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Food-dependent exercise-induced anaphylaxis in Japanese elementary school children

Running title: FDEIA in Japanese elementary school

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Abstract

Background. In 2012, we clarified that the prevalence of food-dependent exercise-induced anaphylaxis (FDEIA) was 0.018% among junior-high students in Yokohama, Japan. Furthermore, although different from FDEIA, one student who had completed oral immunotherapy developed anaphylaxis during exercise after eating causative food. However, there have been few large-scale epidemiological studies of FDEIA in elementary school children, so we conducted the epidemiological study among elementary school children in Yokohama to clarify the frequency and characteristic of FDEIA.

Methods. We sent a questionnaire regarding the occurrence of FDEIA to all 348 public elementary school nurses in Yokohama. We also compared the results with those for junior-high school that we previously reported. We excluded children with past history of immediate food allergy from FDEIA and defined as desensitization status and exercise induced anaphylaxis (DEIA).

Results. Of 348 school nurses, 317 responded (91.1%). Overall, 8 of 170,146 children were diagnosed with FDEIA, which was significantly lower than the prevalence in junior-high

school students (0.0047% vs 0.018%, $p=0.0009$). The causative foods were wheat (4 cases), and soy, fruit, crustaceans, and squid (1 case each). Four children had DEIA and the causative foods were wheat and milk (2 cases each). Multiple episodes occurred in 5 children with FDEIA and 3 children with DEIA.

Conclusions. FDEIA was far less common in elementary school than in junior-high school, and wheat was the major causative food among afflicted children. The emergence of DEIA was notable. Decreasing episode recurrence remains an issue that needs to be resolved.

Key words

Desensitization; Elementary school children; epidemiology;
food-dependent exercise-induced anaphylaxis; oral immunotherapy

Introduction

Food-dependent exercise-induced anaphylaxis (FDEIA) is a distinct type of allergy provoked by a combination of specific food ingestion and physical exercise. There is no way to predict the first onset, but it is thought that determining and eliminating the causative foods before exercise can prevent subsequent anaphylaxis. In 1998, we conducted a large epidemiological study of 80,000 junior-high school students in Yokohama, Japan, and reported that FDEIA had a prevalence of 0.017% (1). At that time, however, FDEIA was not well known in either

school or medical settings, and we speculated that 60% of students with FDEIA experienced several episodes because of this unfamiliarity. Using the same method, we repeated our earlier epidemiological study in 2012, which uncovered that the prevalence, by then 0.018%, had not changed markedly over the 14-year period (2). Despite the increased awareness in schools and medical settings when compared with the previous study, recurrence still occurred in about 60% of cases. Furthermore, exercise-induced anaphylaxis among students who had received oral immunotherapy (OIT) for refractory food allergy, which is considered different to ordinary FDEIA, had developed as a new issue.

No large-scale epidemiological studies have been reported in elementary school students since our research (3). Therefore, we performed this epidemiological study to clarify the frequency and characteristics of FDEIA in elementary school children in Yokohama.

METHODS

Epidemiological study with questionnaire

The study was approved by the Board of Education and the institutional review board at Kanagawa Prefectural Ashigarakami Hospital. We mailed a questionnaire to all nurses in 348 public elementary schools in Yokohama in November 2013. Yokohama is located about 30 km south-southwest of Tokyo and has a population of 3,700,000.

The survey included questions about the nurse's self-perceived familiarity with FDEIA,

the total number of children, and the number of children with FDEIA. In addition, we asked for detailed information about the children with FDEIA, including sex, age, the age at the first episode, other concomitant allergic diseases, symptoms, duration between trigger (exercise and eating food) and onset of the disease, total number of FDEIA occurrences, number of FDEIA occurrences before examination, causative foods, association with OIT, and precautions implemented in schools. Thereafter, we directly called the nurses to confirm the data provided.

The definition of FDEIA

We considered a student as having FDEIA when the following criteria, corresponding with those of the previous study (1, 2), were fulfilled: symptoms provoked by physical exercise after eating a specific food, but not by food or exercise alone; symptoms involving more than two organs; and cutaneous symptoms that must include severe symptoms only, such as generalized urticaria or angioedema of the face.

