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REVIEW ARTICLE

Food-Dependent Exercise-Induced Anaphylaxis—Importance of Omega-5 Gliadin and HMW-Glutenin as Causative Antigens for Wheat-Dependent Exercise-Induced Anaphylaxis—

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ABSTRACT

Food-dependent exercise-induced anaphylaxis (FDEIA) is a special form of food allergy where a food-intake alone does not induce any symptoms. However, allergic symptoms are elicited when triggering factors such as exercise or aspirin-intake are added after ingestion of the causative food. The most frequent causative foodstuff in Japan is wheat. The triggering factors, both exercise and aspirin-intake, facilitate allergen absorption from the gastrointestinal tract, resulting in allergic symptoms in the patients with wheat-dependent exercise-induced anaphylaxis (WDEIA). Analysis using purified wheat proteins revealed that approximately 80% of the patients with WDEIA have IgE reacting to omega-5 gliadin and the remaining of the patients to high molecular weight glutenin (HMW-glutenin). Simultaneous measurement of specific IgE to omega-5 gliadin and HMW-glutenin was found to be highly useful in diagnosing WDEIA compared with the routine diagnostic system for wheat.

KEY WORDS

allergen, anaphylaxis, exercise, gliadin, wheat

INTRODUCTION

Food allergy is an IgE-mediated immediate-type reaction including a series of symptoms elicited after ingestion of food. The allergic response changes with age: immediate-type reaction and atopic dermatitis are common in infants, but food-dependent exercise-induced anaphylaxis (FDEIA) is frequent in adolescence and adults. FDEIA is a peculiar form of food allergy where a food-intake alone does not induce any symptoms. However allergic symptoms are elicited when triggering factors such as exercise are added after ingestion of the causative food. The symptoms appear usually on skin, mucous membrane, respiratory tract, and gastrointestinal tracts, and as anaphylaxis at a high incidence. Elicitation of the allergic symptoms is known to be dependent on amount of the food ingested.[1] Combination of food intake was necessary in some cases of FDEIA in provoking their symptoms.[2,3] In many case reports strenuous exercise, such as playing basketball and tennis or running, triggered anaphylaxis after ingesting specific food(s).[4-6] However, milder exercise often induced the symptoms. One patient was reported who required exercise before eating food to induce the symptoms.[4] Triggering factors in FDEIA includes the patient's general condition, drugs, alcohol, and atmospheric and seasonal conditions in addition to ex-

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Table 1 Triggering factors in FDEIA

Triggering factors	References
Foods (amounts, sort and combination)	1-3
Exercise (strength, type of exercise, duration and timing after meal)	4-6
General conditions (fatigue, sleep, common cold, stress, menstruation)	6-8
Drugs (aspirin, NSAIDs)	6, 9, 10
Atmospheric condition/seasonal	7
Alcohol	3

ercise as listed in Table 1. Fatigue, cold, and lack of sleep appeared to affect the development of the anaphylactic symptoms.[6] Some cases of FDEIA induced only in winter were described.[7] There have also been some cases in which a menstrual cycle affected the onset of FDEIA.[6,8] Aspirin intake has been well-documented to induce symptoms or to provoke more severe symptoms compared with symptoms without aspirin intake.[6,9,10] Aspirin also induces symptoms in combination with food ingestion even without exercise challenge.[10]

CAUSATIVE FOODS AND ALLERGENS RESPONSIBLE FOR FDEIA

Various kind of foods appear to be responsible for FDEIA, including shellfish,[6,9,11-13] wheat products,[2,6,7,9,10,13,14] vegetables,[3,13,15,16] fruits,[6,13,17] nuts,[13] egg,[13,18] mushrooms,[19] corn,[13,20] garlic,[13] pork/beef,[13] rice,[13] and cows milk.[8] A recent review indicates that the foodstuffs involved in FDEIA are characteristic in Japan.[21] In European countries, vegetables are the most common food allergens. Of these, tomatoes were found to be the most frequent. However, in Japan, wheat is the most frequent causative food and accounts for approximately 60% of the total cases.

