

Frequency of food-dependent, exercise-induced anaphylaxis in Japanese junior-high-school students

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Background: Food-dependent, exercise-induced anaphylaxis (FEIA) is classified among the physical allergies. The pathophysiology of FEIA remains unknown, as does the frequency of FEIA in the general population.

Objective: We sought to study the epidemiology of FEIA, especially its frequency in junior-high-school students in Yokohama, Japan.

Methods: A questionnaire asking about the occurrence of FEIA in school students was sent to all 145 public junior-high-school nurses in Yokohama.

Results: One hundred thirty-two junior-high-school nurses responded to the questionnaire, and 13 (11 boys and 2 girls) cases of FEIA among 76,229 junior-high-school students were reported. In addition, 24 (12 boys and 12 girls) subjects with exercise-induced anaphylaxis (EIA) were detected. From this survey, the frequency of FEIA was 0.017% in this population, and its frequency was significantly higher in boys than in girls ($P < .05$). The frequency of EIA was 0.031%, and there was no difference according to sex. Only one third of junior-high-school nurses had any knowledge of FEIA. We also performed provocation tests in 5 of the 13 cases with FEIA after obtaining informed consent from the students and their parents and were able to confirm the diagnosis.

Conclusion: This study showed that FEIA and EIA are relatively rare diseases among junior-high-school students in Yokohama. To avoid serious outcomes, we believe it is important that not only physicians but also school nurses and teachers of physical education be aware of these diseases. (*J Allergy Clin Immunol* 2001;108:1035-9.)

Key words: Epidemiology; food-dependent, exercise-induced anaphylaxis; frequency; questionnaire; junior-high-school student

Exercise-induced anaphylaxis (EIA) is classified among the physical allergies.¹⁻³ A subtype of EIA related to the intake of specific food is known as food-dependent, exercise-induced anaphylaxis (FEIA).^{1,4-7}

Abbreviations used

AC:	Allergic conjunctivitis
AD:	Atopic dermatitis
AR:	Allergic rhinitis
BA:	Bronchial asthma
EIA:	Exercise-induced anaphylaxis
FA:	Food allergy
FEIA:	Food-dependent, exercise-induced anaphylaxis
HRT:	Histamine release test
SPT:	Skin prick test

However, the pathophysiology of FEIA remains unknown. In recent years, FEIA has become more widely known, and there have been an increasing number of reports.^{5,8-15} Many kinds of foods have been reported as the causative allergens.^{4-7,11,14,15} In addition, FEIA has rarely been shown to be provoked by a combination of foods.¹¹

A provocation test in which a suspected food is followed by exercise is required for the diagnosis of FEIA, except in the most severe cases. However, the tests do not always succeed in evoking the clinical symptoms.^{5,8,16} Although the reason for this has not been elucidated as yet, there are several precipitating factors that affect the onset of the disease. For example, it is thought that a certain level of severity of exercise is usually required for the induction of the disease, but this can be variable because even walking can induce FEIA.^{5,14}

Although reports of FEIA have been accumulating, thus far there is little information about the epidemiology of the disease, particularly its prevalence in a given population.¹³ To study and understand the pathophysiology of FEIA, we should have at least this kind of information. Therefore in this study we have tried to determine the prevalence of FEIA, as well as EIA, in approximately 76,000 junior-high-school students in Yokohama, Japan. In addition, after we obtained the informed consent of the students and their parents, we performed blood tests and provocation tests in 5 of 13 students with reported FEIA for further evaluation.

METHODS

Epidemiologic study by questionnaire

We performed this study with the permission of the Board of Education and the Board of Principals in junior high schools in Yokohama City. The questionnaire consisted of questions about the

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TABLE I. Frequency of FEIA_n and EIA_n in junior-high-school students attending 130 schools in Yokohama

	Boys (%)	Girls (%)	Total (%)
Subjects	39,697	36,550	76,229
FEIA _n	11* (0.027)	2* (0.005)	13 (0.017)
EIA _n	12 (0.030)	12 (0.033)	24 (0.031)

**P* < .05.

incidence of FEIA_n or EIA_n among public junior-high-school students in Yokohama. In addition, we asked for detailed information about the students with FEIA_n, including sex; age; clinical signs; symptoms; frequency; timing and season of the disease's onset; types of exercise; suspected foods; duration between exercise, intake of food, and onset of the disease; other concomitant allergic diseases; treatment; and outcome of the attack. We also asked school nurses about their familiarity with the disease and their source of information. In addition, we asked the nurses about other allergic diseases in all junior-high-school students, such as bronchial asthma (BA), allergic rhinitis (AR), allergic conjunctivitis (AC), food allergy (FA), and atopic dermatitis (AD). These diseases were defined as those diagnosed by school doctors, reported by parents, or both at the beginning of an academic year.

