

Food-dependent exercise-induced anaphylaxis: a case related to the amount of food allergen ingested

Y. HANAKAWA, M. TOHYAMA, Y. SHIRAKATA, S. MURAKAMI AND K. HASHIMOTO

Department of Dermatology, Ehime University School of Medicine, Shigenobucho, Onsen-gun, Ehime 791-02, Japan

Accepted for publication 7 January 1998

Summary

A 24-year-old Japanese woman had suffered for 2 years from attacks of urticaria, dyspnoea and syncope associated with exercise after the ingestion of wheat. Specific IgE measurements revealed RAST class 2 for wheat and gluten (a major wheat protein), and class 3 for rye. Skin prick tests with wheat, bread, gluten and udon (a Japanese noodle made of wheat) were all positive. Food-dependent exercise-induced anaphylaxis (FDEIA) caused by wheat was suspected. Challenge tests with bread were performed. Exercise following ingestion of 64 g, but not 45 g, of bread induced generalized urticaria. Challenge tests with udon also triggered allergic reaction in a dose-dependent manner: 200 g, but not 100 g or 150 g, of udon elicited wealing and erythema with exercise. Ingestion of bread or udon alone failed to elicit any allergic reaction. This is the first case of FDEIA in which the dependence of the triggering allergic reaction on the amount of allergen ingested was clearly confirmed.

Exercise-induced anaphylaxis (EIA) is a form of physical allergy in which exercise precipitates attacks of anaphylaxis through mast cell release of mediators.^{1–3} In 1979, Maulitz and associates reported a case of EIA reaction that occurred only after the ingestion of shellfish.⁴ This syndrome was named food-dependent EIA (FDEIA).⁵ FDEIA is an unusual clinical syndrome of immediate allergic reaction requiring both ingestion of an allergenic food and exercise to induce anaphylaxis. However, the dependence of FDEIA induction on the amount of allergenic food ingested has not been well characterized. We report a case of FDEIA in which induction of an allergic response is dependent on the amount of wheat ingested.

Case report

A 24-year-old Japanese woman was admitted to our hospital with a history of recurrent generalized urticaria, dyspnoea and syncope. The initial episode of urticaria had occurred several minutes following her taking a hot bath after having eaten bread and fried eggs. She had experienced similar, more severe episodes, with dyspnoea and syncope, seven times over the following 2 years. These were precipitated by exercise: dancing, jogging and walking. She had taken no drugs

known to be associated with anaphylactoid reactions. She had no relevant past medical history. Her father reported a history of mackerel-induced urticaria. It was discovered that she had consumed wheat-containing foods and taken exercise before each episode, and FDEIA caused by wheat was suspected. Physical examination was normal. Laboratory studies including full blood count, serum electrolytes, liver function tests, creatinine, blood urea and nitrogen and total serum IgE were all normal.

Skin prick tests with various food allergens revealed weal and flare reactions to wheat, bread, udon (a Japanese wheat noodle) and gluten (a major wheat protein). Allergens, except gluten and udon, were obtained from Torii Pharmaceutical Co. Ltd, Tokyo, Japan, and gluten and udon were prepared according to Kushimoto and Aoki.⁶ Radio-allergosorbent testing (RAST) for specific IgE antibody revealed class 2 reactivity for wheat and gluten, and class 3 for rye.

To confirm the diagnosis of FDEIA, the patient underwent specific challenge tests. After 12 h fasting, she ingested 45 g of bread and took 20 min of bed rest, followed by exercise by taking a step on to a 30 cm high stool every 2 s for 10 min and a 10-min walk along a corridor. However, no allergic reaction was induced. The amount of bread was increased in the next challenge test. Ingestion of 64 g of bread, followed by exercise, induced wealing and erythema (Fig. 1).

Correspondence: Dr Koji Hashimoto. E-mail: hashik@m.ehime-u.ac.jp



Figure 1. Weals and erythema induced by the ingestion of 64 g of bread, followed by exercise.

Interestingly, cholinergic-like urticaria, namely small-sized weals (about 3–10 mm in diameter) on an erythematous base, was observed. Challenge tests with udon were also performed, and 200 g, but not 100 g or 150 g, of udon elicited wealing and erythema following exercise. The induction of FDEIA was clearly dependent on the amount of wheat ingested by the patient, and neither ingestion of wheat nor exercise alone would induce urticaria (Table 1).

Serum C3, C4, CH50 and plasma histamine levels were examined before and after the challenge test. Baseline levels were normal and no significant changes were observed following challenge.

