

The necessity for dual food intake to provoke food-dependent exercise-induced anaphylaxis (FEIAn): A case report of FEIAn with simultaneous intake of wheat and *umeboshi*

Yukoh Aihara, MD,^a Takeshi Kotoyori, MD,^a Yuriko Takahashi, MD,^a
Hiroyuki Osuna, MD,^b Sumi Ohnuma MD,^b and Zenro Ikezawa, MD^b *Yokohama, Japan*

Background: Food-dependent exercise-induced anaphylaxis (FEIAn) is classified among the physical allergies. Many different food allergens have been reported, but the pathophysiology of FEIAn remains unknown. Furthermore, provocation tests with a suspected food do not always succeed in patients with FEIAn.

Objective: We sought to clarify and investigate causative foods and mechanisms of FEIAn in a 14-year-old boy. In addition, we tested in vivo and in vitro effects of cromolyn sodium in the same patient.

Methods: We used open challenge tests for the provocation of FEIAn and measured changes in plasma histamine levels and FEV1. In addition, we investigated the mechanism of FEIAn in this case with in vitro histamine release testing.

Results: The patient was diagnosed as having FEIAn by provocation testing with a simultaneous intake of wheat and *umeboshi*, but not when each food was eaten singly, followed by exercise. In addition, his plasma histamine level increased transiently and forced expiratory volume 1, expressed as a percentage change from baseline, decreased significantly. A synergistic effect on in vitro histamine release testing with 2 kinds of the causative foods was shown. Administration of cromolyn sodium proved to be effective on both the in vitro and in vivo tests.

Conclusion: This is the first report of FEIAn provoked by the test with a simultaneous intake of 2 kinds of food. This case might in part explain negative challenge test results in patients with FEIAn. (*J Allergy Clin Immunol* 2001;107:1100-5.)

Key words: Food-dependent exercise-induced anaphylaxis, wheat, *umeboshi*, dual food challenge, histamine release test, cromolyn sodium, forced expiratory volume

Exercise-induced anaphylaxis (EIAN) is a form of physical allergy.¹⁻³ A subtype of EIAN, which requires the combination of exercise and the intake of specific

Abbreviations used

CS:	Cromolyn sodium
ECP:	Eosinophilic cationic protein
EIAN:	Exercise-induced anaphylaxis
FEIAn:	Food-dependent exercise-induced anaphylaxis
HRT:	Histamine release test
SPT:	Skin prick test

food, is known as food-dependent EIAN (FEIAn).^{1,4-7} In recent years there has been an increasing number of reports of FEIAn involving many kinds of foods.⁴⁻⁹ However, the pathophysiologic nature of FEIAn remains unknown. Furthermore, challenge tests with a suspected food followed by exercise do not always provoke the symptoms of FEIAn.^{5,8,10}

In this article, we report a unique case of FEIAn that was diagnosed by provocation testing under certain conditions. Open challenge tests with the suspected combination foods of a lunch menu followed by exercise did evoke the symptoms, but single foods alone or exercise alone or single foods plus exercise did not. In trying to determine the causative allergen in the lunch menu, we finally clarified the necessity for the simultaneous intake of 2 separate food allergens to provoke the symptoms. We also showed that in this case oral administration of cromolyn sodium (CS) was effective in preventing FEIAn in vivo.

CASE REPORT

A 14-year-old boy was referred to our hospital in June 1997 after an episode of dyspnea, generalized urticaria, facial angioedema, and abdominal pain during 15 to 20 minutes of jogging, 30 minutes after eating the contents of a commercially available lunch box. He had experienced similar episodes 4 times in the previous 2 years. He had been diagnosed with bronchial asthma at 4 years of age. However, there had been no respiratory symptoms for more than 7 years except in these episodes. He also had a history of pollinosis to Japanese cedar since the age of 10 years. In his family, his brother has food allergy against yam. From his medical history we suspected him to have FEIAn.