Wheat gluten has been speculated as a causative protein for wheat-dependent exercise-induced anaphylaxis (WDEIA).[5] As a result of increasing numbers patients with WDEIA, wheat allergens have been intensively investigated.[22-24] Wheat protein is fractionated into salt-insoluble protein and salt-soluble non-gluten proteins. The latter consisted of water-soluble albumins and water-insoluble globulins. The former are called gluten and can be fractionated into two further categories of proteins in according to solubility in 70% ethanol. The ethanol-soluble proteins are named gliadins and the ethanol-insoluble proteins are glutenins. Omega-5 gliadin has been recently identified as a major allergen in WDEIA.[22,23] Analysis using a panel of purified gliadins and glutenins revealed that approximately 80% of the patients with WDEIA have IgE antibodies reacting to omega-5 gliadin and the remainder patients to high molecular weight glutenin (HMW-glutenin).[24] When IgE-binding epitopes were investigated using sera of WDEIA patients, four epitopes consisting seven amino acids, QQIPQQQ, QQFPQQQ, QQSPEQQ and QQSPQQQ, were found to be dominant epitopes in omega-5 gliadin, and three epitopes QQPGQ, QQPGQGQQ and QQSGQGQ were identified in HMW glutenin.[24,25] Mutational analysis of the QQIPQQQ and QQFPQQQ peptides indicated that five common amino acids at position 1 (Q), 4 (P), 5 (Q), 6 (Q) and 7 (Q) were critical for IgE-binding in omega-5 gliadin.[24]

USEFUL MEASUREMENT OF OMEGA-5 GLIADIN-SPECIFIC IGE IN THE PATIENTS WITH WDEIA

An enzymatic immunoassay system is a standardized procedure to detect allergen-specific IgE such as CAP-FEIA (ImmunoCAP, Phadia, Sweden) and now widely used for the diagnosis of food allergy. Detection of food-specific IgE concentrations has been reported to be useful in predicting clinical reactivity in egg, milk, peanut, and fish allergy.[26,27] Measurement of gluten-specific IgE as well as wheat-specific IgE is possible in the diagnosis of WDEIA using the ImmunoCAP, however more than 50% of patients with definite WDEIA are negative using these tests, indicating that the patients with WDEIA have very low levels of allergen-specific IgE in their sera (Table 2). In addition, a considerable number of the patients with atopic dermatitis (AD) have positive CAP scores for gluten as well as wheat, although the patients have not experienced episode of immediate-type allergic reactions after ingestion of wheat products (Table 2). Thus, the measurement of food-specific IgE using the ImmunoCAP is not a satisfactory tool for diagnosis of FDEIA.

Recently, recombinant food allergens, which are consistent in quality, have been produced and tried to apply for diagnosis in many food allergies.[28,29] Measurement of specific IgE to omega-5 gliadin and HMW-glutenin was found to be highly useful in diagnosing WDEIA when compared with the routine diagnostic ImmunoCAP for wheat and gluten.[30-32] As shown in Table 1, 82.0% (32/39) of the patients with WDEIA were found to have IgE reacting to recombinant omega-5 gliadin and 92.3% (36/39) of the patients were positive in combination of the recombinant omega-5 gliadin-specific IgE test and the recombinant HMW-glutenin-specific IgE test, whereas

Table 2 Positive rate of ω-5 gliadin-specific IgE and HMW glutenin-specific IgE measurement in the patients with WDEIA and atopic dermatitis (AD)

CAP-FEIA	WDEIA† (*n* = 39)	AD‡ (*n* = 16)	Healthy (*n* = 12)
	%	%	%
Wheat	41.0	87.5	0
Gluten	43.5	18.7	0
Wheat and/or gluten	51.3	87.5	0
ω-5 gliadin	82.0	0.0	0
HMW-glutenin	12.8	12.5	0
ω-5 gliadin and/or HMW-glutenin	92.3	12.5	0

†Positive rate was determined as specific IgE (kUa/L) ≥ 0.7.

‡AD patients had positive IgE antibodies to wheat ≥ 0.34 (kUa/L) but no episodes of of immediate-type allergic reactions.

Table 3 Age associated positive rates of recombinant ω-5 gliadin-specific IgE in the patients with WDEIA

Group	Age	*n* (f/m)	Positive rates of CAP-FEIA (%)		
			Wheat	Gluten	ω-5 gliadin
1	under 20	13 (2/11)	38.4	46.1	46.1
2	20-30	14 (7/7)	35.7	50.0	92.8
3	over 30	28 (11/17)	40.7	47.6	92.8
Total		55 (20/35)	40.0	47.3	81.8

gluten- and wheat-specific IgE tests positively recognized only 43.5% (17/39) and 41.0% (16/39) of these patients, respectively. In addition, specific IgE values to the recombinant allergen were much higher than that to gluten in most patients with WDEIA, indicating a higher capability of the recombinant allergen on the ImmunoCAP to detect allergen-specific IgE.[31] This is due to higher content of IgE-binding epitopes in the recombinant allergen molecules, since gluten contains only 5% of omega-5 gliadin and 9% of HMW-glutenin. When the patients with AD who had specific IgE antibodies to wheat but no obvious allergic reactions to wheat products were tested using the ImmunoCAP with recombinant proteins, positive rates were markedly decreased from 87.5% for gluten to 0% for omega-5 gliadin and 12.5% for HMW-glutenin, indicating higher specificity of the tests (Table 2).

