

# Food-dependent, exercise-induced anaphylaxis: A study on 11 Japanese cases

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*Eleven patients with food-dependent, exercise-induced anaphylaxis were studied. Seven patients experienced anaphylactic symptoms only after eating certain foods, such as shellfish, wheat, and grape before exercise. In the remaining four patients, no specific food could be identified, but the act of eating itself predisposed to anaphylaxis. Their anaphylactic symptoms were all clearly distinguished from cholinergic urticaria by history. Patients who developed anaphylactic symptoms before 20 years of age (N = 7) were atopic themselves or had atopic first-degree relatives. Six patients had increased serum IgE levels, and IgE antibodies against the causative food allergens were detected by the skin prick test or RAST in four cases. In contrast, patients who developed the symptoms after 30 years of age (N = 4) appeared to have a less atopic background, and IgE levels were within normal range except in one case. Three of four patients in the latter group developed symptoms after ingesting food made of wheat followed by exercise. All patients were sensitive to wheat as determined by the skin prick test. In six of 11 patients, a considerable rise in plasma histamine concentration was observed after exercise challenge with treadmill alone, and food intake followed by exercise induced a further increase in one patient. (J ALLERGY CLIN IMMUNOL 1991;87:34-40.)*

EIAN has been recognized as a distinct form of physical allergy. This syndrome is characterized by symptoms of EIAN such as collapse and/or upper respiratory tract obstruction in association with flushing or urticaria,<sup>1,4</sup> a rise in plasma histamine,<sup>2,5</sup> and pathologic findings of mast cell degranulation.<sup>1, 5, 6</sup> Similar clinical<sup>7, 8</sup> and pathologic<sup>9</sup> findings are observed in cholinergic urticaria after exercise. However, passive heat challenge is positive only in subjects with cholinergic urticaria.<sup>10, 11</sup> As predisposing factors of EIAN, a sensitivity to some specific food or food intake itself has been reported,<sup>12-19</sup> and such cases are called "food-dependent EIAN."<sup>12</sup> As a specific food, several cases of celery,<sup>12, 13</sup> shellfish,<sup>14-16</sup> and wheat<sup>17-19</sup> have been reported. Another precipitating factor includes drug intake,<sup>1, 20</sup> and a familial tendency

## Abbreviations used

EIAN: Exercise-induced anaphylaxis  
EIAs: Exercise-induced asthma

has been reported in some studies.<sup>21, 22</sup> As this disease concept has been established and understood, increased numbers of cases of food-dependent EIAN have been also reported from countries other than the United States.<sup>18, 19, 23, 24</sup>

In the present study, 11 patients with food-dependent EIAN in Japan are presented, and their characteristic features are described.

## MATERIAL AND METHODS

### Study population

The study population consisted of 11 Japanese patients (four male and seven female patients) ranging in age at the time of the study from 18 to 43 years (mean, 26.3 years). Patients were diagnosed as having EIAN according to the criteria below<sup>1, 4, 6, 10, 11</sup>: (1) recurrent episodes of collapse (syncope) and/or upper respiratory tract obstruction with flushing or general urticaria in association with exercise at least twice, (2) urticaria is characteristic to EIAN (diameter, 10 to 15 mm), (3) collapse was not due to a dysfunction of an organ, such as the heart, lung, or brain, and (4) ana-

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phylaxis was not experienced in response to warm baths, shower, fever, or other increases in core body temperature.

### Immunologic studies

Total IgE levels in the patients' sera were measured by the radioimmunosorbent test. Each patient underwent a skin prick test to 20 environmental and 10 food allergens (1:10 wt/vol, obtained from Torii Pharmaceutical Co., Ltd., Tokyo, Japan). Tests were read at 15 minutes. A wheal >5 mm and/or a flare >15 mm in diameter were judged to be positive. Specific IgE antibodies to allergens in the serum were measured with RAST (Pharmacia Diagnostics, Upsala, Sweden).