Initially we carried out a series of investigations that included in vivo and in vitro allergy investigations on the contents of the lunch box. The lunch box contained 10 foods. Allergen extracts were commercially available for all of the foods except *umeboshi*. *Umeboshi*

From the Departments of ^aPediatrics and ^bDermatology, Yokohama City University Medical Center, Yokohama, Japan.

Supported by the Grants in Support of the Promotion of Research at Yokohama City University.

Received for publication October 26, 2000; revised March 6, 2001; accepted for publication March 6, 2001.

Reprint requests: Yukoh Aihara, MD, Department of Pediatrics, Yokohama City University Medical Center, 4-57 Urafune-cho, Minami-ku, Yokohama 232-0024, Japan.

Copyright © 2001 by Mosby, Inc.

0091-6749/2001 \$35.00 + 0 1/10/115627

doi:10.1067/mai.2001.115627

is the pickled fruit of the *Prunus mume*, a tree that has grown wild in Japan and China for centuries. The fruit, *ume*, is usually described as a Japanese plum or apricot. For the preparation of *umeboshi*, yellow *ume* are steeped in white liquor and salt for several days; after drying and maturing, the product is sold in plastic packs or small jars. *Umeboshi* is used as an accompaniment to Japanese dinners, served either by itself or with other pickles, usually at the end of a meal. It is considered beneficial to the digestion.

The subject's white blood cell count was 5300/ μ L (eosinophils, 9.3%; normal range, 0% to 6%); the total serum was IgE 330 IU/mL (normal, <250 IU/mL; PRIST, Pharmacia Diagnostic, Uppsala, Sweden), and CAP System FEIA RAST (Pharmacia) results were class 2 for wheat, rice, sesame, buckwheat, house dust, and house dust mite and class 3 for Japanese cedar. We regard RAST class 2 and greater as representing a positive test. Further studies were carried out, and we diagnosed the boy as having FEIAN with a unique pattern of causative foods. We therefore investigated the mechanisms of FEIAN in this patient.

METHODS

Preparation of *umeboshi* allergens

Extracts of all allergens except *umeboshi* in this study are commercially available. To test for *umeboshi* we prepared our own extract. One gram of *umeboshi* flesh was homogenized, and 1 mL of buffered solution (PIPES-AMC24) was added to it. The mixture was then centrifuged at 2000g for 10 minutes. The supernatant was collected as an original *umeboshi* antigen and stored as a stock solution at -80°C until used.

Histamine release test

A histamine release test (HRT; Lucica HRT, Asahi Chemical Industry Co, Ltd, Nobeoka, Japan)¹¹ is available commercially for 20 allergens, including all of those tested apart from *umeboshi*. For this test, class 1 and greater are regarded as positive.

Skin prick test

Skin prick tests (SPTs) were performed with multiple commercial allergens (Torii Pharmaceutical Co, Ltd, Tokyo, Japan) prepared 1:20 wt/vol. Fresh-food prick tests in which the prick + prick technique¹² was used were also performed with *umeboshi*. All SPTs were performed with steel lancets. Responses were read at 15 minutes and graded according to the standard method recommended by the European Academy of Allergy and Clinical Immunology.¹³ Grade + is 25% of the area of wheal induced by the positive histamine control (10 mg/mL), grade ++ is 50%, grade +++ is 100%, and grade ++++ is 200%. Grade + or larger is considered positive.

Provocation test

To carry forward the investigation of this patient, a series of challenge procedures was conducted. A full explanation of the tests to be undertaken was given to the patient and his parents, and informed consent was obtained. Open challenge tests were performed through use of the same lunch menu that produced the symptoms of FEIAN followed by exercise. The exercise part of the challenge consisted of a treadmill ergometric stress test with progressively increasing speeds (up to Bruce's grade V).¹⁴ These exercise tests, each lasting 15 minutes, were carried out by the patient for 30 minutes after a meal with suspected food or foods.

