

Food-Dependent Exercise-Induced Anaphylaxis: Clinical and Laboratory Findings in 54 Subjects

Antonino Romano^{a,c} Marina Di Fonso^a Francesca Giuffreda^a
Giuseppe Papa^a Maria Cristina Artesani^a Marinella Viola^a Alberto Venuti^a
Vincenzo Palmieri^{a,b} Paolo Zeppilli^{a,b}

^aDepartment of Internal Medicine and Geriatrics, UCSC-Allergy Unit, Complesso Integrato Columbus and

^bDepartment of Internal Medicine and Geriatrics, UCSC-Sports Medicine Unit, Rome, and ^cIRCCS Oasi Maria SS, Troina, Italy

Key Words

CAP System FEIA · Anaphylaxis, food-dependent, exercise-induced · Prick plus prick test · RAST

Abstract

Background: In some subjects, specific foods trigger anaphylaxis when exercise follows ingestion (specific food-dependent exercise-induced anaphylaxis, FDEIAN). Skin test and/or RAST positivity to foods suggest an IgE-mediated pathogenic mechanism. Others suffer from anaphylaxis after all meals followed by exercise, regardless of the food eaten (nonspecific FDEIAN). We sought to identify the culprit foods with a diagnostic protocol. **Methods:** We collected detailed histories and performed skin prick tests (SPT) with 26 commercial food allergens, prick plus prick tests (P+P) with 15 fresh foods (including 9 assessed with SPT), and RAST for 31 food allergens. Treadmill stress tests were administered after a meal without any positive food (food plus exercise challenge, FEC). **Results:** Among the 54 patients, 6 could not recall any suspect food. The other 48 suspected a specific food in at least one episode. The most frequent were toma-

toes, cereals and peanuts. Fifty-two subjects were positive to at least one food (22 to more than 20), whereas 2 showed no positive results. All suspect foods were positive. SPT, P+P and RAST displayed different degrees of sensitivity. Each test disclosed some positivities not discovered by others. Two subjects reacted to FEC. Overall, 48 patients probably had specific FDEIAN and the other 6 nonspecific FDEIAN. **Conclusions:** It is useful to test both in vivo and in vitro an extensive panel of foods. Avoidance of foods associated with skin test and/or RAST positivity for at least 4 h before exercise has prevented further episodes in all our patients with specific FDEIAN.

Copyright © 2001 S. Karger AG, Basel

Introduction

Since the syndrome of food-dependent exercise-induced anaphylaxis (FDEIAN) was first reported in 1979 [1], numerous foods (e.g., shrimp, shellfish, chicken, wheat, nuts, fruits such as apples, peaches and grapes, and vegetables like celery, tomatoes, fennel, lettuce and potatoes) have been implicated in this clinical entity [2–4]. In

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2001 S. Karger AG, Basel
1018–2438/01/1253–0264\$17.50/0

Accessible online at:
www.karger.com/journals/iaa

Correspondence to: Dr. Antonino Romano
Unità di Allergologia, Complesso Integrato Columbus
Via G. Moscati, 31, I–00168 Rome (Italy)
Tel. +39 06 3503782, Fax +39 06 3503653
E-Mail columbus.allerg@linet.it

the most recent study, that of Shadick et al. [5], one third of the 279 subjects with exercise-induced anaphylaxis (EIAN) reported one or more food triggers. In some cases, specific foods cause anaphylaxis when exercise follows ingestion, but are tolerated if not followed by exercise (specific FDEIAN or SFDEIAN). Others suffer EIAN after all meals followed by exercise, regardless of the food eaten (nonspecific FDEIAN or NSFDEIAN) [6].

The mechanism by which physical exertion provokes these reactions is not fully understood. These patients' skin test and/or RAST positivity to foods they reportedly consumed prior to the reactions suggest an IgE-mediated pathogenic mechanism. In the non-specific form, reaginic pathogenesis is excluded, especially in patients with food-negative allergologic exams [6–9]. A lower mast cell threshold for mediator release has been reported in some patients with EIAN or food-associated EIAN after exercise alone [10]. Kivity et al. [11] demonstrated increased mast cell releasability in patients with food-dependent urticaria-angioedema only after exercise following the intake of foods to which they were reactive. Furthermore, the increase in serum levels of histamine in some patients with FDEIAN after challenges with the culprit food plus exercise has been correlated with the clinical response [8, 12, 13]. Recently, we found serum levels of eosinophil cationic protein increased in 6 SFDEIAN patients after challenges including both suspect food ingestion and exercise. However, anaphylactic symptoms occurred in only 3 cases [14].

Exercise might increase food allergen distribution by changes in splanchnic blood flow [2]. A dysfunction of the autonomic nervous system [9] and the ability of gastrin to increase cutaneous mast cell mediator release [15] have also been hypothesized to play a part in the pathogenesis of symptoms. Lately, there have been more reports of EIAN, probably because of a greater awareness of this syndrome on the part of physicians and increased athletic activity at all levels [5]. Thus, it is important to recognize and prevent this syndrome.

