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REVIEW



Diagnosis and prevention of food-dependent exercise-induced anaphylaxis

Filipe Benito-Garcia^a, Ignacio Javier Ansotegui^b and Mário Morais-Almeida^a

^aImmunology Department, CUF Descobertas Hospital, Lisbon, Portugal; ^bDepartment of Allergy and Immunology, Hospital Quironsalud Bizkaia, Bizkaia, Spain

ABSTRACT

Introduction: Food-dependent, exercise-induced anaphylaxis (FDEIA) is a rare type of anaphylaxis with a growing incidence. Although the precise mechanism by which the patient reacts only in a combination of a culprit food and cofactors are not currently understood, many advances in diagnosis and management have been made since their first description.

Areas covered: A literature search in PubMed was performed to review the diagnosis and management of FDEIA. Clinicians should have a high level of suspicion for identification of the culprit foods and the cofactors involved. Component-resolved diagnosis and more accurate provocation tests have revolutionized the diagnosis accuracy. Management is not easy and involves educating the patient to evict the combination of exposure to the culprit foods and the cofactors that elicit anaphylaxis, and how to act and treat if a reaction occurs.

Expert opinion: FDEIA is currently misdiagnosed and the authors believe that there are many FDEIA patients labelled as idiopathic anaphylaxis with unnecessary evictions and with a poor quality of life because of the fear of an imminent reaction. Due to recent advances in diagnostic tools and the use of monoclonal antibodies for prophylaxis in persistent cases, FDEIA can have a better prognosis improving the quality of life of the patients and their families.

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Anaphylaxis; augmenting factors; cofactors; exercise-induced anaphylaxis; food allergy; food-dependent exercise-induced anaphylaxis; food-exercise provocation test

1. Introduction

Exercise-induced anaphylaxis is a type of anaphylaxis provoked primarily by exercise [1]. It is subdivided into two groups: anaphylaxis caused exclusively by exercise and anaphylaxis caused by exercise after eating a particular food [2]. The latter is called food-dependent, exercise-induced anaphylaxis (FDEIA) [3] and it can be further classified according to the triggering food. Episodes occurring after the ingestion of certain foods, to which the patient is sensitized, are described as specific FDEIA, while those occurring after the ingestion of any food are described as non-specific FDEIA [4].

Four decades have passed since the first description of the disease by Maulitz RM et al [5], and although little is known about their physiopathology, many advances were made in diagnosis and management of this particular type of anaphylaxis. However, many clinicians are unaware of this entity and the correct diagnosis can be missing.

The authors performed a literature search in PubMed and review the recent advances about this rare but growing entity.

2. Epidemiology

Epidemiologic data regarding the prevalence of FDEIA are scarce. It is an uncommon disorder but with a growing incidence quantified by the increasing number of reports in the last decade. It is frequently misdiagnosed as idiopathic anaphylaxis because the

culprit food cannot be found, and many physicians might be unaware of the condition.

Aihara Y et al determined the prevalence of FDEIA be approximately 0.02% among adolescents and 0.005% in elementary school children; the authors reported that more than half of these patients suffered repeated episodes of EIA [6–8].

The disorder most commonly affects young adults, due to be a more active age group, but a wide age range involving patients from 4 to 74 years are reported [9–11]. There is no gender or ethnicity predominance [12]. Affected individuals tend to have concomitant atopic disorders [6,13].

3. Physiopathology

While the number of reports on FDEIA has been increasing, the precise mechanism by which the ingestion of foods, to which the patients are sensitized, could induce an anaphylactic reaction specifically only when combined with exercise or another cofactor remains unclear.