During the challenge tests, pulmonary function measurements were performed through use of a computerized spirometer (Super-spiro, Chest MI, Co, Ltd, Tokyo, Japan). The values of peak expiratory flow rate and FEV₁ were measured and expressed as percentage changes from baseline (%FEV₁). Maximum percentage falls were calculated as follows: $100 \times (\text{pre-exercise value} - \text{lowest value}$

after exercise) / pre-exercise value.⁹ Blood pressure and pulse rate were also monitored before and after exercise challenge and during reactions. Challenge tests were carried out twice a day, in the morning and in the afternoon. If the challenge was positive, further challenges that day were canceled and no challenges were carried out the next day. When the patient 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.

In vitro *umeboshi* and wheat challenge with HRT

To understand further the pathophysiology between the positive provocation test of FEIAN and the necessity of a simultaneous intake of 2 food allergens, we carried out a further series of investigations. Using whole blood cells from the patient, we measured the amount of histamine released when challenged with the causative allergens. The allergens wheat (Greer Laboratory Co, USA) and *umeboshi* were used for the tests. Through use of glass microfiber plates, 25 μ L of peripheral whole blood was then incubated at 37°C for 60 minutes with 12.5 μ L of *umeboshi* antigen (1:9 dilution) plus 12.5 μ L of buffer, 12.5 μ L of wheat antigen (1:50-1:156,250 dilution) plus 12.5 μ L of buffer, both antigens together, or buffer alone. The amount of histamine released was measured according to the methods of Lucica HRT. In all experiments, triplicate samples were tested.

In vitro effect of CS on HRT with *umeboshi* and wheat

We incubated 25 μ L of peripheral whole blood at 37°C for 120 minutes with or without 12.5 μ L of appropriately diluted CS solution. Dual food antigens were then added: wheat antigen (dilution 1:1250) plus *umeboshi* antigen (dilution 1:9) for 90 minutes at 37°C . Released histamine was then measured. In all experiments, triple samples were tested.

In vivo effect of CS on the provocation tests with *umeboshi* and wheat

To test the in vivo effect of CS in our patient with FEIAN, we orally administered 100 mg of CS to the patient twice—4 hours before and 30 minutes before a challenge test with *umeboshi* and wheat; this was followed by exercise.

RESULTS

Histamine release tests with allergens

The Lucica HRT tests with the whole blood cells gave positive tests as follows: wheat, class 1; *umeboshi*, class 4; rice, class 1; soybean, class 1.

Skin prick testing with allergens

The SPTs were positive as follows: wheat ++; *umeboshi* +++; house dust +++.

Provocation tests

Initially, we confirmed through use of this challenge test protocol that consumption of the full contents of the lunch box followed by exercise produced the clinical symptoms of stridor; dyspnea; itching of the eyes, ears, and nose; sneezing, and generalized urticaria. The maximum fall in FEV₁ was 40% from baseline values. Neither eating the contents of the lunch box alone nor exercise alone induced the symptoms. We therefore made the diag-

