

Accepted Date : 08-Sep-2015

Article type : Original Article

Provocation tests for the diagnosis of food-dependent exercise-induced anaphylaxis

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Running title: Provocation tests for FDEIA

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Pediatr Allergy Immunol

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12489

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Abstract

Background: Little has been reported regarding provocation tests for the diagnosis of food-dependent exercise-induced anaphylaxis (FDEIA), especially in children and adolescents. Hence, we here aimed to examine the usefulness and safety of such tests for FDEIA.

Methods: We retrospectively analyzed 41 patients with 184 provocation tests. The patients underwent ergometer stress tests after ingesting the suspected foods along with aspirin. When one or more allergic symptoms appeared, we judged the provocation test as positive.

Results: Based on 30 positive test results (16%), we diagnosed 20 patients (49%) as FDEIA. The major causative foods were as follows: wheat alone (5 patients), combination of wheat and shrimp (3 patients), combination of wheat and apple (2 patients), and peach alone (2 patients). The symptoms appeared within 45 minutes after initiating exercise in 29 tests (97%). The most frequent symptoms were cutaneous symptoms, which appeared in 25 tests (83%). Of the 30 positive tests, 6 (20%) required administration of adrenaline. After discharge, the patients with negative test results had no episodes of FDEIA due to the suspected foods that they had been tested for.

Conclusion: Provocation tests enabled us to confirm the diagnosis of FDEIA when positive and to exclude the diagnosis when negative. However, since severe symptoms may appear, these tests should be performed in a hospital under constant supervision of a physician.

Key words: Food-dependent exercise-induced anaphylaxis, Provocation test

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Introduction

Food-dependent exercise-induced anaphylaxis (FDEIA) is a type of food allergy in which severe symptoms are elicited upon exercise after ingestion of a certain food (1). It is considered desirable to narrow down the causative foods from the clinical history and allergy tests before carrying out a provocation test (2).

However, the only previous report of collected provocation tests for FDEIA was focused on wheat alone, and the subjects were mainly adults (average age, 34.9 years) (1), whereas there are currently few reports of provocation tests in children.

For this reason, in this study, we evaluated the usefulness and safety of provocation tests for the diagnosis of FDEIA.

Methods

At our hospital, patients are routinely admitted for provocation tests. The subjects of the present study were suspected of FDEIA as a result of allergic symptoms, such as hives or wheezing, appearing after exercising within 4 hours of eating. We excluded patients with simply exercise-induced asthma. The patients did not undergo tests when FDEIA was obvious from the medical interview, or when they disagreed to the tests. Written informed consent was obtained prior to all tests, and the study was approved by the Ethics Committee of our hospital.

Sixty-seven children, adolescents, and young adults suspected of FDEIA visited our clinic between 2006 and 2012. Of these, 41 patients were eventually included in this study (Fig. 1).

We selected the foods to test according to the clinical history and the results of the allergen-specific immunoglobulin E (IgE) tests and skin prick tests. When we could not identify a single culprit food, we tested combined foods. When positive, we tested the single foods afterwards.

The protocol of the provocation tests were based on the Japanese Pediatric Guideline for Food Allergy (3). The use of antihistamines and leukotriene antagonists was stopped 3 days before the provocation tests. Aspirin (10 mg/kg, maximum 500 mg) and the suspected food(s) were administered 90 and 60 minutes before exercise, respectively (1). The patients were given large amounts of the foods (4), for example, 200–400 g Udon noodle (5.2–10.4 g wheat protein), 40–100 g shrimp, or one whole apple. Exercise was performed using an ergometer (Cateye Ergociser EC-1600; CATEYE Co., Ltd., Osaka, Japan) according to the exercise stress tests for bronchial asthma in the Japanese Pediatric Guidelines for the Treatment and Management of Bronchial Asthma (5). The exercise was started at 2.1 W/kg, and increased up to 3 or 4 W/kg, and was conducted for 6 minutes or more according to the patients' athletic abilities, as the level of exertion can influence the test results (6). The target heart rate was >160 beats per minute. We stopped the exercise if the patient was unable to continue. When the exercise was insufficient, we required the patient to run additionally. Lung