### Exercise challenge

Exercise challenge was performed according to the protocol of Bruce et al.<sup>25</sup> that has been used for the diagnosis of ischemic heart diseases. Patients wearing cotton clothes ran on a treadmill with increasing speed and inclination until their heart rate reached a certain level, as determined by sex, age, and athletic history. As a control, eight normal healthy subjects (five male and three female subjects), ranging in age from 31 to 42 years (mean, 34 years) were subjected to the same exercise challenge and under the same conditions as for the patients. One hour after the first exercise challenge, seven patients ingested food that was suspected to induce EIAN, and 30 minutes after the food intake, they underwent a second treadmill challenge. Before and 5, 15, and 45 minutes after each challenge, venous blood specimens were obtained for measurement of plasma histamine. Samples were immediately minced with ethylenediamine tetraacetic acid (EDTA) (final concentration, 5 mmol/L) and centrifuged at 200 g for 10 minutes at 4°C. The upper one third of the plasma was stored at -20°C and used for the histamine assay.

### Histamine assay

Plasma histamine was assayed with a histamine radioimmunoassay kit (Immunotech Ltd., Paris, France). Briefly, sample histamine was acylated and then subjected to competitive binding assay with <sup>125</sup>I-labeled acylated histamine to antiacylated histamine monoclonal antibody. The concentrations of histamine in the samples were determined by a standard curve. Preliminary studies revealed that daily changes in normal healthy control subjects were within 0.08 ng/ml, and changes after food intake were all within this range (data not presented).

## RESULTS

### Patients characteristics

Eleven patients and their characteristic features are presented in Table I. Seven of 11 patients had a specific food as a predisposing factor. The remaining four patients were not sensitive to any specific food, but it was clear from their history that food intake preceding exercise was a predisposing factor. Intake of a specific food or any meal followed by exercise did

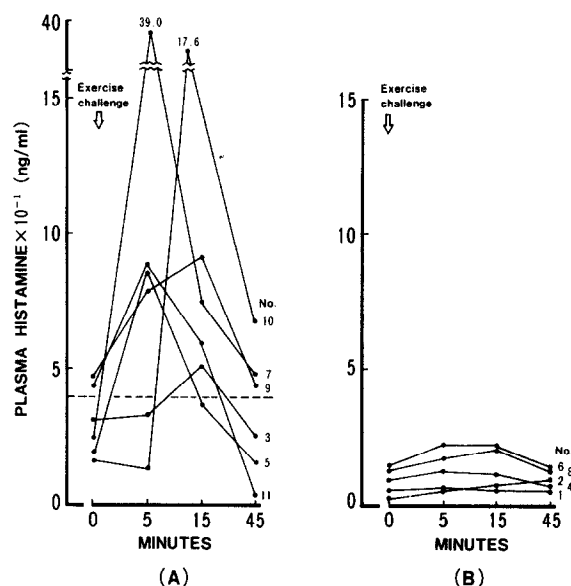


**FIG. 1.** Changes in plasma histamine concentration before and after the exercise challenge in patients with food-dependent EIAN. Patients ran on the treadmill under the same conditions as conditions for normal control subjects. Only one patient (No. 5) ran according to the protocol for EIAs because she had EIAs. After the challenge, plasma histamine concentration increased over the maximal value observed in normal control subjects (0.4 ng/ml) in six of 11 patients (A) 5 to 15 minutes after the challenge. However, five patients (B) did not demonstrate any increase in plasma histamine concentration.