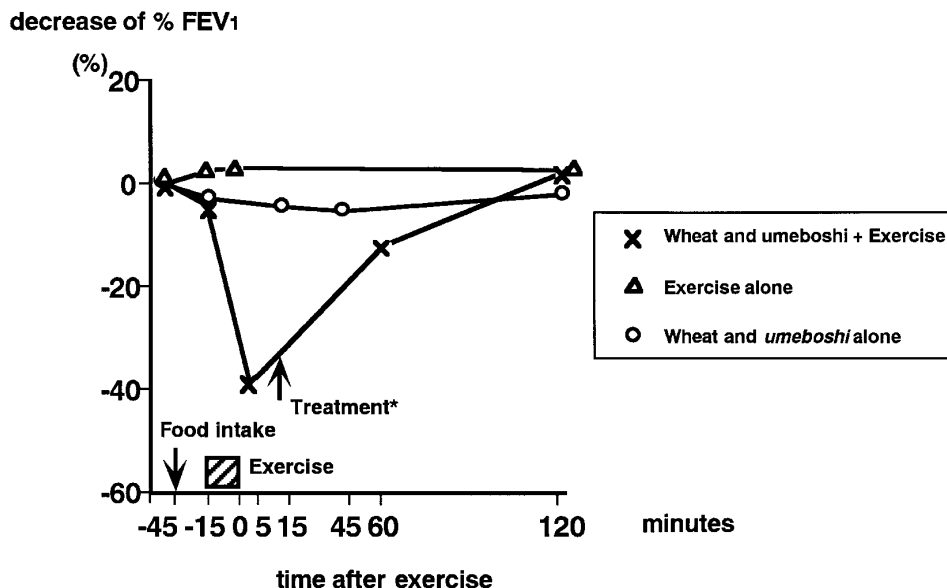


FIG 1. Changes in FEV1 during challenges. Effect on FEV1 with a simultaneous intake of wheat and *umeboshi* followed by exercise. Asterisk indicates that treatment with inhalation of β_2 -stimulant was performed.

nosis of FEIAN. We then began a series of challenge tests to identify the causative food allergen. We divided the 10 foods into 2 groups of 5 and challenged with each group plus exercise. One group gave a positive reaction, the other a negative reaction. We then challenged each of the 5 foods in the positive group individually. Each of these challenges was negative. We then considered the possibility that 2 foods might be required to produce a positive reaction. We decided to challenge with 2 foods and began with those foods that gave the most positive results with regard to HRT, SPTs, and specific IgE: wheat and *umeboshi*. The combination of these 2 foods plus exercise gave a positive challenge test result. Because this combination gave the positive reaction that we were seeking, we did not test any other combination of foods plus exercise; however, we tested our patient 4 times with wheat and *umeboshi* and obtained a positive test each time. Because he belongs to a football team in junior high school and enjoys running, he was quite willing to undertake this number of exercise challenges. The effects on FEV1 of the simultaneous intake of wheat and *umeboshi* followed by exercise and the effects of exercise alone and of wheat and *umeboshi* alone are shown in Fig 1.

In vitro *umeboshi* and wheat challenge with HRT

The amount of allergen-induced histamine release from basophils in vitro (Fig 2) was 3.5 ± 1 ng/mL with 1:250 dilution of wheat antigen and 5.5 ± 1.0 ng/mL with 1:9 dilution of *umeboshi* antigen, but simultaneous stimulation with both allergens at the same concentrations augmented the level of histamine release to 16 ± 2.0 ng/mL (Fig 2). However, under the same conditions no augmented histamine release was observed in another patient with allergy against wheat but not against *umeboshi* (Fig 2).

We also measured levels of plasma histamine by means of a histamine radioimmunoassay kit (Immunotech Ltd, Paris, France). Plasma histamine increased transiently from 3.4 to 7.5 nmol/L (Fig 3) during the positive challenge test (normal, <0.08 nmol/L).

In vitro effect of CS on HRT with *umeboshi* and wheat

To investigate possible therapy for FEIAN, we evaluated the effectiveness of CS both in vitro and in vivo.¹⁵ First, we showed that the amount of histamine released from the patient's basophils when they were stimulated with the allergens was decreased by approximately 50% when his whole blood cells were preincubated with CS for 2 hours at 37°C in vitro (Fig 4).

In vivo effect of CS on the provocation tests

Oral administration of 100 mg of CS to the patient twice both prevented the occurrence of clinical symptoms of FEIAN and inhibited completely the transient decrease of %FEV1 (Fig 3). This treatment with CS also suppressed the transient increase in plasma histamine (Fig 3).

Finally heat challenge with hot bathing at 43°C did not induce any symptoms of FEIAN.