In patients who have a history of severe immediate food allergy, anaphylaxis may be triggered by exercise after consumption of the food to which they had acquired unresponsiveness; this phenomenon is especially observed in patients who have been treated with OIT. Indeed, in the 2012 study, a student who had developed unresponsiveness to wheat allergy after receiving OIT developed anaphylaxis during exercise after consumption of food containing wheat; the case was reported as that of FDEIA by the school nurse.

This condition was desensitization, i.e., intolerance for wheat. The numbers of such cases could increase with the increased popularity of OIT. Therefore, to clarify the current situation, we excluded children with past history of immediate food allergy from FDEIA and defined those patients as desensitization status and exercise induced anaphylaxis (DEIA).

In the present study, the DEIA cases who had been able to eat causative food without limitation and did not include cases receiving OIT at the time of the study.

Criteria for judging causative foods

Causative foods were determined by the provocation test, a combination of eating suspected foods and an exercise challenge. However, provocation tests are highly specialized, and feasible medical settings were often limited, and allergic reactions are not always provoked.

In fact, only 2 of the 14 students with FDEIA in the previous study were diagnosed by the provocation test (2). Therefore, we assessed causative foods based on the following criteria: eating without symptoms until disease onset; positive findings against those with skin-prick tests, and/or antigen-specific immunoglobulin (Ig) E; and when strict elimination before exercise prevented recurrence.

Statistics

For the statistical analysis, we used the Fisher direct test and the χ^2 test for independence to compare the results with those for junior-high school students from the 2012 study. A *p* value

< 0.05 was considered statically significant. IBM SPSS, Version 20.0 (IBM Corp., Armonk, NY, USA) was used for all analyses.

RESULTS

Prevalence of FDEIA

This study included data for 170,146 children in 317 of 348 elementary schools (91.1%).

Reports from the school nurses indicated that 33 students had FDEIA, of which 8 children were considered to have FDEIA and 4 children were considered to have DEIA after

confirming the information from the school nurses (Fig 1). The frequency of FDEIA was

0.0047% (i.e., 1/20,000 people), almost equal to the result of our previous study, which produced a result of 0.0048% (3).

Familiarity with FDEIA among school nurses by self-reported

Among the 317 school nurses, 123 (39%) had reasonable knowledge of FDEIA, 184 (58%) had a little information, and 10 (3%) knew only the name of disease. No school nurses answered that they had no knowledge at all.

FDEIA

The median ages of the 8 children with FDEIA (7 boys and 1 girl) at inclusion in the study

and at disease onset were 10.5 and 10 years, respectively (Table 1). Five had other allergic

disorders, including 4 with allergic rhinitis, 4 with immediate-type food allergy to other foods,

3 with bronchial asthma, and 2 with atopic dermatitis. The causative foods among the

children with FDEIA were wheat (4 cases) and crustaceans, squid, soybean, and fruits (1 case each). In addition, no case was associated with using a facial soap containing hydrolyzed wheat protein (4).

The interval between intake of a causative food and exercise was less than 30 minutes in 5 cases, between 60 and 120 minutes in 1 case, greater than 120 minutes in 1 case, and unclear in another 1 case. The interval between exercise and onset was within 30 minutes in 5 cases, between 30 and 60 minutes in 2 cases, and unclear in 1 case. All diagnosed cases had skin and respiratory manifestations, but 2 also had circulatory manifestations (e.g., hypotension), though none had abdominal symptoms. All had eaten causative foods without symptoms before the onset of FDEIA. Concerning diagnosis, 2 were diagnosed by provocation tests, and 6 were diagnosed by positive antigen-specific IgE results with recurrence prevented after eliminating the causative food before exercise.

Recurrence was not uncommon, with 5 experiencing several FDEIA episodes (3 had two episodes; 2 had three episodes). Moreover, 2 of these children (cases 2 and 4) had attended hospital at the first episode, though no precise examinations had been performed after that episode. Additionally, one child (case 3) had the causative food identified after the first episode, but he failed to eliminate it before exercise.