not always provoke EIAN symptoms. Fatigue, cold, and lack of sleep appeared to affect the development of the EIAN symptoms. In two patients (Nos. 7 and 9), aspirin intake (30 minutes or 1 hour before food intake) provoked more severe EIAN symptoms as compared with symptoms without aspirin intake. A menstrual cycle affected the onset of EIAN in two patients (Nos. 4 and 8). Patients who developed the symptoms before 20 years of age (Nos. 1 to 7) had an atopic history themselves or for first-degree relatives. Moderately increased serum IgE levels ( $941 \pm 408$  IU/ml, mean  $\pm$  SEM) were common (except in No. 1). In four cases in which causative allergens were identified, specific IgE antibodies were detected by a skin prick test and/or RAST. In contrast, four patients who first experienced an EIAN attack after 30 years of age (Nos. 8 to 11) did not have an atopic history themselves nor did their first-degree relatives. The IgE levels in this group (mean  $\pm$  SEM,  $237 \pm 32$  IU/ml) were elevated in only one patient (No. 10). All patients demonstrated a positive skin test to wheat; however, the RAST score to wheat was weakly positive in only one patient and negative in the remaining three patients.

**TABLE I.** Food-dependent EIA: Population and clinical features

| Patient No. | Age (yr) | Sex | Age at onset (yr) | No. of attacks/mo | Food before exercise    | Type of exercise                         | Prodromal/early manifestation                          |
|-------------|----------|-----|-------------------|-------------------|-------------------------|------------------------------------------|--------------------------------------------------------|
| 1           | 20       | M   | 13                | 7/60              | Not identified          | Running                                  | Dyspnea<br>Flushing<br>Pruritus                        |
| 2           | 15       | M   | 14                | 2/12              | Grape                   | Running                                  | Cough<br>Flushing<br>Nasal discharge<br>Pruritus       |
| 3           | 18       | F   | 14                | 2/48              | Crab<br>Shrimp          | Pingpong                                 | Dyspnea<br>Flushing<br>Pruritus                        |
| 4           | 25       | F   | 16                | 30/108            | Not identified          | Basketball<br>Walking                    | Cough<br>Flushing<br>Nasal discharge<br>Pruritus       |
| 5           | 19       | F   | 17                | 2/24              | Abalone                 | Bicycling<br>Running                     | Colic pain<br>Cough<br>Dyspnea<br>Flushing<br>Pruritus |
| 6           | 23       | F   | 18                | 5/60              | Crab<br>Shrimp<br>Squid | Aerobics<br>Dancing<br>Tennis<br>Walking | Colic pain<br>Diarrhea<br>Dyspnea<br>Pruritus          |
| 7†          | 19       | F   | 18                | 3/36              | Not identified          | Basketball                               | Pruritus<br>Headache<br>Flushing                       |
| 8           | 33       | F   | 31                | 5/24              | Wheat<br>(bread)        | Walking<br>30 min                        | Flushing<br>Warmth                                     |
| 9†          | 35       | M   | 34                | 2/24              | Wheat<br>(bread)        | Golf<br>Working<br>in an<br>office       | Flushing<br>Pruritus                                   |
| 10          | 41       | M   | 38                | 15/48             | Wheat<br>(noodles)      | Badminton<br>Tennis<br>Walking<br>30 min | Dyspnea<br>Flushing                                    |
| 11          | 43       | F   | 38                | 4/60              | Not identified          | Volleyball<br>Tennis<br>Running          | Headache<br>Flushing<br>Nausea                         |

AR, Allergic rhinitis; BA, bronchial asthma; AD, atopic dermatitis.

\*Atopic history of first-degree relatives.

†Experienced more severe symptoms after taking aspirin orally followed by food intake and exercise.