In the present study, a specific diagnostic protocol with the standard techniques – both in vivo (skin tests) and in vitro (a second-generation test for detecting specific IgE) – was applied to patients with FDEIAN in an attempt to identify as many positive foods as possible. Such a protocol has been described in a previous study [3], in which 14 subjects of the present one were first evaluated. Our workup also included an exercise challenge after a meal without any of the foods associated with skin test or RAST positivity.

Materials and Methods

We studied all patients seen by our staff between January 1990 and June 1999 reporting at least one EIAN episode that occurred within 2 h after a meal. Patients were diagnosed as having EIAN according to the established clinical criteria [10, 16, 17] as codified by Dohi et al. [8]. In particular, all our subjects had suffered from one or more episodes of severe hypotension or syncope and/or upper respiratory tract obstruction with flushing or general urticaria in association with postprandial exercise. All the allergologic exams were carried out from 1 to 6 months after the last reaction.

We carefully questioned patients to identify all foods ingested during the 24-hour period preceding each reactive episode. Foods repeatedly eaten prior to exercise without provoking symptoms were also noted. After obtaining the informed consent of the patient (or the parents of those under 18 years of age), we performed a physical examination – including electrocardiogram, echocardiogram and pulmonary function tests – to rule out cardiorespiratory diseases, and allergologic investigations comprising the tests listed below.

In vivo

Skin prick tests (SPT) were carried out with multiple commercial allergens (20 airborne and 26 food; Dome/Hollister-Stier, Bayro-pharm, Milan, Italy). Airborne antigens included grasses (*Phleum pratense*, *Lolium perenne*, *Poa pratensis*), mugwort, *Parietaria*, *Plantago*, ragweed mixture, olive tree, birch, beech, cypress and plane tree, *Dermatophagoides pteronyssinus* and *farinae*, dog and cat dander, *Alternaria tenuis*, *Cladosporium herbarum*, *Aspergillus* mixture and *Penicillium* mixture. The food allergen panel, prepared 1:20 (w/v), included a mixture of meats (lamb, rabbit, beef/veal, pork, chicken), egg white, cow's milk, cod, shrimp, wheat, rye, barley, oats, maize, rice, peas, peanuts, soybeans, beans, walnuts, almonds, tomatoes, potatoes, carrots, garlic, onions, apples, celery, bananas and peaches.

Fresh-food prick tests using the prick plus prick technique (P+P) described by Dreborg and Foucard [18] were also performed for the last nine foods cited above and for kiwis, lentils, fennel, parsley, basil and lettuce. All pricks were administered with steel lancets (Allergy Pricker; DHS Prick Lancet). A positive skin test was defined by a wheal at least 3 mm in diameter as recommended by the Sub-Committee on Skin Tests of the European Academy of Allergology and Clinical Immunology [19]. Positive controls were done with histamine at 10 mg/ml.

In vitro

Measurement of total serum IgE levels was performed by Phade-zym IgE PRIST (Pharmacia, Uppsala, Sweden) with a detection range of 5–1,000 kU/l. Measurement of serum levels of specific IgE for each of the food allergens (with the exception of the meat mixture) was determined by an immunofluorimetric method (RAST FEIA, CAP System or CAP, Pharmacia) with a detection range of 0.35–100 kU/l. CAP for the same panel of food allergens was also performed on a control population (21 athletes from the Italian national soccer team with no symptoms or histories of EIAN or food allergies), and the normal cutoff was established using receiver-operating characteristic curve analysis [3].

Food and Exercise Challenges

A treadmill ergonometric stress test with progressively increasing speeds was administered 90 min after the patient had finished a meal

without any of the foods associated with skin test or CAP positivity (food plus exercise challenge, FEC). Each meal contained about 700 kcal and included 40 g of bread and 100 g of pasta (except in patients positive to wheat, in whom such foods were replaced, if negative, by 150 g of potatoes), 120 g of meat or 150 g of fish, 5 ml of olive oil and one fruit. Subjects with negative results in allergologic tests ingested the foods they most frequently consumed before exercising.

During the FEC, the electrocardiogram was continuously monitored, and pulmonary ventilation (l/min), oxygen consumption (ml/min/kg body weight) and carbon dioxide production (ml/min) were measured with an open-circuit spirometer (Oxycon Beta, Mijnhardt, Best, The Netherlands). Equipment and personnel for emergency resuscitation were present during all challenges, and tests were interrupted immediately if the patient began to experience specific symptoms (pruritus, flushing, urticaria, dyspnea or abdominal cramps); otherwise, tests were continued until muscle exhaustion occurred, which was always after the patients had achieved 90% or more of their predicted maximum heart rate and oxygen consumption.