Recent literature suggests that FDEIA is a primary IgE-mediated food allergy augmented by cofactors. Cofactors could lower the threshold for a reaction, increase the severity of the reaction or reverse acquired clinical tolerance. The disease culminates in mast cell degranulation and release of mediators such as histamine, tryptase and arachidonic acid metabolites. Symptoms are caused by the effects of mast cell

Article highlights

- FDEIA is frequently misdiagnosed and a high level of suspicion is necessary.
- The precise prevalence and physiopathology of FDEIA remain unclear.
- As a special type of IgE-mediated food allergy, any food can trigger the condition, and a detailed clinical history is of importance.
- Exercise is not the only cofactor that can elicit a reaction; other cofactors like NSAIDs and alcohol and combinations of two or more cofactors can prompt a reaction.
- Component-resolved diagnosis revolutionized the diagnosis of food allergy and have a crucial role in FDEIA patients.
- FDEIA diagnosis is based on a combination of provocation tests that include a food challenge, a cofactor challenge, followed by a combined food-cofactor challenge or a challenge with high amounts of the culprit food.
- Provocation tests mimicking an environment closer to real life using standardized protocols, and advances in molecular diagnosis will improve diagnosis.
- Management is based on avoidance of the culprit food and the cofactors, especially not combining them, be aware of signs and symptoms and how to act in case of an anaphylactic reaction. Clinicians should prescribe an epinephrine auto-injector to all FDEIA patients and teach them how to use it
- Monoclonal antibodies and food immunotherapy are promising tools for prophylaxis for selected patients: those with more persistent reactions or the ones that food and cofactors avoidance are difficult to accomplish.

mediators on various organ systems. Histamine can induce urticaria, flushing, tachycardia, and bronchoconstriction. Tryptase activates the cascade and complement pathways. Arachidonic acid metabolites can cause vasodilation, increased vascular permeability, and bronchoconstriction [14–20].

The underlying mechanism of mast cell activation is not fully understood. Several theories of FDEIA, mainly based on case reports, have been proposed, particularly originated from mechanisms mediating exercise-induced anaphylactic reactions. None of these theories has been accurately validated and considered alone they can't explain a reaction [1,21–29]:

- Cofactors like exercise, nonsteroidal anti-inflammatory drugs (NSAIDs) and alcohol enhance epithelial cell erosion and induce irritation of the intestinal mucosa. This may modulate changes of the gastrointestinal barrier with increased permeability, and consequently, increased absorption of recently ingested, but incompletely digested, food proteins into the circulation. Then, they migrate into the perivascular and tissue spaces and are exposed to less tolerogenic mast cells, inducing their activation and triggering symptoms.
- Exercise suppresses gastric acid secretion, and consequently, the digestion of some food allergens is reduced, leading to the absorption of more structurally intact allergens across the epithelial barrier, eliciting an IgE-mediated mast cell degranulation. For some allergens, such as lipid transfer proteins (LTP), that are already partially resistant to digestion, this may be particularly significant.
- Exercise induces a blood flow redistribution away from the gastrointestinal tract. This results in a deviation of structurally intact food allergens from the gut to the skin and skeletal

muscle where there are less tolerogenic mast cells, which may have a lower threshold for degranulation.

- Exercise induces a transient serum hyperosmolality due to airway water evaporation, which increases histamine release from the basophils after allergen exposure.
- Intensive exercise can promote an autonomic nervous system dysregulation with resting bradycardia, and increased bronchomotor tone with susceptibility to bronchospasm.
- Changes in an acid-base balance associated with high-intensity exercise can occur. It induces a reduction of cellular pH and consequently mast cell instability.
- In patients with wheat-dependent exercise-induced anaphylaxis (WDEIA), exercise activates the intestinal enzyme tissue transglutaminase that is capable of binding, resulting in peptide aggregation and increased IgE cross-binding, eliciting mast cell degranulation more efficiently. Concomitantly, the contraction of skeletal muscles has been shown to increase interleukin-6, an inflammatory mediator that upregulates the expression of tissue transglutaminase.

4. Clinical presentation

A wide variety of signs and symptoms may arise in patients with FDEIA. They begin at any stage of exercise and occasionally occur just after exercise or associated with another cofactor. The frequency in which symptoms occur varies among patients with FDEIA and can be very unpredictable, even for a given patient [1,3,30].

