

FOOD-DEPENDENT EXERCISE-INDUCED ANAPHYLAXIS - UPDATE AND CURRENT DATA

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SUMMARY: Exercise-induced anaphylaxis (EIA) is defined as the onset of allergic symptoms during, or immediately after, exercise, the clinical signs being various degrees of urticaria, angioedema, respiratory and gastrointestinal signs and even anaphylactic shock. Food-dependent exercise-induced anaphylaxis (FDEIA) introduces food in the syndrome and is revealed by a chronological sequence in which food intake, followed by exercise, induces symptoms after a varying period. When the food intake and the exercise are independent of each other, there are no symptoms. FDEIA is not very frequent. Identifying the culprit food allergen depends on the patient's eating habits. Crustaceans and wheat flour are the two commonest but others foods can be implicated. The patho-physiology of FDEIA has not been clearly established but it appears to result from degranulation of mast cells. As with food allergy, FDEIA diagnosis is based on interview, skin and biological tests and challenge. For the clinical signs of allergy, antihistamines, corticosteroids and epinephrine may be administered. Prophylaxis aims to prevent a recurrence; the patient should be given an emergency kit to deal with any recurrent episode. After the food allergen has been identified, it should be avoided for at least 4 to 5 hours before any exercise.

Key-words : Anaphylaxis – Exercise – Food allergy.

INTRODUCTION

Exercise-induced anaphylaxis (EIA) is defined as the onset of allergic symptoms during, or immediately after, exercise, the clinical signs being various degrees of urticaria, angioedema, respiratory and gastrointestinal signs and even anaphylactic shock. Food-dependent exercise-induced anaphylaxis (FDEIA) introduces food in the syndrome and is revealed by a chronological sequence in which food intake, followed by exercise, induces symptoms after a varying period. When the food intake and the exercise are independent of each other, there are no symptoms.

EIA was reported as early as 1970 and the first case report of FDEIA was by Maulitz in 1979 (1, 2). The author reported the case of a long-distance runner who was allergic to sea food. In 1980, Sheffer described the clinical characteristics of EIA and in 1983 Kidd reported three cases of FDEIA associated with celery (3, 4). Later, many cases were reported. By the end of the 90s, over a thousand cases had been documented (5). A bibliographic search for "exercise-induced anaphylaxis" found 204 publications and a search for "exercise-induced anaphylaxis" linked to "food" found 125 publications, including 58 relating to wheat flour.

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EXERCISE-INDUCED ANAPHYLAXIS (EIA)

EIA is a rare condition, representing only 7 to 9% of anaphylaxis cases (6, 7). Two studies with similar results characterized EIA. The first was by Wade on 199 patients and the second by Shadick in 279 patients, followed-up for 10 years (8, 9).

Clinical characteristics

Skin signs are always present: pruritus, urticaria, angioedema and flush. Respiratory and gastrointestinal signs are less frequent. More rarely, there is malaise, hypotension or even anaphylactic shock (table 1). Perkins identified four successive phases during exercise-induced anaphylaxis: prodromal, early, constituted and late (10). About ten minutes after starting exercise, there is the onset of fatigue, a feeling of heat, pruritus and erythema; these symptoms occur during the prodromal phase and are followed by the early phase which includes urticaria and angioedema of the face, palms and soles. Once the clinical picture is constituted, the patient suffers abdominal pain, nausea, vomiting, respiratory discomfort, hypotension and even loss of consciousness. During the late phase, headache can persist for 24 hours. An episode of EIA usually lasts between 30 minutes and 4 hours after exercise has stopped (10).

Patient characteristics

Sufferers tend to be young adults (mean age : 37.5 years) (table 2). There is a marked predominance of women with a ratio of 2 to 2.5 women/1 man (8, 9). There is often a history of atopy (table 3).

Exercise characteristics

It is interesting to note that jogging, walking and aerobics are more often implicated than cycling, skiing and swimming (table 4).

Associated factors

Certain conditions such as cold, heat, humidity affect the triggering of EIA. Medication such as aspirin or non-steroidal anti-inflammatory drugs is also occasionally involved (table 5). Conversely, food intake 3 to 4 hours before exercise was noted in 37 to 54% of cases (8, 9).

Clinical signs and symptoms	Shadick 279 patients	Wade 199 patients
Pruritus	92 %	100%
Urticaria	86%	83%
Angioedema	72%	78%
Flush	70%	75%
Dyspnea	51%	59%
Dysphagia	34%	-
Tightness in chest	33%	-
Loss of consciousness	32%	32%
Sweating	-	43%
Headache	28%	30%
Gastrointestinal disorders	28%	30%

Table 1: Clinical characteristics of patients presenting with EIA according to Shadick and Wade (8, 9).

