduced eosinophilic chemotaxis in eosinophilia and diminished production of eotaxin and expression of CD29 in epithelial cells<sup>17</sup>. Previous reports have not reached a consensus on the efficacy of ketotifen in preventing EIA<sup>16-18</sup>. In the case reported herein, however, we observed that 1 mg of ketotifen 2 hours before wheat ingestion prevented FDEIA.

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