Early signs and symptoms typically include sudden fatigue, diffuse warmth, pruritus, flushing, and/or urticaria. If the patient stops and rests, symptoms usually resolve, but continued exertion could result in mucocutaneous (angioedema, laryngeal oedema), gastrointestinal (nausea, vomiting, abdominal pain, diarrhoea), respiratory (wheezing, dyspnoea), and cardiovascular symptoms (hypotension, collapse, loss of consciousness) [31].

Vigorous forms of aerobic exercise (jogging, football, dancing) are most often implicated, although lower levels of exertion (brisk walking, yard work or even climbing stairs) are capable of triggering attacks in some patients, especially the elderly. The variability in the intensity of exercise that elicits symptoms can occur even in the same patient [32,33].

5. Causative foods

FDEIA is considered a special type of IgE-mediated food allergy and it should be kept in mind that almost any food group can trigger the condition (Table 1) [34]. As for food allergy in general, geographical differences occur in the implicated foods due to cultural dietary habits and traditions of each region. In Asia, wheat, specifically ω 5-gliadin, shellfish or soy were more frequently reported [35–37], and in the Mediterranean area, fruits and vegetables predominate. In this European region, multiple food hypersensitivity is reported in a large percentage of individuals with FDEIA,

Table 1. Foods involved in food-dependent exercise-induced anaphylaxis reported in the literature. LTP – lipid transfer proteins.

Cereals	Wheat (ω -5-gliadin/LTP), buckwheat, barley, maize, rice
Seafood	Shrimp, oysters, crab, octopus, squid, cuttlefish
Vegetables	Lettuce, celery, pepper, fennel, onion, mustard, carrot, cabbage, paprika
Legumes	Peanut, chickpea, soy, pea, garlic, lentil, potato
Fruits	Peach, apple, pear, orange, tangerine, grape, banana, cherries, apricot, kiwi, lychee tomato
Tree nuts	Hazelnut, chestnut, pine nut, walnut, cashew nut, almond, pistachio
Meat	Beef, pork, chicken, turkey
Others	Fish, cow's milk, egg, mushroom, snails, poppy seed

who also have a high prevalence of sensitization to panallergens, such as lipid transfer proteins (LTP) [38,39].

In some patients, FDEIA develops after ingesting a combination of foods [40,41].

- General conditions: hyperthermia, infections, fatigue, psychological stress, and menstruation/ovulatory phase;
- Bathing;
- Pollen season.

6. Augmenting factors

In a recent study, Christensen MJ et al [42] compared the relative effect of different cofactors in a cohort of patients with confirmed WDEIA and concluded that exercise and NSAIDs augment clinical reactions by lowering the threshold and increasing the severity of the allergic reaction, whereas alcohol gives ambiguous results. Furthermore, the combination of 2 cofactors (exercise and NSAIDs) increases the risk of an allergic reaction. In this cohort, exercise elicits allergic reactions in 92% of patients, NSAIDs in 84%, alcohol in 56% and exercise associated with NSAIDs in 82%. With exercise as a cofactor, the median threshold was 24g, with aspirin 8g, with alcohol 28g, and the combination of 2 cofactors (exercise and aspirin) resulted in a median threshold of 4.3g. Alcohol was the weakest cofactor and is possibly more important in a daily life setting because is often accompanied by exercise, as can be the case of dancing.

Exercise is the most reported cofactor in FDEIA and can often elicit symptoms without additional factors. Pals et al [43] showed that intestinal permeability is increased after 60 minutes of exercise at 80% of peak exercise. The effect appears to be significant only during high intensity or prolonged exercise [44,45]. The intensity of exercise that can elicit symptoms is variable, even in the same subject.

Two mechanisms explain the effect of NSAIDs on the intestinal mucosa: direct irritation and erosion of the mucosa and decreased prostaglandin synthase activity by COX-1 inhibition [46–48].