DISCUSSION

FEIAN is classified as a physical allergy.^{1,4} Although several hypotheses have been suggested, the mechanism of the disease has still not been elucidated. It is likely that release of mediators from mast cells is an essential local feature at the final step of FEIAN as well as EIAN.³ In some cases, participation of the autonomic nervous system,¹⁶ intake of a certain medicine,⁵ consumption of a certain amount of food allergen,¹⁰ family tendency,¹⁷

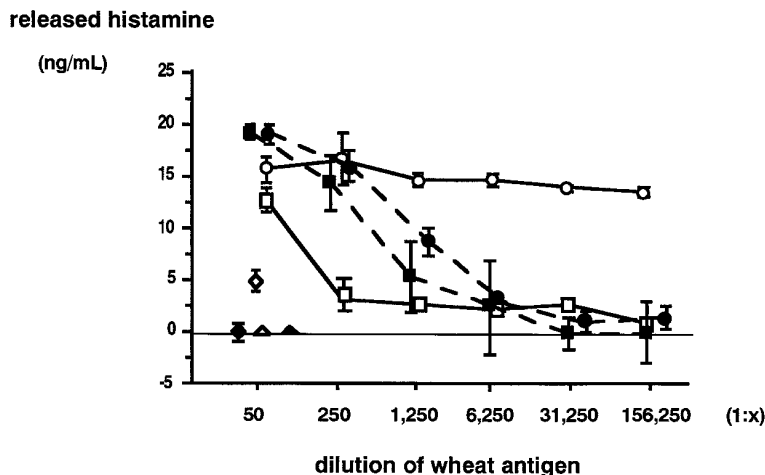


FIG 2. Augmentation of histamine release from peripheral blood cells of the subject with in vitro stimulation with the combination of wheat and *umeboshi* antigen. Open symbols represent patient; closed symbols represent representative control subject with allergy to wheat but not *umeboshi*. ($\diamond$, $\blacklozenge$) = *Umeboshi* antigen alone; ($\square$, $\blacksquare$) = wheat antigen alone; ($\circ$, $\bullet$) = *umeboshi* antigen plus wheat antigen; ($\triangle$, $\blacktriangle$) = buffer alone. Data represent means $\pm$ SDs of released histamine.

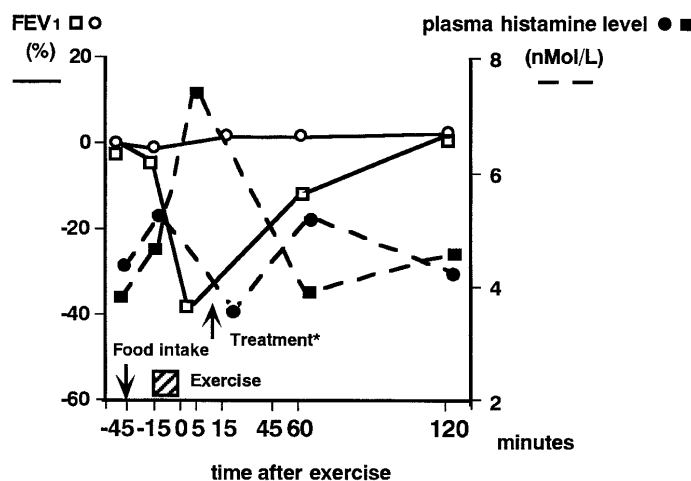


FIG 3. In vivo inhibitory effect of oral administration of CS on change in FEV1 and plasma histamine release in the patient. Solid lines and open symbols represent data for FEV1; dotted lines and closed symbols represent data for plasma histamine levels with CS ($\circ$, $\bullet$) or without CS ($\square$, $\blacksquare$).

weather, humidity, stress, menstruation cycle in females, and general condition of the patient might be responsible for the induction of the symptoms. In most cases, a single food allergen has been reported as inducing the symptoms; in rare cases, however, many kinds of food allergens independently evoked the symptoms.^{8,9}

To diagnose FEIAN correctly, a provocation challenge test with a suspected food is essential and indispensable except in the most severe cases. However, it has been reported that challenge tests do not always provoke the symptoms of FEIAN.^{5,8,10} Reasons for negative tests have not been established to date, and they remain to be clarified.