Discussion

Some 234 cases of FDEIA have been reported in the English or Japanese literature. Among them, 154 patients had RAST examination or skin tests, and 150 patients showed a positive response to suspected food

Table 1. The relationship between the amount of food ingested and weal elicitation

Food	Amount	Eating only	Eating and exercise
Bread	45 g	–	–
Bread	64 g	–	+
Udon	100 g	–	–
Udon	150 g	–	–
Udon	200 g	–	+

–, no weal elicitation; +, weal elicitation.

allergens in at least one determination. Challenge tests were performed in 81 of these 150 patients. Twenty-nine of 81 (36%) patients failed to develop clinical symptoms.^{7–9} Suko *et al.* proposed that insufficient amounts of food allergen ingested or inappropriate exercise could be the cause of false-negative clinical responses to challenge tests.¹⁰ However, the dependence of FDEIA induction on the amount of food allergen ingested has not been clearly confirmed in the 234 cases described. We showed that induction of FDEIA in our patient is dependent on the amount of wheat allergen ingested. As the induction of an allergic reaction was confirmed using two different wheat-containing foods, bread and udon, these observations are corroborative. An insufficient amount of food allergen ingested or subthreshold exercise levels could be possible reasons for the unsuccessful challenge tests noted in several previous reports. However, it remains to be resolved whether induction of FDEIA by allergenic food is a dose-dependent response or shows a discrete threshold, i.e. an all or none response.

Skin prick tests indicated that gluten, a major (approximately 80%) constituent of wheat, was likely to be responsible for the FDEIA in this case. Kushimoto and Aoki found that peptides from pepsin-digested gluten caused a positive skin response in prick tests more effectively than non-digested gluten, while trypsin digestion of gluten abolished the ability of the allergen to induce a positive skin response.⁶ One possible explanation for the induction of FDEIA is that exercise immediately after consuming the food allergen causes incomplete digestion and subsequent production of excessive amounts of allergenic peptides.

It is of interest that cholinergic-like urticaria, namely small-sized weals on an erythematous base, was observed in the challenge test. This raises the question of whether our patient had cholinergic urticaria. However, we excluded cholinergic urticaria for the following reasons: first, the weals (about 3–10 mm in diameter)

were bigger than those seen in cholinergic urticaria. Secondly, the weals rapidly progressed into giant urticaria. It should be noted that the patient had had giant urticaria in all the episodes. Thirdly, warm stimuli, such as a hot Japanese-style bath, by themselves did not elicit urticaria. Kidd *et al.* reported one patient who had FDEIA with similar symptoms.⁵ This indicates that some patients with FDEIA manifest cholinergic-like urticaria as a cutaneous symptom.

Zuberbier *et al.* reported another interesting patient, in whom food intake in combination with a rise in body temperature caused, for example, by taking a hot bath, induced angio-oedema.¹¹ However, there are several differences between this patient and the present case. First, their patient had no extracutaneous symptoms. Secondly, their patient had no food allergy, as shown by negative results in prick tests and RAST. However, the relationship between a rise in body temperature and digestive tract function should be characterized, because a rise in body temperature, with or without exercise, may cause incomplete digestion and subsequent production of excessive amounts of allergenic peptides, as discussed above.

References

- 1 Sheffer AL, Frank A. Exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1980; **66**: 106–11.
- 2 Sheffer AL, Soter NA, Mcfadden ER *et al.* Exercise-induced anaphylaxis: a distinct form of physical allergy. *J Allergy Clin Immunol* 1983; **71**: 311–16.
- 3 Sheffer AL, Tong AKF, Murphy GF. Exercise-induced anaphylaxis. a serious form of physical allergy. *J Allergy Clin Immunol* 1985; **75**: 497–84.
- 4 Maulitz RM, Pratt DS, Schocket AL. Exercise-induced anaphylactic reaction to shellfish. *J Allergy Clin Immunol* 1979; **63**: 433–4.
- 5 Kidd JM, Cohen SH, Sosman AJ *et al.* Food-dependent exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1983; **71**: 407–11.
- 6 Kushimoto H, Aoki T. Masked type 1 wheat allergy. *Arch Dermatol* 1985; **121**: 355–60.
- 7 Romano A, Di Fonso M, Giuffreda F *et al.* Diagnostic work-up for food-dependent, exercise-induced anaphylaxis. *Allergy* 1995; **50**: 817–24.
- 8 Dohi M, Suko M, Sugiyama H *et al.* Food-dependent, exercise-induced anaphylaxis: a study on 11 Japanese cases. *J Allergy Clin Immunol* 1991; **87**: 34–40.
- 9 Okazaki M, Kitani H, Mifune T *et al.* Food-dependent exercise-induced anaphylaxis. *Intern Med* 1992; **31**: 1052–5.
- 10 Suko M, Toyohira H, Miyamoto A *et al.* Exercise induced anaphylaxis. *Allergy Prac* 1989; **9**: 37–41 (in Japanese).
- 11 Zuberbier T, Bohm M, Czarnetzki BM *et al.* Food intake in combination with a rise in body temperature: a newly identified cause of angioedema. *J Allergy Clin Immunol* 1993; **91**: 1226–7.