Brockow et al [49] induced symptoms in patients with WDEIA, with NSAIDs and/or alcohol co-ingestion, in the absence of exercise. This has since been replicated and, therefore, the use of the term FDEIA has been questioned and suggested that FDEIA may be more appropriately named *augmentation factor-induced food allergy*, blurring the line between primary food allergy and FDEIA.

Several other cofactors have been described in case reports [50–56]:

- Drugs: angiotensin-converting enzyme inhibitors, beta-blockers, antacids, and cannabis;
- Extreme weather conditions: cold and hot temperatures, humidity;

7. Diagnosis

The diagnosis of FDEIA is not simple [57]. A high level of suspicion and detailed clinical history is the first step for an accurate diagnosis. A history of signs and symptoms of anaphylaxis at least 4–6 hours from exposure to the culprit food, and a description of all food ingested, and cofactors involved before and after the physical activity that triggered the anaphylactic reaction is of critical importance [58,59]. The onset of symptoms is usually within one hour of starting exercise; however, onset of FDEIA five hours after exercising has also been reported [60,61].

There seems to be a dose-response relationship between both amount of culprit food and the cofactor involved, and the clinician should assess both the amount of food allergen in question and the intensity of the exercise or the quantity of other cofactor involved (NSAIDs, alcohol) [62].

Allergy testing, including skin tests and in vitro tests, and provocation tests are the complementary diagnostic tests of choice for diagnosis of FDEIA, and this diagnosis may be accepted in the presence of the following criteria adapted from those proposed by Feldweg et al [3]:

- Signs and symptoms consistent with anaphylaxis that occurred during or within 1 to 6 hours of exercise that was preceded by ingestion of the culprit food(s);
- No symptoms after food ingestion in the absence of exercise or with exercise alone;
- Specific food(s) is(are) implicated and evidence of specific IgE to the implicated food(s);
- No alternative diagnosis to better explains the patient's symptoms of anaphylaxis.

Brockow K et al [49] and Christensen MJ et al [58] demonstrated that WDEIA can be elicited by challenges with gluten in the absence of any augmenting factor, in 25% and in 55% respectively, indicating that, in some cases, WDEIA is a regular (non-augmenting factor-dependent) wheat allergy where threshold is very high in daily life setting without cofactors.

Before taking on a FDEIA diagnosis, the exclusion of mast cell activation syndromes is of clinical importance because this heterogeneous group of disorders is characterized by an abnormal increase in the number of mast cells and,

consequently, a lower threshold for inducing allergic reactions, more precisely anaphylaxis with physical activity, as well as in response to various other cofactors.

7.1. Skin testing and/in vitro testing

Part of the reaction is elicited by foods, so the identification of sensitization to the culprit food is part of the investigation. Initial evaluation with skin-prick and prick-to-prick tests can be complemented by specific IgE immunoassays [63]. Many foods from the vegetal kingdom like vegetables, tree nuts, and seeds lost part of their allergenicity properties in commercial skin-prick extracts, so prick-to-prick testing is of importance in diagnosing this syndrome due to better accuracy [60].

Testing for aeroallergen sensitization could be useful in the evaluation of FDEIA if specific co-triggers are suspected, namely reactions that occur only during pollen seasons [3].

At present, allergy diagnosis is on the era of precision medicine and is possible to identify culprit foods based on their molecular basis. It is also possible to identify both primary and cross-reactivity patterns because many food allergens involved in FDEIA reactions are panallergens.

Modern immunoassay methods used for the detection of specific IgE against food components are either singleplex (detect specific IgE against a single allergen component), multiparameter (detect specific IgE against a few allergen components at once – usually 10) or multiplex (detect simultaneously specific IgE against many different allergen components – > 100) [64].