function was measured before and at 0, 5, 15, and 30 minutes after exercise. We defined decreased lung function as a 15% decrease in the forced expiratory volume in 1 second or a 20% decrease in the peak expiratory flow (7). We followed the progress of the test attentively for at least 2 hours at their bedside and any changes in lung function were observed. When symptoms appeared, we treated them according to their severities (8). When one or more allergic symptoms (e.g. a hive, wheezing, erythema, or itch) appeared, we judged the provocation test as positive.

The specific IgE levels (ImmunoCAP; Thermo Fisher Scientific, Uppsala, Sweden) were measured, and values ≥ 0.35 UA/ml were considered positive. Regarding the skin prick test, we used bifurcated needles (Allergy Labs of Ohio, Columbus, OH, USA) and commercial allergens (Torii Pharmaceutical Co., Ltd., Tokyo, Japan), or conducted prick-to-prick tests using the allergen itself. Wheals of ≥ 3 mm in diameter were defined as positive (9-12).

We educated the patients with positive test results to withhold exercise for 4 hours before and after eating the causative food, whereas we advised the patients with negative test results to pay attention to allergic symptoms when ingesting the suspected foods after discharge.

We retrospectively analyzed the patients' characteristics, provocation test results, and episodes of FDEIA after the tests.

For the statistical analysis, Chi square and Mann-Whitney U tests were used for comparing differences in the baseline characteristics. All statistical analyses were performed with SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

Results

The patient characteristics are summarized in Table 1. Four patients with food allergy had allergies to cow's milk, hen's eggs and cow's milk, cow's milk and peanuts, shrimp, and crabs; however, these food allergies were determined to not be related to the causative foods of FDEIA.

Twenty (49%) of the 41 patients who underwent the provocation test were diagnosed with FDEIA. The causative allergen, specific IgE level, and results of the skin prick test for each patient are summarized in Table 2. The causative foods were as follows: wheat (5 patients), a combination of wheat and shrimp (3 patients), a combination of wheat and apple (2 patients), and peach (2 patients). Five patients had symptoms due to 2 different allergens (Patients 5, 8, 11, 17, and 19). In Patient 6, the prick test using shrimp extract was negative, but the prick-to-prick test using shrimp itself was positive. In total, 30 of 184 (16%) tests were positive. Out of the single-allergen tests, 14 of 108 (13%) were positive,

while for the combined allergen tests, 16 of 76 (21%) were positive.

The symptoms and treatments are summarized in Table 3. In the 30 positive tests, cutaneous symptoms were seen most frequently, appearing in 25 tests (83%). Decreased lung function was observed along with other symptoms in 5 tests (data not shown). In two of the tests, lung function decreased prior to the appearance of symptoms. We provided medical treatment after 9 tests, including the use of adrenaline for symptoms such as wheezing and hypotension for 6 tests. No test required the use of more than one dose of adrenaline.

As shown in Fig. 2, the symptoms appeared within 45 minutes of initiation of exercise in 97% of the tests. Within 2 hours, symptoms had appeared in all patients. In the patients who required adrenaline, the initial symptoms appeared within 30 minutes.

The results of the wheat-specific IgE and skin prick tests for the diagnosis of FDEIA due to wheat are summarized in Table 4. The sensitivity and specificity of the skin prick tests were higher than those of wheat-specific IgE. The efficiency in the diagnosis of FDEIA of the skin prick test was 67%, while that of wheat-specific IgE was 59%. However, ω 5 gliadin-specific IgE was negative in all patients measured.

There were no differences in the baseline characteristics between patients with positive and negative test results in terms of age, sex, atopic disorders, number of provocation tests, and total IgE (data not shown).