Patient characteristics
Sex Women: 71% Men: 29%
Age Mean: 37.5 years Range: 13 to 77 years
Age at start of symptoms Mean: 26 years Range: 3 to 66 years
Duration of symptoms Mean: 10.6 years Range: 0.3 to 60 yearsEIA (9).

Table 2: Characteristics of patients presenting with EIA (9).

Outcome

A 10-year prospective study in 279 patients with EIA was carried out by Shadick who was able to assess the progress of the disease (9). During the year before this study, the annual incidence of EIA per patient was estimated at 8.3%. Episodes stabilized in nearly all patients (46%) or regressed (47%) during the 10 years of follow-up. These results were most likely due to the preventive measures taken by patients who avoided physical activity during hot and cold weather, during exposure to pollen or after taking food and medication. Episodes increased in only 7% of patients.

History of allergy	Wade 199 patients	Shadick 279 patients
Eczema	12%	10%
Asthma	22%	19%
Allergy to animal epithelia	29%	50%
Hay fever	46%	
Food allergy	34%	-

Table 3: History of allergy in patients presenting with EIA according to Wade and Shadick (8, 9).

Clinical signs and symptoms	Shadick 279 patients	Wade 199 patients
Running	78%	69%
Walking	42%	30%
Aerobics	-	35%
Tennis	28%	21%
Dancing	26%	30%
Cycling	24%	19%
Swimming	-	15%
Gardening	6%	-
Skiing	6%	9%
Basket-ball	4%	-

Table 4: Physical activities triggering EIA according to Wade and Shadick (8, 9).

Factors associated to EIA
Heat: 64%
Cold: 23%
Humidity: 32%
Food intake: 54%
Aspirin or NSAID: 13%

Table 5: Associated factors observed during EIA according to Wade (8).

FOOD-DEPENDENT, EXERCISE-INDUCED ANAPHYLAXIS (FDEIA)

Definition

FDEIA, which can be defined as a particular form of EIA in which a food factor has been identified, has certain features:

- 1°) there is evidence of IgE-mediated sensitization to the food;
- 2°) without exercise, the food is regularly tolerated;
- 3°) exercise without ingestion of the food is not followed by an adverse effect;
- 4°) ingestion of the food followed by exercise induces the symptoms.

Very exceptionally, the triggering food is ingested after exercise (4).

Epidemiology

Whereas food allergy concerns 3.2 to 3.4% of the population, FDEIA is much less frequent (11, 12). Only two Japanese epidemiological studies are available to give an idea of the extent of FDEIA. The study by Aihara in 2001 estimated the frequency of FDEIA at 0.017% amongst 76,229 Japanese adolescents (13). In the study by Tanaka in 11,642 Japanese children and adolescents, there were no cases of FDEIA in infants (nursery school); however, FDEIA affected 0.06% of primary school age children and 0.21% of adolescents in secondary schools, confirming that FDEIA, unlike food allergy, does not appear to affect young children, (14).

Allergens

Identifying the culprit food allergen depends on the patient's eating habits. Crustaceans and wheat flour are the two commonest. Of the 167 FDEIA cases reported in Japan between 1983 and 2000, over 50% were caused by wheat flour, closely followed by shrimp. However, in patients under 20 years, the main allergen was shrimp followed by wheat flour (15). Others, such as Guinnee, have commented on the frequency of wheat flour in FDEIA, since 1/3 of the cases were associated with it (16). Other foods included celery, peach, tomato, grape, onion, apple, nuts, kiwi, chicken, snail, poppy seed, wine, corn and lentils (the list is not complete) (2, 9, 10, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27). One case, suspected to be due to a mould found in a sausage, was described (28). Unlike food allergy not induced by exercise, cow milk, egg and fish seem to be involved only rarely (29, 30, 31). Meats are rarely

implicated, but Sabbah reported one case concerning pork out of 7 case reports (27). Later, one case of FDEIA with a pork-cat cross allergy was described by the same team (32).

FDEIA with wheat flour is very interesting since the causal epitope is the $\Omega 5$ fraction of gliadins, particularly the N-terminal part (33, 34, 35, 36). However, this fraction may not be totally responsible for the FDEIA since Palusuo later found IgE specific against the $\Omega 5$ fraction in 84% of children with immediate allergy to wheat flour (37).

Moreover, transglutaminase plays an essential role in FDEIA related to wheat flour. It is an enzyme with enterocyte activity whose substrate contains products of $\Omega 5$ -gliadin degraded by pepsin. During exercise, the activation of the transglutaminase, combined with $\Omega 5$ -gliadin fractions, exerts high affinity to specific IgE and produces the clinical signs of allergy (38).