The multiplex system offers the advantage of assessing sensitization to a vast panel of allergenic molecules in place of whole-allergen extracts, thus providing better accuracy [65–68]. In a group of Italian FDEIA patients [38], immuno solid-phase allergen chip (ISAC) microarray identify LTP as the most frequent primary allergens involved. Also, in Portugal, our group [39] reported a considerable number of LTP-FDEIA patients whom sensitization was confirmed by ISAC microarray.

Basophil-activation test is gaining importance in the diagnosis of food allergy, and although it allows predicting causative food allergen, the sensitivity and specificity have not been established [67]. An in vitro immunodepletion assay might be a promising tool to help to understand cross-reactivity patterns in individuals with FDEIA, however, application in clinical practice is limited and need further validation [69].

7.2. Provocation tests

FDEIA diagnosis is based on a combination of provocation tests that include a food challenge, a cofactor challenge, followed by a combined food-cofactor challenge. There is no established protocol for food-exercise or other food-cofactor challenge evaluation and several protocols have been used [6,60,68,70,71].

Classically, confirmation of FDEIA includes a negative isolated exercise challenge, a negative food challenge, but a positive combined food-exercise challenge [30,59]. In some WDEIA cases, as reported before, a positive food challenge

with high amounts of wheat can confirm the diagnosis in the absence of augmenting factors [49,58].

During food-exercise challenge, patients run or use an ergometer under strict observation 30–60 minutes after eating the culprit food. The observation period could be extended accordingly to the patient history.

All provocation tests must be performed under strict medical surveillance, by professionals with experience in recognition and management of acute reactions. Epinephrine and other appropriate medication and resuscitation equipment must be always available during the tests [70,72].

Because there are still no specific guidelines on how to perform this challenge test, many authors modify the procedure as they see fit. The specificity and sensitivity remain controversial [1]. Christensen MJ et al [62] proposed a standardized challenge methodology for FDEIA diagnosis, which could be applied in a highly specialized allergological setting.

Food-exercise challenge is the gold standard for diagnosing FDEIA, but only confirms the diagnosis in up to 70% of patients [73]. This lack of sensitivity is related to the difficulty of replicating the conditions in which the reaction occurred, such as the exercise environment (variable intensity, different periods of time after food intake), the amount of food and its processing the ovulatory/menstruation phase, concomitant use of drugs, and other contributing cofactors such stress or weather, namely seasonal pollen exposure in pollen sensitized individuals with cross-reactivity with food allergens and significant environmental temperature variations. The time of the meal and the intensity of exercise needs to be individualized to reproduce, as closely as possible, the events of the patient's previous reactions. Alternative protocols were tried to elicit symptoms with different cofactors or with a combination of cofactors when food-exercise challenge is negative. Asaumi T et al [60] proposed a NSAID-food provocation challenge when exercise-food provocation test is negative, with a total aspirin intake of 10mg/Kg (maximum 500mg) before eating the culprit food. However, some of these strategies that have been proved to increase the rate of positive challenges, can be related to more serious adverse reactions during the procedure [1,49,74–77].

8. Management

FDEIA management is based on preventing a reaction and treating the anaphylactic episode. Currently, there are no guidelines concerning the optimal management of FDEIA, except a mandatory prescription of an epinephrine auto-injector [58].

8.1. Prevention and education

The best prevention is based on the education of the patients about their disease. They must avoid the triggers and the cofactors, especially not combining them, be aware of signs and symptoms and how to act in case of an anaphylactic reaction. Clinicians should prescribe an epinephrine auto-

injector to all FDEIA patients, teach how to use it and review in every appointment.

It is wise to avoid triggering activity/NSAIDs/alcohol in the period between the onset of symptoms and the initial evaluation at an allergy department, but it should not be necessary to refrain physical activity till the conclusion of the diagnostic workup. Until triggers that induce symptoms are identified, exercise should be performed with a partner that is educated to recognize early signs and how to administer epinephrine.