Each challenge was administered at 12:00 noon. The patients had been fasting since the evening before. None of the patients had used steroids, antihistamines or mast cell stabilizers for at least 2 weeks prior to the challenge. Because the patients' histories clearly indicated that the suspect foods were tolerated if not followed by exercise, and considering our previous study in which the oral provocation tests with suspect foods were negative in FDEIAN patients [14], we did not perform such tests.

Results

We studied 54 patients (31 males and 23 females), aged from 13 to 47 years (mean 23.09 ± 4.9). These subjects represented 75% of the 72 patients referred to our department between 1990 and 1999 because of EIAN episodes. Symptom duration since the first attack ranged from 1 to 240 months (mean 45.57 ± 56.8). Twenty subjects had experienced only one FDEIAN episode, 12 patients two episodes, 8 subjects between three and five, 9 between six and ten, and 5 patients more than ten. Fourteen patients had also suffered from one to fifteen episodes of exercise-induced urticaria-angioedema.

Family histories were positive for allergic diseases in 33 subjects. Twelve patients had negative personal allergologic histories. Twenty-nine suffered from oculorhinitis, and of these 9 also experienced bronchial asthma; 16 suffered from seasonal symptoms, and 11 from perennial symptoms with seasonal worsening.

Nine patients presented urticaria and/or angioedema unrelated to food intake or exercise. On the occasion of their FDEIAN episodes, these patients had suffered symptoms in addition to the urticarial eruptions: all had also experienced angioedema (mainly of the face), 6 dyspnea (3 of these also colic, 2 choking and 1 loss of consciousness), and 3 hypotension (2 of these also dyspnea and 1 diarrhea). These additional symptoms allowed us to rule out flares of their chronic urticaria.

Eight subjects had manifested adverse food reactions unrelated to exercise, and 3 reported the oral allergy syndrome. In all patients, the allergologic evaluation was positive for the culprit foods (nuts, vegetables such as eggplant and chicory, and fruits like kiwis and peaches). Two subjects presented cholinergic urticaria. Nine patients reported adverse reactions to acetylsalicylic acid, and 1 also to ketoprofen. All these subjects had experienced urticarial reactions (3 also facial angioedema) within 4 h after drug intake. Six subjects could not recall any suspect food. The other 48 suspected a specific food in at least one episode. These foods are listed in table 1. The most frequent were tomatoes, cereals and peanuts.

The time elapsed between meal and exercise ranged from 30 to 120 min, and the duration of exercise before the onset of symptoms ranged from 10 to 50 min; 8 subjects had their symptoms during the recovery phase. The activities most frequently associated with FDEIAN symptoms were football (40.7% of patients), followed by running (29.6%), dancing (16.7%), gymnastics (13%), tennis

Table 1. Reported food triggers in 48 patients with SFDEIAN

Foods	Patients	
	n	%
Tomatoes	14	29.2
Wheat	8	16.7
Peanuts	8	16.7
Maize	6	12.5
Soybeans	5	10.4
Lettuce	3	6.2
Fennel	3	6.2
Shrimp	3	6.2
Peas	3	6.2
Beans	2	4.2
Lentils	2	4.2
Garlic	2	4.2
Walnuts	2	4.2
Almonds	2	4.2
Peaches	2	4.2
Pork/beef	1	2.1
Hazelnuts	1	2.1
Apples	1	2.1
Rice	1	2.1
Bananas	1	2.1

Table 2. Results of allergologic evaluations of airborne allergens

	Patients positive for a single allergen (n = 13)		Patients positive for multiple allergens (n = 29)	
	number of positivities	% of patients	number of positivities	% of patients
Mugwort	6	46.1	16	55.2
Grasses	4	30.8	22	75.9
House dust mites	2	15.4	11	37.9
<i>Parietaria</i>	1	7.7	14	48.3
Olive tree			7	24.1
Cat dander			7	24.1
Cypress			7	24.1
<i>Alternaria</i>			3	10.3
Plane tree			4	13.8
Birch			4	13.8
Dog dander			2	6.9
Ragweed			1	3.4
Beech			1	3.4

(13%) and aerobics (11.1%). The level of exertion ranged from walking to water polo.

Five of our patients had taken acetylsalicylic acid shortly before one of the attacks, and 3 of these had taken nimesulide, ibuprofen or flurbiprofen before another attack. None of them had experienced adverse reactions to the aforementioned drugs before their FDEIA episodes, and 3 had tolerated acetylsalicylic acid and 1 nimesulide afterwards.

Fourteen subjects recalled other contributing factors on at least one occasion: 5 reported more frequent reactive episodes during spring; 4 (one of whom had also taken nimesulide) were menstruating; 2 were stressed; 1 was both menstruating and stressed, and 2 experienced stress and cold. The most frequent symptoms were pruritus (94.4% of patients), followed by urticaria (85.2%), angioedema (83.3%), flushing (74.1%), dyspnea (70.4%), gastrointestinal disturbances (nausea, diarrhea, colic, vomiting: 35.2%), hypotension (33.3%) and upper respiratory tract disturbances (choking, throat constriction, hoarseness: 29.6%).