After the provocation tests, we were able to follow 30 of the 41 patients for more than 6 months (average follow-up, 39 months). Two patients with positive test results had an episode of FDEIA after discharge. One patient presented with systemic urticaria, cough, and dyspnea due to exercise after accidental ingestion, and was treated using an adrenaline auto-injector. The other patient had an episode of FDEIA due to a food not tested in the hospital. On the other hand, all patients with a negative test results had no episodes of FDEIA as a result of the foods tested.

Discussion

In this study, most of the patients had several suspected foods. Considering the burden of long hospital stays, we had the patients take as many of the suspected food as possible, to exercise to the utmost, and take aspirin. Aspirin is a known co-factor contributing to anaphylaxis through facilitating allergen absorption from the gastrointestinal tract and modulating mast cells (13, 14), and has been shown to improve the reliability of provocation tests (15). There are many reports in which symptoms were induced by combined, but not single foods, including

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reports of symptoms induced by combinations of wheat and umeboshi (16) and wheat, a food additive, and ethanol (17). Thus, for the diagnosis of anaphylaxis in which the cause is not identified, we may need to perform provocation tests with combined foods. However, herein, we were not able to confirm the diagnosis of FDEIA in 21 patients as no symptoms appeared in spite of a past history. One potential problem is the low level of reproducibility of these tests, as there are some previous reports of symptoms only being induced in a warm environment (18) or during the ovulatory phase (19). Kohno et al. reported in their study performed mainly in adults that 17 of 36 (47%) patients tested for wheat-dependent exercise-induced anaphylaxis showed positive results (1). However, from the follow-up survey, 9 patients with negative test results were also considered to have wheat-dependent exercise-induced anaphylaxis. In their study, aspirin was administered in only 2 of the provocation tests. On the other hand, in our study, 20 of 41 (49%) patients who underwent provocation tests had positive results. Unexpectedly, the positivity rate of our study was similar to that of the report by Kohno et al. (1), despite patients with various allergens other than wheat being tested. However, unlike in Kohno's study, the patients with negative test results in our study had no episodes of FDEIA after discharge due to the foods for which they had tested, suggesting that provocation tests with aspirin are effective and useful for providing daily life guidance for patients based on the test results.

In our study, 5 (25%) out of the included 20 patients had FDEIA due to wheat. According to the study by Harada et al., in which the average age of the subjects was 22.5 years, wheat was the causative food in 70 of 125 (56%) Japanese patients (20). The difference in the observed frequency of wheat as the causative food between the two studies is likely due to two main reasons. First, our subjects consisted mainly of children. Second, the patients may have been referred to our department only when the cause of anaphylaxis was unknown. In other words, if they were diagnosed as FDEIA due to wheat in other hospitals, it is likely that they would not have been referred to our hospital. Furthermore, there were some patients in our study who did not undergo provocation tests for wheat upon the diagnosis of FDEIA due to wheat being apparent from their clinical history and due to the results of the blood tests. Moreover, 5 patients in this study had FDEIA due to 2 different allergens and Caffarelli et al. also reported 3 patients with FDEIA due to multiple allergens (21); thus, we need to keep in mind that there may be more than one responsible allergen and carry out provocation tests for all foods suspected from the clinical history.

Of note, cutaneous symptoms appeared most frequently, similar to in

immediate-type food allergy. All initial symptoms appeared within 2 hours, and in the 6 tests that required the use of adrenaline, the initial symptoms appeared within 30 minutes. There are some concerns about the safety of using aspirin in provocation tests, and, in fact, adrenaline was administered in 20% of the positive tests; however, by observing the patients at their bedside and periodically measuring their lung function, prompt action was taken and there were no patients experiencing near fatal reactions. When exercising after meals, patients with FDEIA need to pay careful attention, especially during the initial 30 minutes. Moreover, even if patients diagnosed as FDEIA are aware of the causative agent, they should consider carrying an adrenaline auto-injector in preparation for accidental ingestion and for the risk of developing FDEIA to other foods. Provocation tests are burdensome to the patients and are associated with a risk of anaphylaxis. However, if the culprit food is not identified, there will always be a fear of anaphylaxis. After the tests, the patients can eat anything except the allergen without fear. As it is difficult, and definitely not preferred, to avoid all exercise in school, performing all these tests, although extensive, hence results in improved quality of life of the patients. Therefore, in cases where we cannot identify the culprit food, provocation tests should be performed.