Chronology and time to onset of FDEIA

The time between ingestion and the onset of clinical signs ranges from 30 to 120 minutes (17, 31). Maulitz documented extreme values in an incident occurring in a 10 to 15 km race where the food was eaten 20 hours before the onset of clinical signs (2). To prevent FDEIA, fasting for 4 or 5 hours before exercise has been recommended (16, 17, 31). Clinical signs usually appear between 5 and 50 minutes after the start of exercise (17, 31, 39). The episode may last for 3 to 4 hours after exercise has ceased (10).

Co-factors affecting clinical signs of FDEIA

The intensity of FDEIA episodes varies and it does not always recur (32). This was also noted during challenges (eating followed by exercise) which were not reproducible. Hanakawa analyzed 234 case reports published in Japan between 1983 and 2000 and found only 36% of positive challenge with the suspected food during skin tests and/or specific IgE tests (40). Various hypotheses have been suggested: the amount of food, concomitant medication, individual and environmental factors.

■ **Food:** The amount of food eaten before exercise influences the onset of clinical signs and their intensity. Hanakawa observed threshold doses above which symptoms appeared, and in cases of allergy to wheat flour, it was often high (up to 100 grams) (40).

Some patients present multiple allergies. Caffarelli reported 3 patients for whom 2 or 3 foods caused FDEIA: the author listed wheat flour, marrow and tomato for one patient; tomato and peanut for another and rice and peanut for a third (41).

Aihara demonstrated how FDEIA could be triggered by two foods eaten together. When each was taken separately, FDEIA did not occur (42).

■ **Medication:** The role of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) taken before exercise in exacerbating FDEIA was confirmed by Aihara and Harada (31, 42, 43, 44). For some patients, aspirin taken before food and followed by exercise resulted in positive challenge whereas without aspirin it remained negative. For one patient, the amount of triggering food allergen was reduced by pre-treatment with aspirin (43, 44). The role of aspirin and NSAIDs in exacerbating FDEIA is explained by two mechanisms of action. They increase gastrointestinal permeability which in turn increases the absorption of food allergens. Also it has been demonstrated that prostaglandins inhibit mast cell release. By inhibiting cyclo-oxygenase, aspirin and NSAIDs prevent the synthesis of prostaglandins which no longer exert any inhibitory activity on the release of histamine from mast cells (45, 46, 47).

■ **Individual and environmental factors:** Certain authors have noted the effects of environmental factors: exercise during pollen season in a patient with pollinosis. Individual factors such as stress or menses can favor the onset of FDEIA (3, 10, 31, 48, 49). It should be noted that the type of exercise is also significant since certain activities occur in all reports; running and walking more often than cycling, but no patho-physiological explanation is provided.

Outcome of FDEIA

After an episode of FDEIA the following may be seen: residual asthenia, headache persisting up to 72 hours, hepatic cytolysis (1 case) (10, 50). No death has been reported. In theory, inaugural and fatal signs may not be recognized. Fatal anaphylactic shock after eating a buckwheat-based food before swimming was reported by a Japanese team but it is difficult to differentiate between food allergy exacerbated by exercise and genuine inaugural FDEIA (51).

Patho-physiological explanations

The patho-physiology of FDEIA has not been clearly established but it appears to result from degranulation

of mast cells and may be seen by electron microscopy in skin biopsies and measured from the increase in histamine and tryptase in plasma of patients with FDEIA (22, 52, 53). Therefore, the role of mast cells is essential, with a reduced activation threshold or exacerbated degranulation during exercise (10, 54, 55). Endorphines and gastrin are released during exercise, thus inducing histamine release (10, 48, 56, 57).

Conformational modification of food proteins induced by gastrin, together with the decrease in gastric and plasma pH, generates new epitopes resulting in mast cell stimulation (10, 58).

Exercise increases the permeability of the small intestine related to enterocyte disjunction resulting in an increased absorption of food allergens. Increase in body temperature, reduced gut blood flow during exercise and non-steroidal anti-inflammatory drugs all increase intestinal permeability (10, 59).

Abnormalities of the autonomic nervous system response in some FDEIA patients may cause splanchnic vaso-dilatation causing food allergens to be circulated throughout the body (10, 60).

Differential diagnosis

Cholinergic urticaria is easily distinguished by the very small papules occurring during stress and exposure to heat (61).

Effort-induced asthma is easily recognized since the clinical picture only rarely includes skin signs or cardiovascular collapse, though one should bear in mind that FDEIA may be accompanied by bronchial signs (10, 62, 63). Food induced anaphylaxis, exacerbated by exercise, may be identified since symptoms may occur after ingestion of food but without exercise (64, 65).

Mastocytosis should be always considered with urticaria pigmentosa, malaise during exercise or food intake and medication. High tryptase concentrations in the absence of clinical signs will confirm the clinical suspicion (66).