This questionnaire was sent to all 145 public junior-high-school nurses in Yokohama, Japan, in October 1998. To avoid bias, we prepared and sent them a leaflet that described the diseases and introduced the questionnaire. After collecting the reports in January 1999, we called each nurse to confirm the details of the report. Then we selected the patients with FEIA_n or EIA_n from the reports according to our criteria on the basis of clinical signs and symptoms. Cases of FEIA_n or EIA_n had to fulfill our tentative criteria of generalized urticaria; angioedema of the face; symptoms related to more than 2 organs, such as respiratory, gastrointestinal, and cardiovascular symptoms; and occurrence after exercise, irrespective of whether preceded by a meal.

IgE assay

Total IgE levels were determined by means of IgE PRIST (normal value, <250 IU/mL; Pharmacia, Uppsala, Sweden). Specific IgE levels for each allergen were measured by using an immunofluorometric method (FEIA RAST, CAP System, Pharmacia), the detection range of which was 0.35 to 100 IU/mL.

Histamine assay

At each blood sampling, 3 mL of heparinized blood was drawn and kept on ice, and plasma was separated. Then plasma histamine levels were measured with a histamine radioimmunoassay kit (Immunotech Ltd, Paris, France). The normal range of this test was 0.74 to 1.54 nmol/L.

Histamine release test

By using peripheral blood cells from the subjects, histamine release tests (HRTs) were performed with Lucica HRT (Asahi Chemical Industry Co, Ltd, Nobeoka, Japan).¹⁷ For this test, class I and greater results are regarded as positive.

Skin prick test

Skin prick tests (SPTs) were performed with multiple commercially available allergens (Torii Pharmaceutical Co, Ltd, Tokyo, Japan) and prepared as a 1:20 solution. If a particular allergen was not available, as in the case of umeboshi, the fresh food was used with the prick-plus-prick technique.¹⁸ All SPTs were performed with steel lancets. Responses were read at 15 minutes and graded

according to the standard method.¹⁹ Grade + is 25% of the area of a wheal induced by the positive histamine control (10 mg/mL); grade ++ is 50% of the area, grade +++ is 100% of the area, and grade ++++ is 200% of the area. Grade + or greater is considered positive, provided the response to the test solution is also larger than that to the negative control.

Provocation test

A series of challenge procedures were carried out to further investigate the patients with FEIA_n. A full explanation of the tests to be undertaken was given to the students and their parents, and informed consent was obtained. Open challenge tests were performed with the suspected food or foods that produced the symptoms of FEIA_n, followed by exercise.¹¹ The exercise part of the challenge consisted of a treadmill ergonometric stress test with progressively increasing speeds (up to Bruce grade V).²⁰ The students did these for 15 minutes and 30 minutes after a meal containing the suspected food or foods.

During the challenge tests, pulmonary function was evaluated. The peak expiratory flow rate and FEV₁ were measured and expressed as percentage changes from baseline. Maximum percentage decreases were calculated.²¹ Blood pressure and pulse rate were also monitored. In addition, peripheral blood samples were collected serially to measure the levels of plasma histamine and eosinophilic cationic protein.²² Challenge tests were carried out twice a day in the morning and afternoon. When the students demonstrated a definitive fall in FEV₁ during a challenge, this was reversed with inhaled salbutamol (albuterol). If urticaria persisted after a challenge, this was treated with oral chlorpheniramine.

Statistics

For the statistical analysis, we used the Fisher direct test and the χ^2 test for independence to compare the frequency of the disease according to sex. Differences with a *P* value of less than .05 were considered statistically significant.