Physical examinations and instrumental studies revealed hypertrophy of the right ventricle of the heart in 1 patient, hypertension in another, and a mitral valve prolapse in 2 others.

Allergologic Test Results

Normal Cutoff Values for CAP. In 17 of the 21 control subjects (aged 22–34 years; mean 27.19 ± 3.07), serum-specific IgE levels were <0.35 kU/l for all of the allergens

tested. The remaining 4 had levels of >0.35 kU/l in 10 determinations. Of a total of 651 assays, 1.60 kU/l (for rye) was the highest value of specific IgE among the ten positivities revealed [3]. According to the receiver-operating characteristic curve analysis, the cutoff value for CAP findings was 1.5 kU/l.

Skin Test, PRIST and CAP Results. The allergologic exams were positive for airborne allergens in 42 patients: the 29 symptomatic subjects (oculorhinitis) plus 13 who did not suffer from respiratory symptoms (table 2).

On the basis of skin test positivity, using 1.5 kU/l as the cutoff value for CAP, 52 patients presented positivity to at least 1 food, 14 to up to 5 foods and 38 to more than 8; 22 of the latter were positive to more than 20. Two subjects displayed no positive results.

Table 3 shows the foods assessed, the total number of subjects positive to each food, and the number of positivities detected only by SPT, P+P or CAP, respectively.

The foods to which patients were most frequently positive were parsley (37/54 patients), followed by apples, soybeans and peanuts (36 patients each). Surprisingly, none of the patients were positive to cow's milk, eggs or fish, which are among the most common causes of classic food allergies. Only 3 subjects were negative to vegetable foods. One displayed positivity to both shrimp and meats; the latter was not, however, confirmed by CAP (performed only in this case). Two patients presented hypersensitivity only to shrimp. On the other hand, several subjects had multiple positivities to vegetables, particularly to those commonly used as condiments (onions, garlic, basil, pars-

Table 3. Results of allergologic evaluations of food allergens

Food	No. Pos.	SPT	P+P	CAP
Meat mix	1	1	n.p.	0
Egg white	0	0	n.p.	0
Cow's milk	0	0	n.p.	0
Fish	0	0	n.p.	0
Wheat	27	1	n.p.	10
Rye	29	1	n.p.	12
Barley	26	2	n.p.	10
Oats	28	0	n.p.	11
Maize	35	3	n.p.	11
Rice	32	8	n.p.	4
Peas	30	7	n.p.	7
Peanuts	36	5	n.p.	7
Soybeans	36	4	n.p.	14
Beans	28	25	n.p.	0
Walnuts	32	2	n.p.	11
Almonds	23	15	n.p.	2
Shrimp	5	4	n.p.	1
Tomatoes	32	1	1	6
Carrots	11	0	5	1
Garlic	35	0	2	6
Onions	34	0	0	3
Apples	36	0	2	29
Celery	31	2	6	1
Bananas	19	0	13	3
Peaches	35	0	0	22
Potatoes	14	0	4	5
Kiwis	23	n.p.	23	0
Lentils	35	n.p.	12	1
Fennel	34	n.p.	14	5
Lettuce	32	n.p.	7	8
Parsley	37	n.p.	9	7
Basil	28	n.p.	6	6

The difference between the total positivities and the sum of those detected only by a single test is accounted for by those detected by more than one test. Food = Food assessed; No. Pos. = total positivities; SPT = positivities detected only by SPT; P+P = positivities detected only by P+P; CAP = positivities detected only by CAP; n.p. = not performed.

ley). The foods suspected on the basis of history data had positive results in all cases.

Each of three methods (SPT, P+P and CAP) disclosed some positivities not discovered by the other two (in fig. 1–3, the three methods are correlated). For foods tested with both SPT and P+P, the latter confirmed positive results obtained with commercial extracts in almost all cases and revealed other sensitivities that were not diagnosed with SPT, particularly those to bananas, apples, peaches and potatoes (fig. 1).

CAP proved to be more sensitive than SPT, except for beans, almonds, shrimp, celery and rice (fig. 2).

Regarding foods assessed with both P+P and CAP, the latter method was much more sensitive for apples and peaches, and P+P for kiwis and celery (fig. 3). Total serum IgE levels ranged from 11.8 to 745 kU/l (mean 158.7 ± 172.1 kU/l). Fourteen patients presented levels >150 kU/l.

FEC Results. Fifty-one subjects agreed to undergo the FEC. Two experienced isolated premature beats during the recovery phase. Three subjects reacted to this challenge: 1 patient with cholinergic urticaria developed classic papules (<10 mm) during the stress test (which, however, was considered negative); the remaining 2, 1 of whom suffered from cholinergic urticaria, experienced pruritus, flushing, urticaria, dyspnea and hypotension. Thus, FEC was considered positive only in these 2 subjects.