Comparison with the study of junior-high-school students

We compared the present results with those of the junior high school students in 2012 (Table 2). There was a significant difference in the prevalence of FDEIA between elementary school students (0.0047%) and junior-high school students (0.018%) ($p = 0.0009$). Although crustaceans (7 of 14 students; 5 definitive, 2 suspected) was the main causative food in junior high school students, wheat was the most common cause (4 of 8 students) among elementary school children (only 1 case was caused by crustaceans).

Desensitization status and exercise induced anaphylaxis (DEIA)

The ages of the 4 children with DEIA (3 boys and 1 girl) at the time of inclusion in the study ranged from 7 to 12 years (Table 3). Three had other allergic disorders, including 2 who had immediate-type food allergies to other foods, and 1 each had bronchial asthma and atopic dermatitis. All of them had received OIT and the causative foods were cow's milk and wheat (2 cases each).

The interval between eating a causative food and exercise was less than 30 minutes in 2 cases, between 60 and 120 minutes in 1 case, and unclear in another 1 case. The interval between exercise and onset was within 30 minutes in 3 cases and unclear in 1 case. All students had skin and respiratory manifestations at presentation, and all were diagnosed as having DEIA based on receiving OIT previously. Unfortunately, 3 had experienced several episodes, and 3 had developed anaphylaxis at school, but did not carry an epinephrine

auto-injector at the first time of anaphylaxis. Two of these students had recurrences in school, relying on restricting exercise after eating to prevent recurrence.

DISCUSSION

We found that the morbidity rate of FDEIA was much lower among elementary school students than among junior-high school students. Further, crustaceans were the most common causative foods among the junior-high school students, while wheat was the most common among the elementary school students.

High-intensity exercise is known to be one of the major triggers for the onset of FDEIA (5). Exercise intensity of elementary school children tends to be lower than that of junior-high school students, which is the likely reason for the observed differences in frequency. In the 1998 junior-high school study, crustaceans were also the most common causative food, being responsible for episodes in 7 of 11 students with FDEIA (1). However, among the FDEIA cases caused by crustaceans, many patients avoided the culprit food completely because it is relatively easy to do so. Therefore, it is conceivable that some cases with immediate crustacean allergy have been misdiagnosed as case of FDEIA. Further investigation is required to determine whether crustacean is the most common cause of FDEIA among junior-high school students.

The recurrence rate of 63% was also similar to that among junior-high school students (1, 2). High recurrence rate is an important point to be considered. A major challenge is the

difficulty in determining the causative food of FDEIA; provocation tests for FDEIA typically have low reproducibility.

Kohno reported that out of 36 subjects who were suspected of having wheat-dependent exercised-induced anaphylaxis (WDEIA), only 17 tested positive at the first provocation test. Of the remaining 19 subjects, 9 (47%) subjects were finally diagnosed as WDEIA based on the subsequent clinical course (6). Additionally, specific IgE and skin-prick tests against suspected foods were often negative in children with FDEIA (7, 8). Therefore, it should be borne in mind that determining causative foods is not easy.

Inadequate health education aimed at preventing subsequent episodes seems to be another important factor. It is important to underscore the possibility of FDEIA and to stress the necessity of avoiding exercise after eating until the causative food responsible for the first episode is determined. In the present study, 2 children experienced second episode before receiving examination at a hospital. Appropriate steps taken after the first episode may have prevented the second episode.

It is noteworthy that 4 children had DEIA in the present study. Recently, the efficacy of OIT for refractory food allergy has been reported (9-11). However, despite completing OIT, some subjects experience allergic reactions after consuming the causative food after exercise. In particular, anaphylaxis following the combination of food and exercise in those with wheat and cow's milk allergy has been reported (12-15). A nationwide survey conducted in Japan

showed a 5.7-fold increase in the number of cases treated with OIT from 2011 to 2015(16).

With the increased use of OIT, cases of DEIA could be set to increase, and the number might eventually exceed that of FDEIA. Thus, we recommend that FDEIA and DEIA should be clearly distinguished to avoid confusion in school and clinical settings.