In our case, we confirmed the diagnosis of FEIAN associated with a simultaneous intake of 2 kinds of food on the basis of (1) the patient's symptoms, (2) his histo-

ry of similar episodes, (3) laboratory investigations, including in vitro and in vivo testing for specific allergens, and especially (4) provocation testing. That is, we could succeed in provoking the symptoms of FEIAN in the open challenge test with the simultaneous intake of wheat and *umeboshi* followed by exercise but not with each single food or with exercise alone. In addition, we demonstrated both a decrease of %FEV1 (Fig 1) and the transient increase of plasma histamine level (Fig 3) during the positive test. However, there was no change in CH50 value¹⁸ and no correlation between serum level of eosinophilic cationic protein (ECP)¹⁹ and number of peripheral blood eosinophils (data not shown).

Furthermore, the synergistic effect on in vitro histamine release from basophils was shown with a simulta-

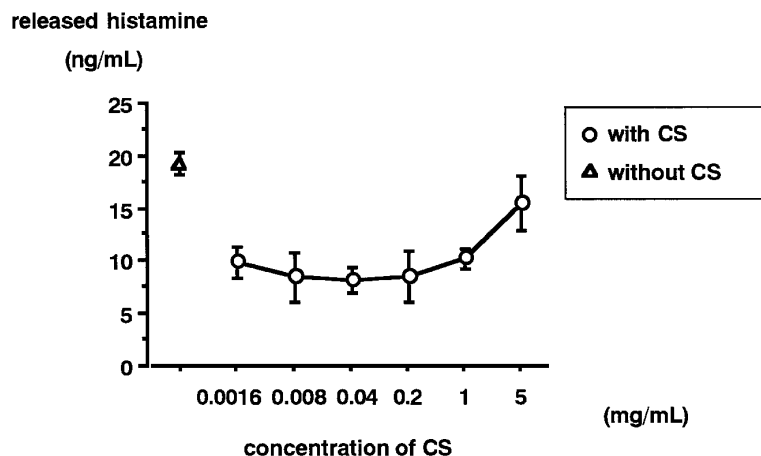


FIG 4. Inhibitory effect of in vitro pretreatment with CS on histamine release from peripheral blood cells with wheat and *umeboshi* antigen, with (○) or without (△) 12.5 μ L of appropriately diluted CS solution. Data represent means $\pm$ SDs of released histamine.

neous addition of 2 causative allergens (Fig 2). From these data it can be hypothesized that to provoke the symptoms of FEIAN, as in this case, the amount of released chemical mediators, including histamine, needs to exceed a certain threshold level. This hypothesis was supported in part by the report in which a large amount of causative food allergen was critical to inducing the symptoms of FEIAN in the provocation test.¹⁰ Although we did not determine whether other combinations of food allergen would induce the symptoms of FEIAN, we did show that 2 kinds of allergens, wheat and *umeboshi*, were necessary to induce both symptoms and reach a particular plasma histamine level. Similar phenomena have been reported in cases of drug eruption with simultaneous intakes of 2 kinds of drugs.²⁰ Moreover, some medications, including nonsteroidal anti-inflammatory drugs, have been shown to augment the symptoms of FEIAN.⁵ This too might support our explanation in terms of the threshold level of chemical mediators; it also might explain, in part, the negative challenge test in FEIAN with a suspected food followed by exercise.

Nevertheless, we could not rule out the possibility that a difference in quality between the 2 allergens, wheat and *umeboshi*, affected the release of chemical mediators, including histamine, from the patient's peripheral blood cells. However, from our in vitro data, it is reasonable to assume that the quantity of histamine released can be critical (Fig 2).

It is possible that the histamine in the plasma, which increases during the food + exercise challenge, does not come from blood basophils. Orally administered CS is poorly absorbed, and peak plasma levels of CS after single oral doses of 100, 200, and 300 mg in both healthy subjects and food allergic patients have been recorded as 8 ng/mL, 9 ng/mL, and 10.75 ng/mL, respectively.^{21,22} These levels are far lower than the 1600 ng/mL that we used in our in vitro experiments and that gave optimal inhibition of histamine release from blood cells. Levels

of this order will probably be reached in the gut mucosa, and the fact that we showed treatment with oral CS to prevent the increase in plasma histamine suggests that cells in the gut mucosa, and not blood basophils, are the source of this histamine.