RESULTS

Subjects of the study

One hundred thirty-two (91.0%) of 145 junior-high-school nurses in Yokohama completed the questionnaires, which were collected in January 1999. Seventy-six thousand two hundred twenty-nine students (39,697 boys and 36,550 girls) were included (Table I). One hundred thirty of 132 school nurses provided precise information regarding the students with FEIA_n, and 123 provided details of other allergic disorders in 71,796 students (37,307 boys and 34,489 girls). In this population 8.6% had AR, 5.9% had AD, 5.3% had BA, 2.4% had AC, and 1.0% had FA (Table II). In all allergic disorders except AD and FA, there was a significantly higher percentage of boys (*P* < .001-.01), whereas AD was predominant in girls (*P* < .001).

Frequency and features of the patients with FEIA_n

From this survey, 13 (11 boys and 2 girls) students with FEIA_n and 24 (12 boys and 12 girls) with EIA_n were collected from the reports (Table I). The incidence of FEIA_n was 0.017%. The percentage of affected boys was significantly higher than that of girls (*P* < .05). The incidence of EIA_n was 0.031%, with no sex difference. The 13

TABLE II. Frequency of allergic disorders in junior-high-school students attending 123 schools

Allergic disorders	Boys (%)	Girls (%)	P value*	Total (%)
BA	2360 (6.3)	1435 (4.2)	<.001	3795 (5.3)
AD	2103 (5.6)	2114 (6.1)	<.01	4217 (5.9)
AR	3494 (9.4)	2668 (7.7)	<.001	6162 (8.6)
AC	1002 (2.7)	748 (2.2)	<.001	1750 (2.4)
FA	381 (1.0)	327 (1.0)	NS	708 (1.0)
Others	370 (1.0)	270 (0.8)	<.01	640 (0.9)
Total	9710 (26.0)	7562 (21.9)		17,272 (24.1)
	n = 37,307	n = 34,489		n = 71,796

NS, not significant.

*Statistical analysis (χ^2 test for independence) of the frequency of allergic disorders in boys and girls.

patients with FEIAN presented relatively severe signs and symptoms related to more than 2 organs: skin manifestations (100%), such as facial urticaria and generalized urticaria; respiratory symptoms (67%), such as stridor and dyspnea; eye and nasal symptoms (50%), such as nasal obstruction and rhinorrhea; conjunctivitis (50%); abdominal cramps (33%); hypotension (25%); and unconsciousness (25%). There were no cases of convulsion.

Most of the patients with FEIAN had experienced similar episodes several times: more than 10 times in 1 patient; 7 times in 1 patient; 3 times in 5 patients; 2 times in 3 patients; 1 time in 2 patients; and an unknown number of times in 1 patient. The interval between the intake of the causative food or foods and exercise was within 60 minutes in 6 of 9 patients at the onset of FEIAN. All of them, except 4 patients, experienced FEIAN within 3 hours of the interval. There was no information in this regard about the other 4 patients. The duration of exercise was less than 30 minutes in 8 of 11 patients. In all, except for 2 patients, the FEIAN episodes occurred within 45 minutes of exercise, and for the other 2 patients, there was no information in this regard.

The causative food or foods in the 13 patients were Crustacea, such as shrimps and crab (n = 7); wheat (n = 4); grapes (n = 1); vegetables (n = 1); buckwheat (n = 1); and unknown foods (n = 2). In 3 patients more than 2 foods could cause FEIAN, and interestingly, there was one exceptional case in which FEIAN was induced with simultaneous intake of 2 foods followed by exercise.¹¹

With respect to the type of exercise related to FEIAN, in 9 of the 13 patients, this was running-jogging; for 2 it was playing soccer, for 1 it was cycling, and for 1 it was unknown. Six patients had FEIAN episodes during training after school lessons, 5 during physical education class, 1 at lunch break, and 1 at an unknown time. FEIAN occurred in the morning in 5 patients, in the afternoon in 8 patients, and at an unknown time in 1 patient. There was 1 student who experienced FEIAN both in the morning and in the afternoon. There was no seasonal pattern in the 12 patients with FEIAN (ie, 6 patients in spring, 4 in summer, 4 in autumn, and 4 in winter). Three of these patients experienced the episode in more than 2 seasons. There was no information in this regard in 1 patient. The age at the first episode of FEIAN in all patients except one was more than 9 years old; the other patient was 5 years old.