Hypoglycemia and vasovagal malaise are easily differentiated from FDEIA.

Diagnosis of FDEIA

As with food allergy, FDEIA diagnosis is based on interview, skin and biological tests and challenge (17, 31).

The interview may reveal a history of atopy and define the clinical circumstances with clinical signs and symptoms, the triggering exercise, suspected foods and finally any treatment.

If a particular food is suspected as a result of prick-tests with native foods and/or evidence of circulating specific IgE, confirmation should be obtained by challenge tests in hospital under strict medical monitoring and with the patient's informed consent (65, 67). Challenge tests will not be carried out where the patient has severe anaphylaxis or cardiac, respiratory, hepatic or renal disease. The session should start by challenge to a single food, followed the next day by treadmill exercise with no food intake (17) and finally, a food challenge followed by exercise within 30 to 90 minutes (17, 42). The ideal way to perform these tests would be double-blind challenge to avoid any subjectivity, but this complicates diagnosis.

Treatment

■ **Treatment of the event:** The patient must stop all exercise and lie down as soon as signs appear. A quick but precise clinical examination will detect any serious signs: hemodynamic (BP, pulse) and respiratory disorders (bronchospasm) (68, 69).

For the clinical signs of allergy, antihistamines, corticosteroids and epinephrine may be administered. Antihistamines or corticosteroids may be given if edema should occur. The patient must be monitored carefully for any sign of anaphylactic shock which may be preceded by skin signs. In the event of anaphylactic shock or laryngeal edema, epinephrine must be given quickly and the patient monitored in hospital for 24 hours. Plasma histamine and tryptase should be assayed to confirm the diagnosis of anaphylaxis. The patient should consult an allergologist later for further investigation (68, 69).

■ **Prophylaxis:** Prophylaxis aims to prevent a recurrence; the patient should be given an emergency kit to deal with any recurrent episode. After the food allergen has been identified, it should be avoided for at least 4 to 5 hours before any exercise (16, 31). Patients should be informed of exacerbating co-factors. They should avoid certain medication (aspirin, NSAIDs, beta-blockers and angiotensin-converting enzyme inhibitors). Exercise should be avoided during periods of allergenic stimulation (pollen season for patients with hay fever).

The emergency kit should contain an oral antihistamine and corticosteroid, and the patient must have an

auto-injector with epinephrine (Anapen®). They and their families must be trained to use the auto-injector.

CONCLUSION

FDEIA is a rare clinical condition, but must be identified. With the general increase in sporting activities, this particular form of food allergy may unfortunately occur more often. Experimental studies are needed for a better understanding of the patho-physiological mechanism.

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PRESS RELEASES

MEDIA ALERT:

THE AAAAI RECOMMENDS THE FLU SHOT FOR ASTHMATICS

Vaccinating all children with asthma could prevent up to 78% of asthma hospitalizations and emergency room visits during influenza season, according to the American Academy of Allergy, Asthma & Immunology (AAAAI). The AAAAI is recommending that children with asthma and other chronic health conditions receive flu shots as soon as possible. To help prepare for the upcoming flu season, the AAAAI has developed a list of common questions patients with asthma may have regarding the flu shot.

How can the flu shot help patients with asthma and other chronic health conditions?

The symptoms of the flu, which include fever, chills, generalized muscle pains, headache, fatigue and cough, can be especially severe for patients with respiratory diseases, such as asthma. In some cases, the influenza virus can damage the lungs, and influenza may make patients more susceptible to pneumonia. In severe cases influenza can be fatal.

The flu shot can protect against acute asthma exacerbations in children. Research has found that the flu shot decreases the risk of asthma exacerbations in patients by as much as 22% to 41%.

When should patients receive the flu shot?: Patients often wait until they are exposed to the influenza virus to get immunized; however, the optimal time for patients to receive the shot is before they are exposed to the virus. Typically, influenza cases peak in January and February. Getting the flu shot now gives your body time to build immunity to the strains of influenza predicted to be most prevalent in the months to follow.

Are there risks from getting the flu shot?: You cannot get the flu from the flu shot. If you feel sick with flu-like symptoms after the shot, you may have caught another respiratory virus or already had the flu virus in your system when you got the shot. The flu shot does pose some concern for people allergic to eggs. The influenza vaccine is grown in chicken eggs. Although almost all the egg protein is filtered out of the vaccine, people with egg allergy should check with their allergist/immunologist before receiving the flu shot.

The AAAAI is the largest professional medical specialty organization in the United States representing allergists, asthma specialists, clinical immunologists, allied health professionals and others with a special interest in the research and treatment of allergic disease. Established in 1943, the AAAAI has more than 6,000 members in the United States, Canada and 60 other countries. The AAAAI serves as an advocate to the public by providing educational information through its Web site at www.aaaai.org.