After confirmation of the diagnosis and the culprit food(s) identified, patients may restart exercise gradually, starting with low intensity and, then gradually increasing it. For non-specific FDEIA, avoidance of any type of meals 4 to 6 h before exercise and within 1 h after is recommended, and in some cases, could be reduced for a minimum of 2 to 3 hours. Good advice is to practice physical activity in the morning before eating anything. If a diagnosis of specific FDEIA is established, all foods that contain that allergen should be avoided during the same period. For patients in which physical activity is intrinsically part of the daily routine, it is safer to strictly avoid the food allergen from the diet. Therefore, in some cases, it might be needed to change work or daily routine conditions.

Combination of NSAIDs and culprit food(s) should be avoided for patients in whom the confirmation of FDEIA results in a positive challenge with this cofactor. Patients taking β -blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers must be cautious because these drugs may increase the severity of anaphylaxis and reduce the response of epinephrine [30].

Coexisting allergic disorders should be optimized and in some patients with pollinosis caution should be used if exercising outdoors during the pollen season.

Patients should have a written action plan that explains how to recognize the symptoms and how to act in case of anaphylaxis. It is also prudent to practice physical activity carrying a cellular phone [1,3,24,30,34,70].

8.2. Acute treatment

FDEIA episodes are not entirely predictable as the cofactors threshold for eliciting anaphylaxis are individual and may even vary over time for the individual patient [58]. Treatment of FDEIA includes immediate cessation of exercise at the earliest warning sign/symptom and emergent treatment of the anaphylactic reaction. An epinephrine auto-injector should be used if symptoms do not immediately improve with the cessation of exercise.

Any patient who has self-administered epinephrine should seek immediate medical care for further monitoring and treatment, as the anaphylactic reaction might have ongoing life-threatening effects, like a biphasic reaction [30,40].

Epinephrine 1:1000 (1 mg/mL) at a dose of 0.3–0.5 mg in adults and 0.01 mg/kg in children, by the intramuscular route is the recommended first-line intervention in the emergency room. Depending on the initial response and the severity of the reaction, the dose can be repeated every 5 to 15 min, as needed. The patient should be positioned and maintained in the Trendelenburg position to preserve fluid in the circulation

and prevent an empty vena cava syndrome. Second and third-line medications can also be used but should not delay the administration of epinephrine.

9. Prophylaxis

Despite education and preventive measures, some FDEIA patients continue to have anaphylactic reactions. Several case reports describe the limited clinical experience by using sodium cromoglycate, misoprostol and anti-histamines for preventing episodes of FDEIA, although there is inadequate evidence to support these prophylactic measures [31,40]. These medications are not a reliable alternative to avoidance of the culprit food, but an additional protective measure with a mild effect. Premedication with antihistamines is still controversial due to the possibility of masquerading early symptoms [1,3,78].

Omalizumab, an anti-IgE monoclonal antibody, has been described in several case reports of FDEIA patient's refractory to other prophylactic treatments with good outcomes [79–81].

Numerous studies on food immunotherapy have been published [82,83]. In theory, in selected patients, particularly patients sensitized to LTP with an allergy to multiple vegetables/fruits in whom avoidance is difficult or not taken, lowering the food threshold and inducing food tolerance could be beneficial. However, due to a great diversity of protocols and outcomes, it is not yet approved to be used in regular clinical practice [63]. Furthermore, reports of individuals who developed FDEIA during or after food immunotherapy have been published [84–86].

10. Prognosis

By definition, anaphylaxis is a potentially life-threatening disease and some fatalities have been attributed to FDEIA [87,88]. Since diagnosis, the number of reporting anaphylaxis decreases due to early recognition of symptoms and prompt actuation with the administration of epinephrine auto-injector, modifications of exercise habits and avoidance of culprit foods and/or cofactors. Studies concerning prognosis are scarce: Shadick NA et al [89], in a ten-year follow-up study, reported that 47% of FDEIA patients stated that the number of anaphylactic episodes decreased after avoiding the causative

foods, whereas 46% of the patients stated that the number of episodes remained the same.