In this study, we examined the diagnostic efficiency of wheat-specific IgE and skin prick tests for FDEIA due to wheat, but found that it was relatively low. In adult FDEIA, it has been reported that $\omega 5$ gliadin-specific IgE is useful in the diagnosis, as it is in immediate-type wheat allergy. However, we did not detect $\omega 5$ gliadin-specific IgE in any of the patients in our study. Accordingly, further studies are needed to determine its usefulness in children. On the other hand, it has been reported that the prick-to-prick test is useful for the diagnosis of FDEIA (22). In our study, there was one patient in whom the skin prick test by shrimp extract and shrimp specific-IgE were negative, while the prick-to-prick test by shrimp itself was positive. In this way, when skin prick tests using commercial allergens and specific IgE are negative, the prick-to prick test may represent a good diagnostic tool, and its usefulness should be further examined in other similar situations.

Lastly, there were some limitations to our study. First, it was limited by its retrospective nature. Moreover, some patients with negative test results may have still avoided certain foods at home, and we were not able to follow all patients for a long period. Thus, it was difficult to know whether these patients really did not have FDEIA or whether they simply managed to avoid the development of symptoms. Lastly, we did not measure the specific IgE levels or perform the skin prick test in all patients. Nevertheless, a strength of this study

is that we, for the first time, demonstrated several of the potential challenges in confirming the diagnosis of FDEIA in children and adolescents.

In conclusion, provocation tests for FDEIA enabled us to confirm the diagnosis when positive and to exclude the diagnosis when negative. That is to say, FDEIA provocation tests are useful for providing guidance of daily life to the patients. However, since severe symptoms may appear after the tests, these tests should be performed in a hospital under constant supervision of a physician.

Acknowledgments

We appreciate the aids of our colleges in Sagamihara National Hospital and Dr. Tomikawa from Odasaga Pediatrics and Allergy.

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Figure legends

Figure 1. Flow diagram of the study subjects.

The included subjects were 41 children, adolescents, and young adults with available provocation tests, excluding those with immediate-type food allergy and exercise-induced anaphylaxis. FDEIA, food-dependent exercise-induced anaphylaxis.

Figure 2. Onset of initial symptoms.

Most initial symptoms appeared within 45 minutes after the provocation tests.

Table 1. Patient characteristics

Characteristic		
Age (years)		12 (5-22)
Male:female		30:11
Number of provocation tests per person		4 (1-15)
Total IgE (IU/ml) *		542 (39.2-3550)
Associated atopic disorders	Bronchial asthma	8 (20)
	Atopic dermatitis	9 (22)
	Allergic rhinitis	18 (44)
	Allergic conjunctivitis	13 (32)
	Food allergy (other than FDEIA)	4 (10)

The data are presented as median (range) or n (%), as appropriate.

*Data were not available in one case.

Abbreviations: IgE, immunoglobulin E; FDEIA, food-dependent exercise-induced anaphylaxis.