The positive rate of the omega-5 gliadin-specific IgE was rather specific to the adult-patients with WDEIA as shown in Table 3. In the group of the aged patients with WDEIA, the test identified 92.8% of the patients positively, whereas the test only 46.1% of the children with WDEIA. On the other hand, most of the children negative to the omega-5 gliadin-specific IgE had specific IgE to the HMW-glutenin. These observations were further confirmed in the European patients with WDEIA using the omega-5 gliadin ImmunoCAP.[33]

Measurement of specific IgE to omega-5 gliadin was also useful in identifying the AD children who have allergic symptoms against wheat products.[34] The mean concentration of serum IgE specific to omega-5-gliadin in the children with wheat allergy was significantly higher than those in children with no wheat allergy. In addition, children reacting with severe symptoms upon wheat-challenge tests had significantly increased levels of serum omega-5 gliadin-specific IgE compared to children with moderate, mild or no symptoms.[34] In contrast, recent studies in German and American children show that omega-5 gliadin-specific IgE antibodies did not correlate with the outcomes of oral food challenges in wheat-sensitized children with suspected wheat allergy.[35] These results suggest that wheat allergens need to be further investigated in the children with wheat allergy.

MECHANISMS ELICITING ALLERGIC SYMPTOMS IN FDEIA

WDEIA is considered to be IgE-mediated hypersensitivity to wheat allergens, because IgE antibodies against the wheat allergens are detected in their sera using recombinant wheat proteins in the most patients with WDEIA.[31] The mechanisms by which exercise induces the reaction have been controversial. A case of WDEIA, in which pretreatment with sodium bicarbonate inhibits the reappearance of anaphylactic symptoms as well as elevation in plasma histamine

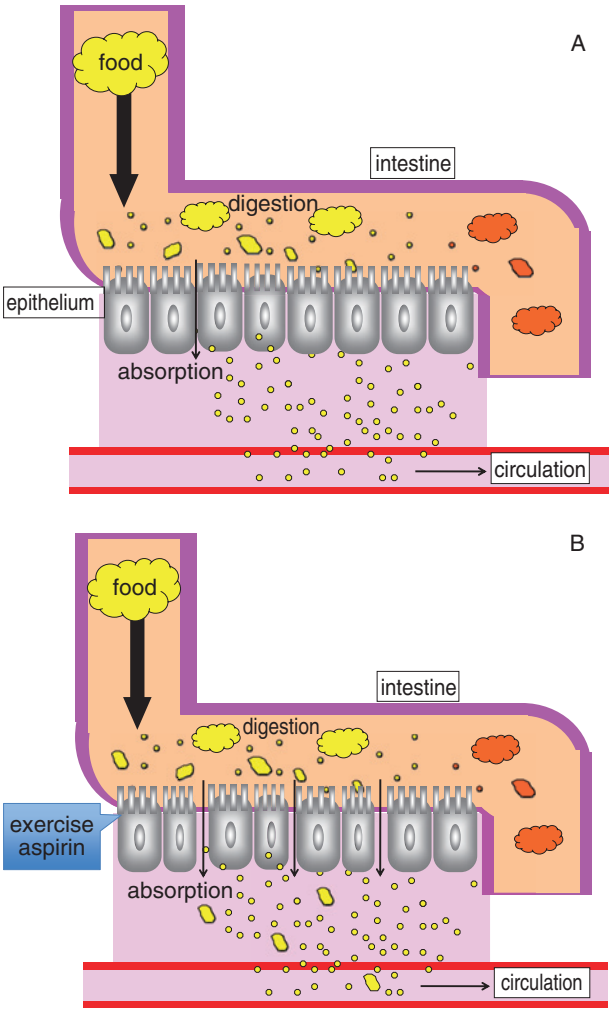

Fig. 1 Schematic figures of food allergen absorption in gastrointestinal tract in the patients with FDEIA. **A**: Ingested foods are digested in the intestine, and no immunoreactive allergens entered into circulation. **B**: Exercise and/or aspirin enhance absorption of undigested immunoreactive allergens into circulation.

levels following wheat and exercise provocation, was reported, suggesting a decrease in blood pH associated with exercise may play some role in mast cell activation.[36] On the other hand, when serum gliadin levels were evaluated using a gliadin-specific sandwich enzyme-linked immunosorbent assay, immunoreactive gliadins were found to appear in the sera of patients during the wheat challenge test combined with exercise, and these gliadins were concurrent with allergic symptoms.[37] The result indicates that exercise enhances absorption of allergens from the gastrointestinal tract as undigested forms (Fig. 1). The exercise-induced enhancement of allergen absorption was even seen in healthy subjects where the levels of serum gliadins were monitored before and after eating wheat,[37] indicating that the exercise-enhancement in antigen absorption occurs not only in allergic patients but also in healthy subjects.