| Complete clinical syndrome                                 | IgE (IU/ml) | Prick test positive                  | RAST score                             | Atopic history |          |
|------------------------------------------------------------|-------------|--------------------------------------|----------------------------------------|----------------|----------|
|                                                            |             |                                      |                                        | Personal       | Family*  |
| Collapse<br>Urticaria<br>Wheezing                          | 128         | Mite                                 | Mite (4)                               | AR             | —        |
| Angioedema<br>Collapse<br>Urticaria<br>Wheezing            | 606         | Grape                                | —                                      | —              | BA<br>AD |
| Diarrhea<br>Urticaria<br>Wheezing                          | 3286        | Crab<br>Mite<br>Shrimp               | Crab (3)<br>Mite (4)<br>Shrimp (3)     | BA             | BA       |
| Angioedema<br>Choking<br>Collapse<br>Diarrhea<br>Urticaria | 498         | Mite                                 | Mite (2)                               | AR<br>AD       | —        |
| Angioedema<br>Choking<br>Collapse<br>Diarrhea<br>Urticaria | 480         | Abalone<br>Mite                      | Mite (3)                               | EIAs           | —        |
| Choking<br>Collapse<br>Urticaria                           | 408         | Crab<br>Mite<br>Shrimp               | Crab (2)<br>Mite (1)<br>Shrimp (2)     | —              | BA       |
| Angioedema<br>Collapse<br>Urticaria                        | 1180        | Wheat<br>Shrimp<br>Egg white<br>Mite | Wheat (1)<br>Egg white (3)<br>Mite (3) | AD             | —        |
| Choking<br>Collapse                                        | 110         | Wheat                                | —                                      | —              | —        |
| Collapse                                                   | 118         | Wheat                                | —                                      | —              | —        |
| Angioedema<br>Choking<br>Collapse<br>Urticaria<br>Wheezing | 557         | Wheat                                | Wheat (1)                              | —              | —        |
| Angioedema<br>Choking<br>Collapse<br>Urticaria             | 161         | Wheat                                | —                                      | —              | —        |

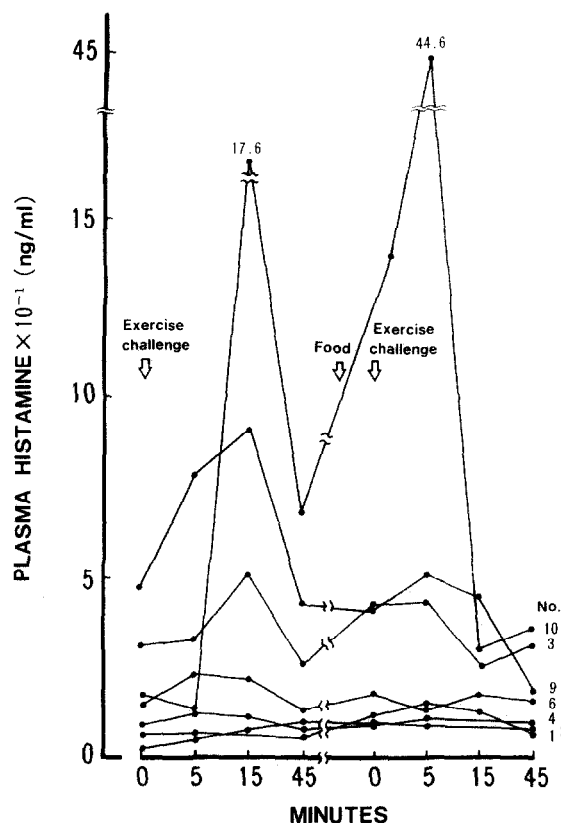


**FIG. 2.** Changes in plasma histamine concentration before and after food-exercise combination challenge. Seven of 11 patients with EIAN ingested food that was suspected to provoke symptoms in each patient 1 hour after the first exercise challenge (Nos. 1, 4, 9, and 10, bread; Nos. 3 and 6, shrimp; No. 2, grapes); 30 minutes later, exercise challenge was repeated. Three patients demonstrated an additional increase in histamine concentration. Food intake clearly enhanced this increase in only one patient (No. 10).