Five of the 27 patients positive to wheat reported that they had often exercised shortly after meals containing bread and/or pasta without any symptoms whatsoever. Because these foods represented important components of these patients' diets, the FEC was repeated with meals that included bread and/or pasta, and the results were negative.

Conclusion

Overall, 48 patients probably had SFDEIAN and the other 6 NSFDEIAN, even though only 2 of the latter reacted to the FEC. In the former, the histories, allergologic data and responses to elimination diets suggest a possible etiological role for specific foods. Patients were instructed to avoid all positive foods during the 4 h preceding physical exercise, and none of the 43 SFDEIAN subjects followed by us for 49.30 ± 27.27 months (range 6–114 months) experienced reactions; 5 subjects dropped out. This response provides indirect evidence that one or more of the positive foods might have triggered an EIAN reaction.

Among subjects suspected of NSFDEIAN, 2 displayed negative results in allergologic tests for food allergens; in the remaining 4 cases, each of whom was positive to two foods (rye and shrimp; wheat and rye; bananas and kiwis; celery and parsley), the presence of specific IgE antibodies does not appear to have played an etiological role in the reactive episodes.

All 6 subjects reported that the attacks had occurred after a meal followed by exercise and that they did not suspect any specific food. Four of these subjects had negative histories for allergic diseases, 1 suffered from urticar-

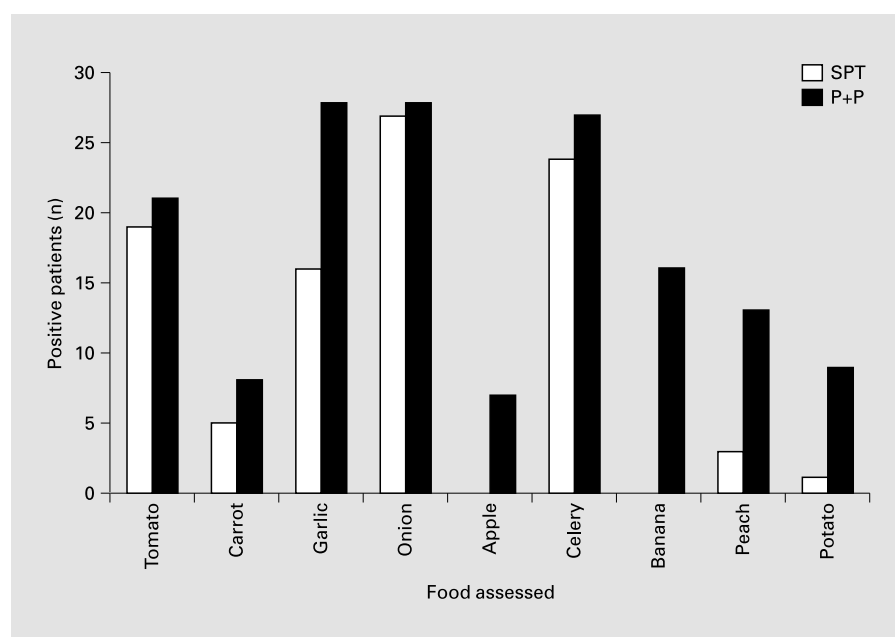


Fig. 1. Number of patients shown to be positive to various allergens by SPT and P+P.

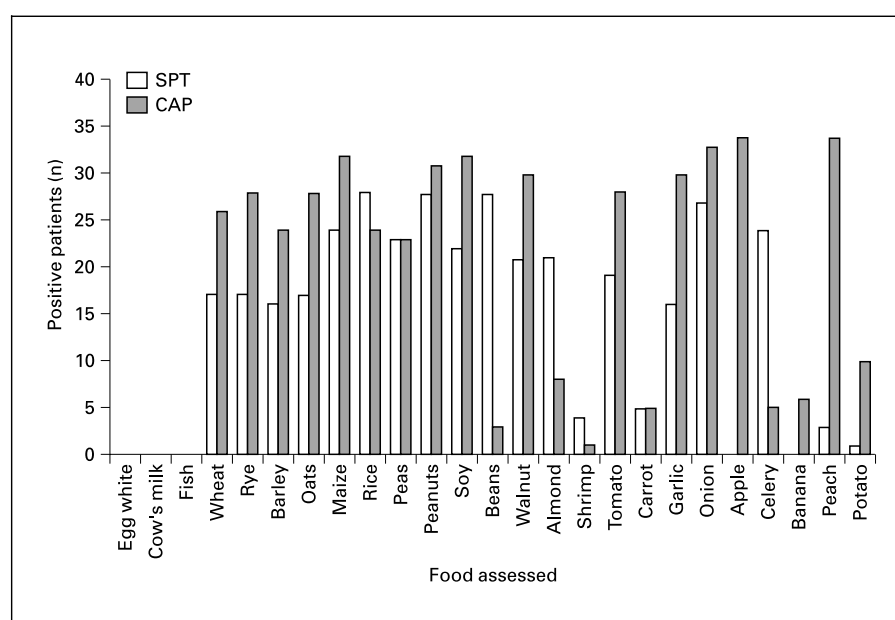


Fig. 2. Number of patients shown to be positive to various allergens by SPT and CAP.

ia-angioedema, and another from cholinergic urticaria. Avoiding exercise for at least 4 h after any meal was sufficient to prevent all exercise-related symptoms in all 5 NSFDEIAN subjects who were followed up by us for 50.40 ± 29.61 months (range 19–99 months); 1 subject dropped out.