A fact that has been well-established is that the symptoms are triggered by aspirin intake in the patients with FDEIA.[38,39] This was observed even in the patients with FDEIA who had no previous history of aspirin hypersensitivity or precipitation of symptoms by non-steroidal anti-inflammatory drugs.[38] Two possible mechanisms by which aspirin/non-steroidal anti-inflammatory drugs induce the symptoms have been considered: (1) aspirin enhances antigen uptake across the intestinal epithelium into circulating blood, and (2) aspirin itself activates mast cells in combination with IgE cross-linking of antigen. An enhancement of serum gliadin levels by aspirin was also demonstrated in combined challenge testing with wheat and aspirin, supporting the former hypothesis that aspirin as well as exercise, facilitates allergen absorption from the gastrointestinal tract (Fig. 1).[37] However, the latter possibility is supported by the fact that skin prick test was enhanced by pre-treatment with oral aspirin in five of eight patients with WDEIA.[39] The aspirin-induced enhancement of the allergic symptoms is possibly due to an inhibition of cyclooxygenase, as the symptoms can be diminished by co-ingestion of prostaglandin E1 (data in preparation).

Recently, a case of aspirin-associated WDEIA, which was elicited during low dose aspirin therapy for prevention of cerebral or myocardial infarction, was reported.[40] Taken into consideration with the data reported by Matsuo *et al.* that an increase in the serum gliadin level was observed in 5 of 7 subjects by administration of low dose aspirin (100 mg),[41] low-dose aspirin therapy may be also a risk factor for WDEIA.

An enhancement of aspirin is involved in induction of not only WDEIA but also various foodstuff-associated FDEIA because some cases of other foodstuff-associated FDEIA have been reported.[42]

MONITORING OF SERUM GLIADIN LEVELS IN CHALLENGE TESTS

Food-challenge test is now widely utilized to identify causative foods and to evaluate the outgrowing of food allergy. However, the test becomes rather complicated in case of FDEIA as ingestion of the causative food alone usually does not induce symptoms. A combination of the food intake and a second triggering factor, such as intense physical exercise, is necessary. Thus, for the definitive diagnosis of FDEIA, the challenge tests consist of three steps: food-challenge alone, exercise-challenge alone, a combination of food- and exercise-challenge.[37] With these procedures, standard food allergy as well as exercise-induced anaphylaxis can be eliminated. Recently, as described in the introduction and the mechanism section, aspirin is well-known triggering factor in inducing symptoms in combination with food-intake, even

in the patients with FDEIA who had no previous history of aspirin hypersensitivity. A combination challenge of food and aspirin-pre-treatment and/or triple combination challenge of aspirin-pretreatment, food and exercise can be performed as subsequent steps.[37]

If symptoms are induced by the combination challenge tests, the diagnosis of FDEIA is definite and the causative food is determined. However, in cases where the challenge test is negative, FDEIA cannot be excluded, as the symptoms are not always evoked by the challenge test. A false-negative challenge could be possible when either insufficient amount of food is ingested or an inappropriate triggering factor is challenged. According to the results that serum gliadin levels correlate well with allergic symptoms in the patients with WDEIA,[37] a monitoring of serum gliadin levels could be a useful marker in evaluating the challenge test. In the case of a negative challenge test, WDEIA could be excluded if a marked increase of serum gliadin levels was detected. Conversely, WDEIA could not be ruled out if the serum gliadin levels were under the detection limit. In the latter condition, additional challenge tests should be done to simulate the situation of episodes more strictly. In this case monitoring of the serum gliadin levels is also useful in assessing the strength of the challenge tests.

CONCLUSION

Wheat allergens were analyzed for WDEIA and it was found that omega-5 gliadin and HMW-glutenin are major allergens. Simultaneous detection of specific IgE to both recombinant omega-5 gliadin and recombinant HMW-glutenin is a reliable tool in identifying the patients with WDEIA. On the other hand, immunoreactive gliadins appeared in the sera of patients during the challenge tests with both wheat-exercise and wheat-aspirin challenges in parallel with allergic symptoms. These findings suggest that exercise and aspirin facilitate allergen absorption from the gastrointestinal tract in FDEIA.

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