### Exercise challenge

**Normal control subjects.** Eight healthy control subjects ran on the treadmill according to the protocol of Bruce et al.<sup>25</sup> No symptoms other than fatigue were provoked by this exercise. Plasma histamine concentrations before exercise were  $<0.3$  ng/ml, and the maximal level after the challenge was 0.4 ng/ml. The change in plasma histamine was  $\pm 0.2$  ng/ml in most of the control subjects (data not presented).

**Patients with EIAN.** Ten patients underwent exercise challenge with the same protocol and under the same conditions as healthy control subjects. One patient (No. 5) who had a history of EIAs was challenged by a protocol for EIAs (6 km/hr, 10%, and for 6 minutes). After the challenge, three patients complained of itching. Flushing and local urticaria were observed. The diameter of the urticaria was  $>10$  mm and characteristic to EIAN. Two patients who had a history of

atopic asthma (No. 3) and EIAs (No. 5) complained of wheezing. These symptoms were mild and gradually disappeared within 30 minutes to 1 hour. A decrease in systemic blood pressure or loss of consciousness was not observed in any patient. In six of 11 patients, plasma histamine concentration elevated over the maximal level detected in healthy control subjects (0.4 ng/ml) 5 to 15 minutes after the challenge. The other five patients did not demonstrate any appreciable increase in plasma histamine (Fig. 1). After the food-exercise combination challenge, three of seven patients demonstrated a second increase in histamine concentration (Fig. 2). However, food intake clearly enhanced an increase in histamine concentration after exercise in only one patient (No. 10). The other four patients did not demonstrate any increase in histamine. The results of exercise challenge are summarized in Table II.

### DISCUSSION

In this article, we have presented 11 patients with food-dependent EIAN. The patients were diagnosed as having definite EIAN and were all clearly distinguished from having cholinergic urticaria because<sup>1, 4, 6, 9, 10</sup> (1) they all demonstrated systemic manifestations, including collapse (syncope), upper airway tract obstruction, or abdominal pain, which are rare in exercise-induced cholinergic urticaria, (2) urticaria observed in the patients was characteristic to EIAN, and (3) they have not experienced anaphylaxis in response to warm baths, shower, or other increases in core body temperature. One patient (No. 5) had a history of EIAs. Thus, in this patient, dyspnea could be due to EIAs. However, the dyspnea observed in this patient was "choking of the throat" or "lump in the throat" associated with angioedema, urticaria, and syncope. Therefore, the dyspnea was believed to be caused by angioedema of upper airway tract mucosa and not by smooth muscle spasm of the lower respiratory tract.<sup>1</sup> Seven patients developed the symptoms before 20 years of age. All the patients had a background of atopy. Most (six of seven patients) had increased IgE levels, and specific IgE antibody to food allergen was detected in four cases. The other four patients developed the symptoms after 30 years of age. Their atopic background was less clear compared to background of the patients in the early onset group. Our observation is in agreement with the results observed in the previous studies on Japanese subjects<sup>16, 18, 19</sup> and also coincides with studies from other countries,<sup>12-15, 17</sup> although there were some exceptions and overlaps.<sup>17</sup> Our results might suggest that EIAN is heterogenous. However, to establish this speculation, accumulation of more cases, especially cases of the late onset group, would be necessary. Two