Discussion

In the etiopathogenesis of SFDEIAN, an essential role is played by the ingestion of one or more foods to which the patient is sensitive. The aim of our diagnostic protocol was to identify these foods. In this connection, we emphasize the usefulness of testing both in vivo and in vitro a great number of foods. The combined use of SPT, P+P and CAP allowed us to identify numerous positivities.

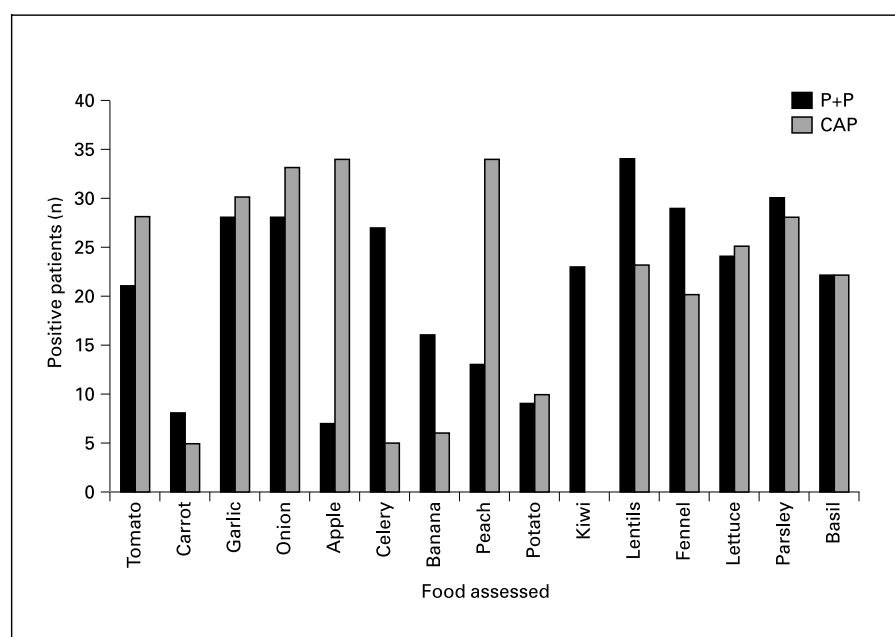


Fig. 3. Number of patients shown to be positive to various allergens by P+P and CAP.

Generally, each test disclosed some positivities not discovered by others: in particular, those to kiwis (all 23 positivities detected only by P+P) and beans (28 SPT positivities with only 3 CAP confirmations) (table 3).

The P+P revealed positivities (especially to fruits and vegetables) not disclosed by SPT. The negative results in some FDEIAN patients reported by others [7–9] could thus be explained by the fact that they did not use prick tests with fresh foods – which are often more sensitive than those with commercial extracts [20–22], even in case of FDEIAN [6, 12] – and/or by their use of a limited panel of allergens. Many uncommon food antigens may be ingested in composite dishes like salads, sauces, pizzas and certain ethnic foods. Stricker et al. [23], using a panel of 79 food antigens, demonstrated that 7% of cases reported as idiopathic anaphylaxis were not truly idiopathic.

The PRIST was not useful. We noted cases with high total IgE levels and a limited number of skin test and/or CAP positivities and vice versa. CAP disclosed numerous positivities, and in some cases proved to be more sensitive than in vivo tests, probably because its tridimensional solid phase allows faster and more efficient binding of specific IgE [24]. These features have made it useful in the diagnosis of classic food allergies [25].

The irregularity or unpredictability of FDEIAN – which may or may not occur even given the same level of exertion or the same amount of time elapsed after appar-

ently identical meals – may be partially explained by sensitizations to condiments, such as garlic, onions, basil and parsley present in many dishes, but rarely recalled by patients and almost never included in allergen panels. However, the irregularity might also be explained by contributing factors we noted – and also reported by others [10, 16, 17, 26, 27] – such as the use of nonsteroidal anti-inflammatory drugs prior to physical exertion, stress, menstruation, and seasonal or unfavorable climatic conditions. Nonsteroidal anti-inflammatory agents can increase digestive tract permeability, thus allowing relatively intact food antigen absorption [28].