In the present study, 3 of the 4 children with DEIA did not carry an epinephrine auto-injector at the first episode. Additionally, 2 children were only subject to exercise restriction after eating in an attempt to prevent recurrence; however, these children experienced recurrence despite this intervention.. Patients and their parents should be advised about the necessity of carrying epinephrine auto-injector as a precautionary measure against anaphylaxis even after the child is deemed to be unresponsive. And if anaphylaxis is induced after eating the food, we should instruct them to eliminate the causative food again at school, because exercise restriction after eating is difficult in case of elementary school children. School personnel also should understand the phenomenon of DEIA and the precautionary measures to prevent recurrence.

In conclusion, the frequency of FDEIA was 1/20,000 among elementary school children, which was much less than the rate we previously reported among junior-high school students. The main causative food was also different (wheat rather than crustaceans). Proper assessment and education in medical settings at the first episode is important to decrease the recurrence of FDEIA. However, based on our data, we anticipate that cases of DEIA could

increase in the future. Patients who have a history of severe immediate food allergy should be educated about the potential risk of DEIA. And if they develop DEIA, they should avoid the causative food before exercise.

School staff must be provided with adequate information about how to manage these students and improve their care. Finally, we should point out that this study, and its conclusions, are limited by the potential information bias and lack of accurate diagnosis introduced by using the questionnaire survey.

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DISCLOSURE

The authors declare no conflict of interest.

Authors' contributions

T. M. and Y. A designed the study, T. M. and N. O collected data, T. M analyzed data, wrote the manuscript and performed statistical analysis, Y. A critically reviewed the manuscript and

supervised the whole study process. All authors read and approved the final manuscript.

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Table 1. Characteristics of the patients with FDEIA

Patients	Age (y)	Gender	Concomitant Allergic disease	Age at the first episode (y)	Causative foods	No. of episodes
1	12	M	BA, AD, FA	11	Wheat	3
2	7	M	AR	6	Soybean	3
3	12	M	AR, FA	11	Wheat	2
4	10	M	BA, FA	7	Wheat	2
5	10	M	none	9	Fruits	2
6	11	M	BA, AD	11	Squid	1
7	8	M	none	8	Wheat	1

8	12	F	none	11	Crustaceans	1
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Abbreviations: FDEIA, Food-dependent exercised-induced anaphylaxis; BA, Bronchial Asthma; AD, Atopic Dermatitis; AR, Allergic Rhinitis; FA, Food Allergy, other foods different from the cause of FDEIA; y, Years

Table 2. Comparison between junior-high and elementary school students with FDEIA

	Junior-high school	Elementary school	<i>p</i>
Study period	2012	2013	
Number of students	76,534 (0.018%)	170,146 (0.0047%)	
Number of patients with primary FDEIA (%)	14	8	0.0009 [†]
Boys/Girls	7/7	7/1	0.17 [‡]
Causative foods (number)	Crustaceans (5)	Wheat (4)	
	Wheat (4)	Crustaceans (1)	
	Unknown (5)	Squid (1)	
		Soy (1)	

		Fruits (1)	
No. of patients with recurrence	9 (64.3%)	5 (62.5%)	0.7 [‡]
of episodes (%)			

Abbreviations: FDEIA, Food-dependent exercised-induced anaphylaxis

[†]X² test

[‡]Fisher's exact test

Table 3. Characteristics of the patients with DEIA

Patients	Age (y)	Gender	Concomitant Allergic disease	No. of episodes	Causative food	Place at the first episode
1	7	M	BA, FA	5	Cow's milk	School
2	12	M	AD	1	Cow's milk	School
3	9	M	none	3	Wheat	School
4	9	F	FA	2	Wheat	Home

Abbreviations: DEIA, desensitization and exercised-induced anaphylaxis; BA, Bronchial Asthma; AD, Atopic Dermatitis; FA, Food Allergy, other foods different from the cause of DEIA; y, Years

Figure legends

Fig 1. Flow diagram of the study

Thirty-three cases of FDEIA were reported by the school nurses. Twenty-five of these children were excluded after confirmation of the diagnosis. Abbreviations: FDEIA, Food-dependent exercised-induced anaphylaxis