11. Conclusion

FDEIA is a rare form of anaphylaxis with a considerable increasing number of reported cases in the last decade. It is an unpredictable disease that usually affects otherwise healthy and active individuals with potentially high impact on patient's quality of life.

Due to its complexity, a high level of suspicion is required and an exhaustive investigation to find the culprit food is required. Although provocation tests can only confirm the diagnosis in 70% of patients, provocation tests with aspirin/NSAIDs should be tried, in proper facilities, to increase accuracy.

The mainstay approach to FDEIA is education: avoid the culprit food associated and the cofactors (or not combine them), be aware of signs and symptoms of anaphylaxis, how to use the medications with the appropriate timing and administration method.

12. Expert opinion

The term food-dependent exercise-induced anaphylaxis will soon fall into disuse because exercise, although the most frequent, is not the only cofactor that can elicit a reaction. Other cofactors like NSAIDs and alcohol and combinations of two or more cofactors can prompt a reaction. This entity may be more appropriately named as *augmentation factor-induced food allergy*.

This complex type of food allergy has an increasing incidence in the past years mostly because a significant number of cases labelled as idiopathic anaphylaxis are now being correctly diagnosed as FDEIA. Although many reports are due to wheat, numerous case reports of FDEIA induced by LTP have been emerging. LTP sensitization is frequently associated with severe systemic reactions and is pandemic in the Mediterranean area. The complex management associated with this panallergen syndrome turns out a real problem, as patients did not know with what fruits and vegetables could potentially react and live with a constant fear of an imminent reaction.

It is also difficult when the medical community is not aware of this condition and many patients are frequently labelled as idiopathic anaphylaxis. There has been an evolution in the diagnosis and in addition to skin-prick tests, prick-to-prick tests and specific IgE immunoassays were all negative, a molecular allergen study must be done in order to diagnose more accurately.

Component-resolved diagnosis revolutionized the diagnosis of food allergy and have a crucial role in FDEIA patients, as it supports a better understanding of cross-reactivity patterns in patients who reacted with multiple foods, could diagnose culprit foods that have negative in vivo or in vitro tests, and can assess individual risk of anaphylaxis. Basophil-activation test has also been a promising diagnostic tool for food allergy, especially in patients with severe anaphylaxis.

An exercise-food challenge can confirm a diagnosis of FDEIA but cannot definitively exclude the disease. It allows diagnosis in 70% but a significant number of patients are not diagnosed, and the investigation should focus on this field. These patients cannot be left undiagnosed as they are associated with life-threatening reactions. Moreover, this diagnostic tool has not been standardized and many protocols have been used. When an exercise-food challenge is negative, an aspirin-food challenge or an aspirin-exercise-food challenge should be tried. It is necessary to reproduce the environment in which the reaction occurs to allow better diagnostic accuracy. Further research and standardized protocols are needed.

Despite advances in diagnosis and management, little is known about the pathophysiology of the disease. Currently, we cannot explain why a patient reacts when combining the ingestion of sensitized food and cofactor(s). The underlying mechanism of mast cell activation is unknown, and the

individual theories advocated are not enough to explain the mechanisms alone and many are hypothesized in the laboratory and are not compatible with life. It is the case, for example, of the acid-base balance and serum hyperosmolality theories. When discoveries will be made in this field, advances in diagnostic accuracy and novel prophylactic treatments will appear.

Although there is no current treatment or approved prophylactic medications, the future will pass undoubtedly for biologic drugs for preventing imminent allergic reactions, and various case reports are in line with that. Omalizumab by blocking IgE will refrain mast cells degranulation and these patients can be protected.

Food immunotherapy could be an option in selected patients and will offer positive outcomes with great impact on the quality of life. If we cannot control all the cofactors involved in a particular patient, we can control the threshold for eliciting a food allergic reaction. Particularly in cases of LTP sensitization, positive results of researches on Pru p 3 immunotherapy open a window of new treatments. In whom concern other food immunotherapies, more standardized and homogenous protocols must be validated.

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