The season during which subjects affected by pollinosis were active in sports was also an important contributing factor, as previously observed [10, 16, 17, 26, 27]. It is interesting to note, with regard to pollen sensitization, that 9 out of the 14 subjects in whom tomatoes were the suspect food suffered from seasonal allergic rhinitis and displayed skin test positivity for grasses which have structures cross-reacting with tomatoes [29]. All had manifested their seasonal symptoms before suffering EIAN episodes, supporting the hypothesis that sensitization to pollen allergens represents the primary event leading to the induction of IgE antibodies that may then cross-react with homologous food allergens [30].

In FDEIAN subjects with multiple food allergies, the composition of the meal consumed prior to physical exercise might play a part. As hypothesized for urticarial erup-

tions [31], some EIAN episodes might result from the ingestion of several different foods at the same time or be influenced by the volume of food and the season in which it is consumed.

Recently, Hanakawa et al. [32] described a case of wheat-dependent EIAN in which the amount of wheat ingested was crucial for the response to the exercise challenge.

The interval between a meal containing the culprit food(s) and exercise also proved to be an important factor. In some of our subjects, a specific food had caused a reactive episode when ingested less than 2 h prior to exercise, but not when the interval was longer.

Multiple food hypersensitivity may represent a hallmark of some FDEIAN patients. Interestingly enough, no patients were positive to milk, fish or eggs, which frequently cause classic food allergies.

In subjects with multiple food hypersensitivity, probably not all the positive foods were responsible. It would be useful to establish the causative role played by each one by performing exercise challenges after their ingestion. However, such a procedure is not only uncomfortable for the patients, but also time-consuming, because of the numerous positive foods. Moreover, these tests failed to provoke clinical symptoms in about one third of the more than 80 subjects known to have been assessed [32], including 8 of the present patients, whom we have described in a previous paper [3].

The above considerations induced us to abandon the routine use of such tests, which might, however, be performed for investigative purposes or to clarify the causative role of foods important in an athlete's diet.

We emphasize the usefulness of the FEC in our diagnostic protocol. If negative, FEC indicates foods that can safely be consumed prior to exercise. A negative FEC also reassures patients that postprandial exercise will not cause symptoms when the suspect positive food is not eaten. A positive FEC is indicative of NSFDEIAN. The lack of response to this challenge observed in 4 out of 6 NSFDEIAN subjects may be related to our use of a standardized interval between the meal and the exercise (90 min), since most of the EIAN episodes reported by these subjects had occurred 1 h or less after meals. This hypothesis suggests that the timing of FEC should be individualized.

In conclusion, FDEIAN is, in many cases, an extremely complex form of food allergy which appears in association with exercise and sometimes other factors. It is thus important to carefully assess hypersensitivity to foods in these patients, as also suggested by others [33]. In our study, we used the same extensive panel of food allergens for each patient. In clinical practice, this panel could be individualized in order to limit investigation costs. For the same reason, in vitro tests for foods to which the patients have proved to be not very sensitive could be omitted.

Avoidance of foods associated with skin test and/or CAP positivities for at least 4 h before exercise allowed all our SFDEIAN patients to continue their physical activity without any problems, and actually eliminated the unpredictability of this syndrome.

References

- 1 Maulitz RM, Pratt DS, Schocket AL: Exercise-induced anaphylactic reaction to shellfish. *J Allergy Clin Immunol* 1979;63:433-434.
- 2 Du Buske LM, Horan RF, Sheffer AL: Exercise-induced allergy syndromes; in Weiler JM (ed): *Allergic and Respiratory Disease in Sports Medicine*. New York, Dekker, 1997, pp 253-278.
- 3 Romano A, Di Fonso M, Giuffreda F, Quarantino D, Papa G, Palmieri V, Zeppilli P, Venuti A: Diagnostic work-up for food-dependent, exercise-induced anaphylaxis. *Allergy* 1995;50:817-824.
- 4 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;98:762-765.
- 5 Shadick NA, Liang MH, Partridge AJ, Bingham C, Wright E, Fossel AH, Sheffer AL: The natural history of exercise-induced anaphylaxis: Survey results from a 10-year follow-up study. *J Allergy Clin Immunol* 1999;104:123-127.
- 6 Kidd JM III, Cohen SH, Sosman AJ, Fink JN: Food-dependent exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1983;71:407-411.
- 7 Novey HS, Fairshir RD, Salness K, Simon RA, Curd JG: Postprandial exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1983;71:498-504.
- 8 Dohi M, Suko M, Sugiyama H, Yamashita N, Tadokoro K, Juji F, Okudaira H, Sano Y, Ito K, Miyamoto T: Food-dependent, exercise-induced anaphylaxis: A study on 11 Japanese cases. *J Allergy Clin Immunol* 1991;87:34-40.
- 9 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;68:438-445.
- 10 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;75:479-484.
- 11 Kivity S, Sneh E, Greif J, Topilsky M, Mekori YA: The effect of food and exercise on the skin response to compound 48/80 in patients with food-associated exercise-induced urticaria-angioedema. *J Allergy Clin Immunol* 1988;81:1155-1158.

