

Aspirin enhances the induction of type I allergic symptoms when combined with food and exercise in patients with food-dependent exercise-induced anaphylaxis

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Summary

We examined the effect of aspirin as a substitute for exercise in inducing urticaria/anaphylaxis in three patients with food-dependent exercise-induced anaphylaxis (FDEIA). Two of the patients had specific IgE antibodies to wheat and the other had antibodies to shrimp. Administration of aspirin before ingestion of food allergens induced urticaria in one patient and urticaria and hypotension in another, while aspirin alone or food alone elicited no response. The third patient developed urticaria only when he took all three items, i.e. aspirin, food and additional exercise, whereas provocation with any one or two of these did not induce any symptoms. These findings suggest that aspirin upregulates type I allergic responses to food in patients with FDEIA, and further shows that aspirin synergizes with exercise to provoke symptoms of FDEIA. This is the first report of a synergistic effect of aspirin in inducing urticaria/anaphylaxis, which was confirmed using challenge tests in patients with FDEIA.

Key words: aspirin, food-dependent exercise-induced anaphylaxis

Food-dependent exercise-induced anaphylaxis (FDEIA) is characterized by anaphylactic symptoms such as weals, angio-oedema, wheezing, dyspnoea and loss of consciousness after eating certain foods and then exercising.¹ The mechanism of FDEIA is so far unclear, but it has been speculated that exercise triggers allergic reactions in individuals who have low-grade type I allergies specific for certain foods.²

Aspirin is another well-known cause of urticaria and anaphylaxis in certain individuals,³ but to date the mechanism of aspirin-induced urticaria has not been clarified. Dohi *et al.*⁴ recently reported two patients with FDEIA who had a history of taking aspirin just before the onset of symptoms. However, the effect of aspirin in provoking the symptoms of FDEIA has not yet been identified. We report three patients with FDEIA and show that aspirin can substitute for, or synergize with, exercise in inducing urticaria/anaphylaxis caused by foods in those patients.

Case reports

Patient 1

A 34-year-old-man described a 6-year history of occasional urticaria and loss of consciousness, especially when he exercised after meals. He used to take aspirin because of frequent headaches, but we could not confirm whether he took aspirin before the attacks. Blood cell counts, liver function tests and total IgE (214 IU mL⁻¹) were normal. Radioallergosorbent testing (RAST) for specific IgE revealed grade 3 reactivity to wheat but no reaction to egg white, egg yolk, pork, beef, chicken, crab, shrimp, rice or soya bean. Intradermal skin testing to a series of 20 food allergens confirmed his positive response to wheat but not to any other allergens.

Because it has been shown that gluten is the major allergen in patients who develop FDEIA after taking wheat,⁵ gluten 40 g was administered as a substitute for wheat, resulting in induction of a few moderate weals. The provocation of ingesting gluten followed by exercise after 30 min provoked numerous weals

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without anaphylaxis. To test the effect of aspirin in triggering anaphylaxis, we administered aspirin 500 mg 30 min before challenge with gluten or exercise. Administration of aspirin followed by gluten challenge but without exercise induced anaphylactic symptoms, including general fatigue, hypotension and slight dyspnoea in addition to weals. Aspirin or exercise alone, or the combination of aspirin and exercise, did not provoke any symptoms. The combination of aspirin, gluten and exercise was not tested because of the possible risk of severe symptoms.

Patient 2

A 48-year-old man first developed urticaria at age 39 years. Since then he frequently developed many weals and sometimes experienced anaphylaxis, including loss of consciousness associated with abdominal pain, vomiting and dyspnoea, especially during exercise after eating. Blood cell counts, liver function tests and total IgE (74 IU mL^{-1}) were normal. Specific IgE determination revealed grade 2 IgE to wheat and no reactivity to soya bean, crab, shrimp, rice, cuttlefish, strawberry, apple and cheese. Intradermal skin testing did not show a positive response to wheat or to any other of the 40 food antigens tested.

Gluten 25 g alone did not provoke any symptoms, but ingestion of gluten followed by exercise provoked numerous weals, confirming this as a case of FDEIA. Based on our experience with patient 1, we tested whether aspirin could provoke his symptoms. Provocation with food, aspirin or exercise alone resulted in no evident symptoms. To our surprise, he developed an urticarial rash after taking aspirin and ingesting gluten, even without exercising, even though he had never previously taken aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs). Further provocation testing revealed that the combination of aspirin

500 mg, gluten and exercise resulted in the induction of much more severe symptoms, including numerous weals accompanied by malaise and a drop in blood pressure. Aspirin with exercise did not provoke any symptoms.

Patient 3

An 18-year-old man first developed anaphylaxis at the age of 15 years, with angio-oedema of his tongue and lips, and weals over his entire body, during running, but it was uncertain whether he had eaten foods before the anaphylactic attack. He had recently experienced a similar episode during running after eating lunch, which included fried shrimp. Blood cell counts, liver function tests and total IgE (182 IU mL^{-1}) were normal. RAST for IgE revealed grade 1 reactivity to shrimp and grade 2 to crab, but no reactivity to wheat, egg white, egg yolk, milk, pork, beef, chicken, cuttlefish, octopus or horse mackerel. Intradermal skin tests confirmed positive responses for shrimp and crab.

Next, we examined whether aspirin could induce his symptoms. Provocation tests with the combination of aspirin, a head of shrimp and subsequent exercise induced a number of weals. None of the other foods, including crab and gluten, provoked any symptoms even after loading with both aspirin and exercise, and neither aspirin nor exercise alone induced any symptoms.

The results of provocation tests in these three patients are summarized in Table 1.