In the differential diagnosis of FEIAN, cholinergic urticaria is known to be important.²³ However, we were able to rule out this possibility with the heat challenge test, in which clinical symptoms were not induced. In addition, we excluded an association of additives in *umeboshi* in this case by using several kinds of commercially available *umeboshi* with and without additives in our in vitro histamine release tests.

CS is known to be a useful drug for the treatment of allergic conditions, including food allergy.^{24,25} Its primary mode of action is thought to be the inhibition of chemical mediators from effector cells, including mast cells and basophils.^{26,27} Furthermore, it has a direct inhibitory effect on allergic inflammatory cells in vitro.²⁸ It is reported to have been effective in a case of FEIAN.¹⁵ Therefore, we examined the usefulness of CS in our patient. In vivo administration of CS prevented induction of the symptoms of FEIAN, the decrease of %FEV1 value, and the increase in plasma histamine (Fig 3). In vitro pretreatment of whole blood with 40 μ g/mL of CS solution inhibited the histamine release from basophils maximally (Fig 4). Since the initial investigations we have administered CS to this patient for more than 2 years without any episode of FEIAN. Thus although the effectiveness of CS in patients with food allergy is still controversial,^{15,29} at least in our case, CS was useful.

Finally, for patients with FEIAN, an accurate diagnosis is recommended to avoid unnecessary dietary restriction and prevent serious reactions. A provocation test with a suspected food followed by exercise is essential for the diagnosis. However, the frequency of positive reactions in such tests is not very high. Our case might suggest that an excess of the released chemical mediators, such as

histamine, by several kinds of allergens over threshold values would be necessary to provoke the symptoms. We believe that this case presentation does contribute useful information about the pathophysiologic nature of, as well as the therapy for, FEIAN.

We thank Mr H. Nagai and Dr K. Ohyama, Pharmaceutical Division, Asahi Chemical Industry Co (Shizuoka, Japan), and Dr K. Tsubaki, Basic Research Laboratory, Asahi Denka Co (Tokyo, Japan), for preparation of allergens and analyses of in vitro histamine release test with the 2 causative allergens, and we thank Dr A. Edwards, Southampton General Hospital (Southampton, United Kingdom), for critical discussions.