Table 2. Characteristics of the patients with positive tests

Patient	Age (y)	Sex	Cause(s)	Specific IgE (UA/ml)	Skin prick test	Prick-to-prick test
1	9	M	Wheat	Wheat <0.35	Wheat (-)	
2	10	M	Wheat	Wheat <0.35, gluten <0.35, ω 5 gliadin <0.35	Wheat (+)	
3	12	M	Wheat	Wheat 2.42, gluten 0.35	Wheat (+)	
4	12	M	Wheat	Wheat <0.35, gluten 3.73, ω 5 gliadin <0.35	Wheat (-)	
5	14	M	Wheat	Wheat <0.35, gluten <0.35, ω 5 gliadin <0.35	Wheat (-)	
			Buckwheat	Buckwheat <0.35	Buckwheat (+)	
			Wheat + buckwheat			
6	16	F	Wheat + shrimp	Wheat <0.35, ω 5 gliadin <0.35, shrimp <0.35	Wheat (-), shrimp (-)	Shrimp (+)
7	15	F	Wheat + shrimp	Wheat <0.35, ω 5 gliadin <0.35, shrimp <0.35		
8	10	M	Wheat + shrimp	Wheat <0.35, ω 5 gliadin <0.35, shrimp <0.35	Wheat (-), shrimp (-)	
			Wheat + corn			
			Wheat + shrimp + corn			
9	15	M	Wheat + shrimp + taro	Wheat <0.35, ω 5 gliadin <0.35, shrimp 1.04		
10	14	M	Wheat + apple	Wheat <0.35, apple 1.24	Apple (+)	
11	14	M	Wheat + apple	Wheat <0.35, ω 5 gliadin <0.35, apple <0.35		
			Peach			
12	14	F	Corn	Corn 0.46	Corn (+)	
13	8	M	Carrot	Carrot 1.43		
14	9	F	Carrot + orange	Carrot 2.29, orange 1.24	Carrot (+)	Orange (+)
15	14	F	Orange	Orange 2.34		Orange (+)
16	11	M	Tangerine			
17	14	M	Apple	Apple 0.75		
			Peach	Peach 1.83		
18	14	F	Shrimp	Shrimp <0.35	Shrimp (-)	
			Shrimp + egg + wheat + kiwi			
19	10	M	Flat fish	Flat fish <0.35	Flat fish (+)	
			Hoki + hake			
			Chicken			
20	16	F	Chicken + wheat + potato			
			Chicken + egg + rice			

For the skin prick test, wheals ≥ 3 mm in diameter were defined as positive.

Abbreviations: IgE, immunoglobulin E.

Table 3. Symptoms and treatments

Total number of challenges		184	
Symptoms	Skin	25	(83%)
	Urticaria	18	
	Erythema (without urticaria)	6	
	Itchy (without urticaria)	3	
	Respiratory	9	(30%)
	Cough	5	
	Dyspnea	4	
	Decreased SpO ₂	3	
	Wheeze	2	
	Nasal discharge	2	
	Mucosal	8	(27%)
	Edema of eyelids	6	
	Oral discomfort	4	
	Itchy eyes	3	
	Gastrointestinal tract	3	(10%)
	Abdominal pain	1	
	Vomiting	1	
	Diarrhea	1	
	Nausea	1	
	Multiple organ systems	11	(37%)
Treatment	Antihistamine (oral or intravenous)	7	(23%)
	Steroid (intravenous)	6	(20%)
	Adrenaline (intramuscular)	6	(20%)
	β ₂ -stimulant (inhalation)	4	(13%)
	Oxygen	3	(10%)
	Adrenaline and betamethasone (inhalation)	2	(7%)

Additional adrenaline was not used.

The total number of adverse reactions was 30/184 challenges.

Table 4. Concordance of the wheat provocation test and specific immunoglobulin E (IgE) or skin prick test to wheat

	Wheat IgE	Skin prick test
Provocation test-positive (n) (+/-)	1/4	2/3
Provocation test-negative (n) (+/-)	10/19	5/14
Sensitivity (%)	20	40
Specificity (%)	66	74
Positive predictive value (%)	9	29
Negative predictive value (%)	83	82
Efficiency (%)	59	67

For the IgE levels, values ≥ 0.35 UA/ml were considered positive.

For the skin prick test, wheals ≥ 3 mm in diameter were defined as positive.