- 12 Buchbinder EM, Bloch KJ, Moss J, Guiney TE: Food-dependent, exercise-induced anaphylaxis. *JAMA* 1983;250:2973–2974.
- 13 Katsunuma T, Iikura Y, Akasawa A, Iwasaki A, Hashimoto K, Akimoto K: Wheat-dependent exercise-induced anaphylaxis: Inhibition by sodium bicarbonate. *Ann Allergy* 1992;68:184–188.
- 14 Romano A, Fanales-Belasio E, Di Fonso M, Giuffreda F, Palmieri V, Zeppilli P, Ansotegui IJ, Venuti A, Paganelli R, Aiuti F: Eosinophil-derived proteins in post-prandial (food-dependent) exercise-induced anaphylaxis. *Int Arch Allergy Immunol* 1997;113:505–511.
- 15 Tharp MD, Thirlby R, Sullivan TJ: Gastrin induces histamine release from human cutaneous mast cells. *J Allergy Clin Immunol* 1984;74:159–165.
- 16 Sheffer AL, Austen KF: Exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1980;66:106–111.
- 17 Sheffer AL, Soter NA, McFadden ER Jr, Austen KF: Exercise-induced anaphylaxis: A distinct form of physical allergy. *J Allergy Clin Immunol* 1983;71:311–316.
- 18 Dreborg S, Foucard T: Allergy to apple, carrot, and potato in children with birch pollen allergy. *Allergy* 1983;38:167–172.
- 19 Dreborg S, Backman A, Basomba A, Bousquet J, Dieges P, Malling HJ: Skin tests used in type I allergy testing. Position paper. EAACI Subcommittee on Skin Tests. *Allergy* 1989;44(suppl 10):1–59.
- 20 Ortolani C, Ispano M, Pastorello EA, Ansaloni R, Magri GC: Comparison of results of skin prick tests (with fresh foods and commercial food extracts) and RAST in 100 patients with oral allergy syndrome. *J Allergy Clin Immunol* 1989;83:683–690.
- 21 Rosen JP, Selcow JE, Mendelson LM, Grodofsky MP, Factor JM, Sampson HA: Skin testing with natural foods in patients suspected of having food allergies: Is it necessary? *J Allergy Clin Immunol* 1994;93:1068–1070.
- 22 Rancé F, Juchet A, Brémont F, Dutau G: Correlations between skin prick tests using commercial extracts and fresh foods, specific IgE, and food challenges. *Allergy* 1997;52:1031–1035.
- 23 Stricker WE, Anorve-Lopez E, Reed CE: Food skin testing in patients with idiopathic anaphylaxis. *J Allergy Clin Immunol* 1986;77:516–519.
- 24 Yman L: Standardization of IgE antibody assays. *J Int Fed Clin Chem* 1991;3:198–203.
- 25 Sampson HA, Ho DG: Relationship between food-specific IgE concentrations and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997;100:444–451.
- 26 Wade JP, Liang MH, Sheffer AL: Exercise-induced anaphylaxis: Epidemiologic observations. *Prog Clin Biol Res* 1989;297:175–182.
- 27 Shimizu T, Furumoto H, Kinoshita E, Ogawara Y, Nakamura C, Hashimoto Y, Nagai K, Muto M: Food-dependent exercise-induced anaphylaxis occurring only in winter. *Dermatology* 2000;200:279.
- 28 Bjarnason I, Smethurst P, Clark P, Menzies I, Levi J, Peters T: Effects of prostaglandin on indomethacin-induced increased intestinal permeability in man. *Scand J Gastroenterol* 1989;24(suppl 164):97–103.
- 29 Petersen A, Vieths S, Aulepp H, Schlaak M, Becker WM: Ubiquitous structures responsible for IgE cross-reactivity between tomato fruit and grass pollen allergens. *J Allergy Clin Immunol* 1996;98:805–815.
- 30 Valenta R, Kraft D: Type I allergic reactions to plant-derived food: A consequence of primary sensitization to pollen allergens. *J Allergy Clin Immunol* 1996;97:893–895.
- 31 Lehmach JG, Rosenstreich DL: Clinical aspects of chronic urticaria. *Clin Rev Allergy* 1992;10:281–301.
- 32 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.
- 33 Guinépain M-T, Eloit C, Raffard M, Brunet-Moret M-J, Rassemont R, Laurent J: Exercise-induced anaphylaxis: Useful screening of food sensitization. *Ann Allergy Asthma Immunol* 1996;77:491–496.

Copyright: S. Karger AG, Basel 2001. Reproduced with the permission of S. Karger AG, Basel. Further reproduction or distribution (electronic or otherwise) is prohibited without permission from the copyright holder.