**TABLE II.** Results of exercise challenge according to protocol of Bruce et al.<sup>25</sup>

| Patient No. | Maximum exercise |                | Challenge-induced symptoms                         | Peak histamine concentration (ng/ml) |          |               | Response to challenge |
|-------------|------------------|----------------|----------------------------------------------------|--------------------------------------|----------|---------------|-----------------------|
|             | Grade (degree)   | Duration (min) |                                                    | Baseline                             | Exercise | Food-exercise |                       |
| 1           | IV               | 12             | None                                               | 0.06                                 | 0.07     | 0.15          | —                     |
| 2           | V                | 15             | Flushing<br>Pruritus<br>Urticaria                  | <0.03                                | 0.10     | 0.10          | +                     |
| 3           | III              | 9              | Wheezing                                           | 0.31                                 | 0.51     | 0.44          | +                     |
| 4           | III              | 8              | None                                               | 0.10                                 | 0.13     |               |                       |
| 5*          | 6 km/hr, 10%     | 6              | Wheezing                                           | 0.18                                 | 0.88     |               | +                     |
| 6           | IV               | 10.5           | None                                               | 0.15                                 | 0.23     |               | —                     |
| 7           | IV               | 11             | None                                               | 0.25                                 | 3.90     |               | +                     |
| 8           | IV               | 10.5           | None                                               | 0.13                                 | 0.21     |               | —                     |
| 9           | IV               | 11             | Flushing<br>Pruritus<br>Urticaria                  | 0.47                                 | 0.91     | 0.51          | ++                    |
| 10          | III              | 8.5            | Flushing<br>Pruritus,<br>Facial edema<br>Urticaria | 0.17                                 | 1.76     | 4.46          | ++                    |
| 11          | III              | 9              | None                                               | 0.44                                 | 0.88     |               | +                     |

—, Neither symptoms nor increase in histamine concentration; +, either symptoms or increase in histamine concentration; ++, both symptoms and increase in histamine concentration.

\*Exercise challenge was performed on a treadmill according to a protocol for EIAs.

patients experienced anaphylactic symptoms when they took aspirin before food intake and exercise. This observation is quite interesting and may help to elucidate the mechanisms of EIA, although the mechanisms remain obscure at present.

We found a discrepancy between the results of the skin prick test and RAST to wheat allergens. One possible explanation is that this discrepancy derives from the different sensitivities of the two assays. In general, the skin test is more sensitive than RAST in patients with food allergy.<sup>26</sup> Another possible explanation may come from the fact that the allergen preparations for the skin test and the RAST are different. The wheat allergen used for the skin prick test is a crude extract of wheat prepared by Torii Pharmaceutical Co. Ltd. In contrast, the wheat allergen for the RAST is composed of molecules that can be conjugated to the CNBr-activated paper disk supplied by Pharmacia Diagnostics.

Previous studies<sup>18, 19</sup> and our study on Japanese subjects demonstrate that there is a higher incidence of sensitivity to wheat in food-dependent EIA than in subjects in the United States. Recently, wheat consumption has been increasing significantly in Japan. This may influence the immunologic as well as non-immunologic response of Japanese subjects to wheat. The case of a 29-year-old Japanese man whose symp-

toms of wheat-induced urticaria became worse when he was in the United States has been reported.<sup>18</sup> He ate a larger quantity of bread in the United States than when he was in Japan. This finding may support the speculation above.

Our results on exercise challenge reveal that exercise challenge alone (without food intake) caused an increase in plasma histamine concentration in six of 11 patients with food-dependent EIA. This indicates the possibility that patients with EIA have increased histamine releasability from mast cells responding to exercise as compared to normal individuals and that food intake may accelerate the process.

In previous articles,<sup>2, 3, 5, 7, 17</sup> the exercise conditions were more severe and the degrees of increase in histamine were greater than conditions and degrees in this study. Challenge-negative patients in our study may have demonstrated symptoms or an increase in histamine if the conditions of the challenge had been more intense; that is, the results of exercise challenge are affected by the intensity of the challenge and the patient's condition. Therefore, negative exercise challenge results do not necessarily rule out the possibility of EIA.

The method used to measure plasma histamine was a radioenzyme assay in most of the previous studies.<sup>1, 3, 5, 7</sup> This method is not completely free of cross-

reactivity between net histamine and methylhistamine or L-histidine. Therefore, the histamine concentration may be overevaluated. The method of assay used in the present study was radioimmunoassay with anti-acetylated histamine monoclonal antibody, which is specific to histamine and more sensitive. Therefore, slight differences in plasma histamine concentration between normal control subjects and patients with EIAN could be detected with a mild degree of exercise challenge in our study.

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