Discussion

FDEIA was first reported by Maulitz *et al.* in 1979,² when they described a 31-year-old man who developed anaphylaxis during long-distance running after eating shellfish. Since then, numerous foods have been

Table 1. Summary of the characteristics of the three patients

Patient no.	Age (years)/sex	Responsible food	Skin test/IgE RAST	Provocation test					
				Food alone	Exercise alone	Aspirin alone	Food+ exercise	Aspirin+ food	Aspirin+ food+ exercise
1	34/M	Wheat	Wheat	Minimal urticaria	None	None	Urticaria	Systemic symptoms*	ND
2	48/M	Wheat	Wheat	None	None	None	Urticaria	Urticaria	Systemic symptoms
3	18/M	Shrimp	Shrimp, crab	None	None	None	None	None	Urticaria

RAST, radioallergosorbent testing; ND, not done. *Generalized urticaria, hypotension, dyspnoea, fatigue.

implicated as causes of FDEIA, including wheat, raw celery, shellfish, cabbage, peaches, grapes, chicken, hazelnuts and apples.⁶ Two of our patients had allergies to wheat and the other was allergic to shrimp. According to references reporting 125 cases of FDEIA in Japanese subjects, the responsible food determined most frequently is wheat (70 cases) followed by shrimp (34 cases). This tendency is quite different from other countries, where a variety of foods has been identified as allergens.⁶

The major allergen for a type I allergic reaction to wheat has been reported to be gluten, which is the chief component of wheat protein.⁴ Recently, γ -gliadin-like gliadin in gluten has been shown to be the major antigen of wheat.^{7,8} Interestingly, the antigenicity of gluten in patients with FDEIA was shown to increase when gluten was digested with pepsin, but decreased when digested with trypsin.⁵ This suggests that the antigenicity of gluten could be enhanced in the stomach and attenuated in the duodenum. Based on that result, Palosuo *et al.*⁸ hypothesized that exercise may induce an increase in mucosal absorption of food peptides, including pepsin-digested gluten, in the gut, resulting in IgE-mediated allergic reactions in sensitized subjects.

Other investigators have hypothesized that FDEIA could be a subtype of exercise-induced anaphylaxis (EIA), where exercise is the major factor for the development of FDEIA.⁹ A more credible hypothesis is that an IgE-mediated type I allergic reaction to food is the essential part of this disease and that exercise is just a triggering factor.¹⁰ In fact, RAST for IgE and skin testing are positive for causal foods in most patients with FDEIA. It is therefore likely that IgE-dependent mast cell degranulation plays a major role in the aetiology of this disorder. The combination of food and exercise significantly enhances the skin weal response to compound 48/80 but not to histamine, indicating that the combination can lower the threshold for the degranulation of mast cells.¹¹ These results suggest that exercise may act through two different pathways in modulating the potential of mast cell degranulation: (i) exercise may upregulate intestinal absorption, resulting in an increase in the amount of food antigens with high antigenicity in the circulating blood, and (ii) exercise itself may activate mast cells in combination with IgE cross-linking through an unknown mechanism.

Aspirin seems to play an important role in inducing symptoms of FDEIA as well as EIA. There have been several reports showing the relationship between

aspirin and FDEIA/EIA.^{1,10,12–16} Dohi *et al.*⁴ reported two patients with FDEIA who had a history of taking aspirin before their symptoms were provoked, although the study did not confirm the effect of aspirin in their cases. Ours is the first report that confirms the effect of aspirin in the induction of anaphylactic symptoms by food. It is of interest that the combination of food and aspirin, even without exercise, could induce anaphylaxis in two of our patients, despite the fact that one of them had never been suspected of having FDEIA symptoms induced by NSAIDs. Whether aspirin plus food allergens can induce anaphylaxis in other FDEIA patients needs to be determined in the future.

A different viewpoint in considering the present two cases is how and why urticaria/anaphylaxis was induced by the combination of aspirin and food without exercise, even though no symptoms were induced by either item alone (Table 1). Aspirin itself is a well-known trigger of urticaria/anaphylaxis in sensitive individuals,³ and other acidic NSAIDs, such as indomethacin, ibuprofen and diclofenac sodium, can also induce urticaria/anaphylaxis in those who have aspirin sensitivity.¹⁷ There are no common cross-reactive structures among these drugs, and skin testing to these drugs usually fails to show any positive responses. Furthermore, subjects having IgE antibodies for aspirin have rarely been found,¹⁸ with a few exceptions.¹⁹ It is therefore believed that aspirin-induced anaphylaxis (AIA) is not usually provoked by IgE-mediated type I allergy to aspirin or other NSAIDs.²⁰ Aspirin inhibits cyclooxygenase function in the arachidonic acid cascade, which results in a decrease of prostaglandin synthesis and an increase of leukotriene synthesis.²¹ Increased leukotriene levels may cause the symptoms of AIA. However, it is controversial whether leukotriene receptor antagonists are effective²² or ineffective²³ in inhibiting urticaria in aspirin-sensitive individuals. It is thus unclear whether or not increased leukotrienes play a major role in AIA. Aspirin and other NSAIDs have been shown to augment allergic histamine release from human leucocytes under conditions when an allergen is present.²⁴ This *in vitro* evidence is compatible with the results of this study, and the sum of the evidence strongly supports the idea that aspirin and NSAIDs upregulate type I allergic responses to foods in certain individuals.

In conclusion, this study on three patients with FDEIA suggests that not only exercise but also aspirin can modulate the development of immediate-type hypersensitivity to foods. A better understanding of

the role of aspirin in FDEIA may contribute to symptom control.

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