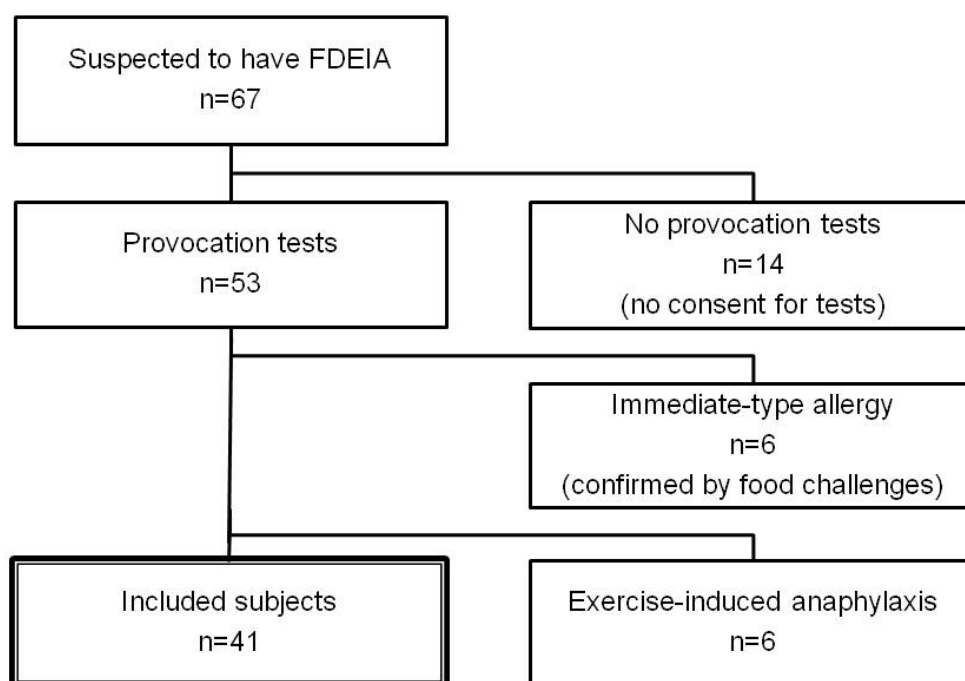


Figure 1

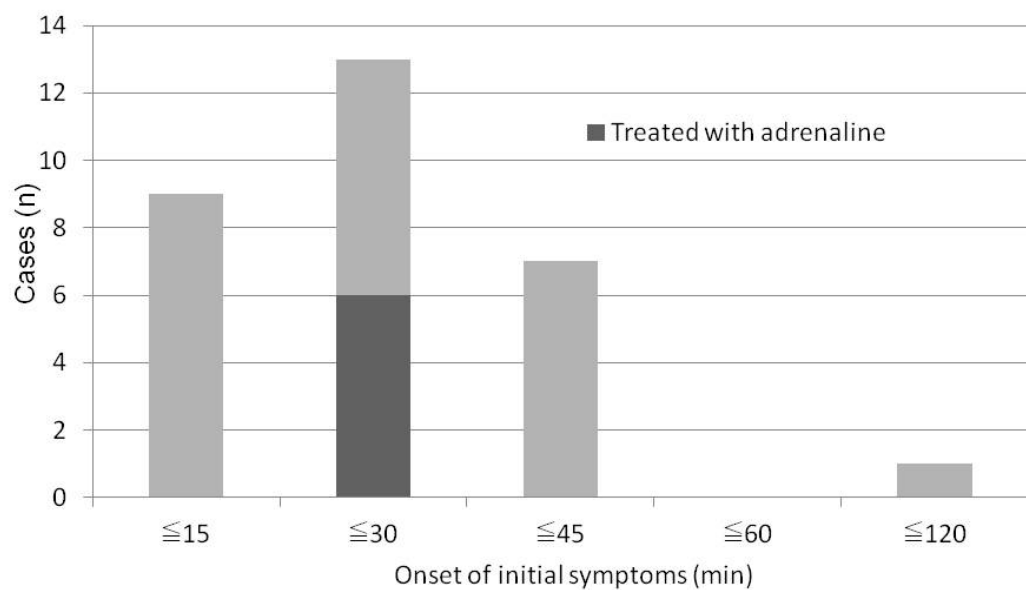


Figure 2