Ten of 12 patients with FEIAN had other allergic disorders: AR in 5 patients, BA in 4 patients, AD in 4 patients, FA in 3 patients, AC in 3 patients, and contact dermatitis in 1 patient. There was no information about 1 patient. Although some of the students with FEIAN had experienced shock, fortunately there was no serious outcome in this survey. All the students recovered completely in 24 hours after the onset of FEIAN. One of them was hospitalized for 2 days at the time of the episode.

Further evaluation of 5 patients with FEIAN

As shown in Table III, we further evaluated 5 patients, who were all boys. Their blood tests included measurement of total IgE and IgE antibodies to specific allergens. Their peripheral white blood cell count was $5340 \pm 297/\mu\text{L}$ (mean $\pm$ SD), percentage of eosinophils was $7.5\% \pm 2.6\%$, and total serum IgE level was 776 ± 1068 IU/mL. All but one had multiple allergies and a family history of allergic conditions. For the identification of causative allergens, SPTs were the most reliable method used; that is, in all patients SPT responses, but not HRT or CAP-RAST results, were always positive for the causative food or foods.

Provocation tests

To further evaluate and confirm the diagnosis of the patients with FEIAN, we performed provocation tests in 5 of 13 patients with FEIAN after obtaining informed consent. In all 5 patients we succeeded in provoking symptoms of FEIAN, such as urticaria, dyspnea, rhinorrhea, and itching of the eyes. The degree of the symptoms in each case varied from mild to severe. Transient increases in plasma histamine levels ($167\% \pm 28\%$ from the baseline levels [mean $\pm$ SD]) were observed during the tests in all cases. There were no correlated changes in serum eosinophilic cationic protein levels during the tests (data not shown). Changes in FEV₁ were also measured; there was a significant decrease in percentage FEV₁ in 2 patients. Therefore on the basis of the results of the provocation tests and laboratory data, we could confirm the diagnosis of FEIAN in at least 5 of 13 patients in this survey.

Familiarity of school nurses and practitioners with FEIAN

At the time of this survey, the familiarity of 50 junior-

TABLE III. Summary of 5 patients with FEIAN diagnosed by means of the provocation tests

Items	Patient no.				
	1*	2	3	4	5
Age/sex/onset age (y)	14/M/12	14/M/10	15/M/15	13/M/12	14/M/12
No. of episodes/exercise†	3/running	≥10/soccer	3/running	2/cycling	7/running
Serum IgE, IU/mL	330	150	2680	380	340
WBC, μ L (% eosinophils)	5300 (9.3)	5300 (8.6)	4900 (10.0)	5500 (3.7)	5700 (5.8)
CAP-FEIA RAST (class ≥ 2)	Mite, rice, Japanese cedar, HD, wheat, sesame	Japanese cedar	Wheat, shrimp, crab, mite, HD	Shrimp, Japanese cedar, HD, mite, crab	Wheat, HD
HRT (Class ≥ 1)	Umeboshi, wheat, rice	Negative	Crab, shrimp	NT	Negative
SPT ($\geq 1+$)	HD, umeboshi, wheat, mite	Wheat, shrimp, crab, rice, potato	Wheat	Shrimp, crab	Wheat, mite
Causative food(s)	Wheat + umeboshi	Shrimp, wheat, tomato	Crab, shrimp, wheat	Crab, shrimp	Wheat
Allergic disease of subject/family	AR, BA/+	AR/+	AD, AR/+	AC, AR/+	None/none
Provocation test‡§	U, D, R, C	U, R, C	U, D, R	U, R	U, C
Histamine/‰ FEV ₁ ‡	+60%/-43	+110%/0	+77%/-22	+53%/-1	+35%/-1

WBC, White blood cell count; HD, house dust; NT, not tested; U, urticaria; D, dyspnea; R, rhinorrhea; C, conjunctivitis.

*See reference 11.

†Exercise at the episodes of FEIAN.

‡See Methods section.

§Symptoms at the provocation test.

||Transient percentage increase of plasma histamine levels from baseline levels.

high-school nurses with FEIAN in Yokohama was very low; only 1 (2%) nurse had reasonable knowledge of the disease, 15 (30%) had little information, 16 (33%) knew only the name of the disease, and 18 (35%) did not know it at all. The sources of the information about the disease for the 32 nurses were derived mainly from the magazines for nurses (26%) and the mass media (21%), such as television programs and newspapers. Although in this study we found 13 patients with FEIAN, the practitioners and school doctors had made only 4 diagnoses correctly. In the other patients correct diagnosis was not made before our survey.