REFERENCES

- Sheffer AL, Soter NA, McFadden ER Jr, Austen KF. Exercise-induced anaphylaxis: a distinct form of physical allergy. *J Allergy Clin Immunol* 1983;71:311-6.
- Casale TB, Keahey TM, Kaliner M. Exercise-induced anaphylactic syndrome. *JAMA* 1986;255:2049-53.
- Sheffer AL, Tong AKF, Murphy GF, Lewis RA, McFadden ER Jr, Austen KF. Exercise-induced anaphylaxis: a serious form of physical allergy associated with mast cell degranulation. *J Allergy Clin Immunol* 1985;75:479-84.
- Kidd JM III, Cohen SH, Sosman AJ, Fink JN. Food-dependent exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1983;71:407-11.
- Dohi M, Suko M, Sugiyama H, Yamashita N, Tadokoro K, Juji F, et al. Food-dependent, exercise-induced anaphylaxis: a study on 11 Japanese cases. *J Allergy Clin Immunol* 1991;87:34-40.
- Maulitz RM, Pratt DS, Schocket AL. Exercise-induced anaphylactic reaction to shellfish. *J Allergy Clin Immunol* 1979;63:433-4.
- Buchbinder EM, Bloch KJ, Moss J, Guiney TE. Food-dependent, exercise-induced anaphylaxis. *JAMA* 1983;250:2973-4.
- Romano A, Di Fonso M, Giuffreda F, Quarantino D, Papa G, Palmieri V, et al. Diagnostic work-up for food-dependent, exercise-induced anaphylaxis. *Allergy* 1995;50:817-24.
- Caffarelli C, Cavagni G, Giordano S, Terzi V, Perrone F. Reduced pulmonary function in multiple food-induced, exercise-related episodes of anaphylaxis. *J Allergy Clin Immunol* 1996;98:762-5.
- Hanakawa Y, Tohyama M, Shirakata Y, Murakami S, Hashimoto K. Food-dependent exercise-induced anaphylaxis: a case related to the amount of food allergen ingested. *Br J Dermatol* 1998;138:898-900.
- Skov PS, Norm S, Weeke B. A new method for detecting histamine release. *Agents Actions* 1984;14:414-6.
- Dreborg S, Foucard T. Allergy to apple, carrot, and potato in children with birch pollen allergy. *Allergy* 1983;38:167-72.
- Dreborg S. Skin tests used in type I allergy testing. Position paper. *Allergy* 1989;44(Suppl 10):22-30.
- Bruce RA, Blackmon JR, Jones JW, Strait G. Exercise testing in adult normal subjects and cardiac patients. *Pediatrics* 1963;32:742-56.
- Juji F, Suko M. Effectiveness of disodium cromoglycate in food-dependent, exercise-induced anaphylaxis: a case report. *Ann Allergy* 1994;72:452-4.
- Fukutomi O, Kondo N, Agata H, Shinoda S, Shinbara M, Orii T. Abnormal responses of the autonomic nervous system in food-dependent exercise-induced anaphylaxis. *Ann Allergy* 1992;68:438-45.
- Grant JA, Farnam J, Lord RA, Thueson DO, Lett-Brown MA, Wallfisch H, et al. Familial exercise-induced anaphylaxis. *Ann Allergy* 1985;54:35-8.
- Obata T, Kishida M, Okuma M, Walsh GM, Ikura Y. A case of exercise-induced anaphylaxis: evidence of an association with the complement system. *Acta Paediatr Jpn* 1989;31:340-5.
- Romano A, Fanale-Belasio E, Di Fonso M, Giuffreda F, Palmieri V, Zepilli P, et al. Eosinophil-derived proteins in postprandial (food-dependent) exercise-induced anaphylaxis. *Int Arch Allergy Immunol* 1997;113:505-11.
- Verbov J. Fixed drug eruption due to a drug combination but not to its constituents. *Dermatologica* 1985;171:60-1.
- Iwasaki E, Baba M. Absorption and excretion of oral administration of disodium cromoglycate. *Yakuri to Chiryo* 1982;10:2919-25.
- Andre F, Andre C, Feknous M, Colin L, Cavagna S. Digestive permeability to different-sized molecules and to sodium cromoglycate in food allergy. *Allergy Proc* 1991;12:293-8.
- Soter NA, Wasserman SI, Austen KF, McFadden ER Jr. Release of mast-cell mediators and alterations in lung function in patients with cholinergic urticaria. *N Engl J Med* 1980;302:604-8.
- Brostoff J, Carini C, Wraith DG. Production of IgE complexes by allergen challenge in atopic patients and the effect of sodium cromoglycate. *Lancet* 1979;1(8129):1268-70.
- Papageorgiou N, Lee TH, Nagakura T, Cromwell O, Wraith DG, Kay AB. Neutrophil chemotactic activity in milk-induced asthma. *J Allergy Clin Immunol* 1983;72:75-82.
- Orr TSC, Cox JSG. Disodium cromoglycate, an inhibitor of mast cell degranulation and histamine release induced by phospholipase A. *Nature* 1969;223:197-8.
- Orr TSC, Pollard MC, Gwilliam J, Cox JSG. Mode of action of disodium cromoglycate, studies on immediate type hypersensitivity reactions using 'double sensitization' with two antigenically distinct rat reagents. *Clin Exp Immunol* 1970;7:745-57.
- Kay AB, Walsh GM, Moqbel R, MacDonald AJ, Nagakura T, Carroll MP, et al. Disodium cromoglycate inhibits activation of human inflammatory cells in vitro. *J Allergy Clin Immunol* 1987;80:1-8.
- Burks AW, Sampson HA. Double-blind placebo-controlled trial of oral cromolyn in children with atopic dermatitis and documented food hypersensitivity. *J Allergy Clin Immunol* 1988;81:417-23.