DISCUSSION

FEIAN is classified as a physical allergy.^{1,4} Although several hypotheses have been suggested, the mechanism of the disease has not yet been elucidated. It is likely that release of a sufficient amount of mediators from mast cells is an essential local feature at the final step of both FEIAN and EIAN^{3,11} and several factors have been reported to be responsible.^{5,8,10,12,14,23} In most cases a single food allergen has been reported as inducing FEIAN.¹⁴ However, in rare cases many kinds of food allergens independently evoked the symptoms.^{14,16,21} Recently, we reported a rare case of dual food intake (ie, wheat and umeboshi were both required to induce FEIAN).¹¹ This case also suggested that to provoke the symptoms of FEIAN, the amount of released chemical mediators, including histamine, must exceed a certain threshold.

The reason we chose this population is that in Japan most students usually experience a certain level of exercise for the first time in junior high school. Attendance at junior high school is compulsory for all Japanese chil-

dren from 13 to 15 years of age, and more than 95% of the students attend such schools in Yokohama. Previously, it was thought that Japanese patients with FEIAN were predominantly aged 10 to 20 years.¹⁴ Therefore we believed that junior-high-school students were the most suitable population to examine the epidemiology of FEIAN. In addition, it was thought that the episodes of FEIAN were clinically so severe that school nurses should know and remember them precisely. Therefore we decided to send the questionnaire to school nurses.

From this study, we gathered that FEIAN and EIAN are rare diseases in junior-high-school students in Japan. However, we knew that there was a limitation of this study with the questionnaire to the school nurses. Compared with a previous report, in which the frequency of FEIAN was 0.21% of junior-high-school students (8 patients: 6 boys and 2 girls, $n = 3753$),¹³ the incidence in our survey was lower. The reason for this difference could be explained in part by the possibility that students with mild FEIAN were not included in our study because of our stricter criteria for selecting the students with the disease. However, we confirmed the accuracy of our diagnosis in 5 of 13 students with FEIAN with the provocation tests. We therefore believe that our survey could be more reliable than the previous one¹³ in terms of severe cases of FEIAN. The other reason might be the scale effect of our study (ie, the number of students was larger in our study than in the previous study).

The causative food in our patients was quite similar to that found in previous reports in our country.^{5,14} That is, Crustacea, such as shrimps and crabs, were the most frequent causative food, and wheat was second. The most frequently related exercise was jogging-running. The dif-

ference in sex in terms of the frequency of the disease was also seen in other reports.^{5,13,14} This difference might reflect in part that a certain level of strength in exercise was required to induce FEIAN. Boys prefer more active sports than do girls in Japan. However, this explanation does not apply to the difference in sex of EIAN.

The frequencies of other allergic disorders other than FEIAN and EIAN in this population were similar with those of a previous report.²⁴ This suggested that the school nurses had enough information about the allergic disorders other than FEIAN and EIAN and supported the belief that our survey of FEIAN would be properly performed.

A provocation challenge test with the suspected food is essential and indispensable in the correct diagnosis of FEIAN, except in the most severe cases. However, it has been reported that challenge tests do not always provoke the symptoms of FEIAN.^{5,8,16} Reasons for negative test results have not been established to date, and they remain to be clarified. We performed the provocation tests with the causative foods in 5 of 13 students with FEIAN. In all 5 patients we could provoke the clinical symptoms to some degree. Furthermore, we found that plasma levels of histamine increased transiently during the tests in all 5 patients. This high frequency of positive provocation test results might be explained by our severe criteria in selecting subjects and the precise in vitro and in vivo tests for seeking allergens before the provocation tests, as well as the performance of several times of provocation tests.

Finally, for students with FEIAN, an accurate diagnosis is recommended to avoid unnecessary diet, exercise restriction, or both and to prevent serious reactions. Unexpectedly, in this study we found that only 4 of 13 students with FEIAN were given correct diagnoses. This suggested that not only are school nurses not familiar with FEIAN but also that physicians and school doctors are unfamiliar with the disease. Therefore we should introduce FEIAN to school nurses and school doctors, as well as to practitioners, and inform them of this disease to prevent misdiagnosis.

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