Case series

Whoever goes slowly (after eating) goes far

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Abstract. Food-dependent exercise-induced anaphylaxis (FDEIA) is an uncommon IgE-mediated hypersensitivity disease with limited prevalence data. Recently, reported cases of FDEIA have been increasing both in adults and children. FDEIA pathogenetic mechanisms are not yet completely understood. Factors that add up their effects are food ingestion and physical effort and, in some cases, concomitant diseases, alcohol, drugs, emotional stress, menstruation, and particular weather conditions contribute to enhancing the reaction. Food-specific FDEIA (sFDEIA) implies the presence of an IgE-mediated sensitization to one or more foods, while in unspecific FDEIA (nsFDEIA), any food can induce anaphylaxis without sensitization. Among causative foods, the most dominant trigger of FDEIA is wheat, in particular the allergen ω-5 gliadin (Tri a 19). Other common foods are seafood, seeds, grains, nuts, vegetables and fruit, cow's milk, meat, and eggs. We present three cases of sFDEIA in children with clinical features and laboratory findings; the first was induced by a culprit food less frequently involved in sFDEIA than the others (www.actabiomedica.it).

Keywords: clinical history, culprit food, food-dependent exercise-induced anaphylaxis (FDEIA), specific IgE.

Introduction

Food-dependent exercise-induced anaphylaxis (FDEIA) is a nosological condition partly related to exercise-induced anaphylaxis (EIA) but more specifically classified as an event of summation anaphylaxis (multiple factors involved). FDEIA can be defined as a rapid onset of anaphylaxis that occurs during or after a physical exercise and is preceded by ingestion of one or more triggering foods (1-6). In FDEIA, both causative food allergens and exercise are separately tolerated (1-6).

Pathogenetic mechanisms are not yet completely understood, but the end-stage culminates with mast cells degranulation, histamine release, synthesis of arachidonic acid metabolites (e.g., prostaglandins, leukotrienes, and platelet-activating factor), and increase of tryptase (4).

Two types of reactions are included in FDEIA. Food-specific FDEIA (sFDEIA) occurs when physical activity is associated with one or more foods, and unspecific FDEIA (nsFDEIA) that is less frequent occurs when any food can induce anaphylaxis without sensitization. Among causative foods, wheat is the principal allergen (particularly Tri a 19 ω-5 gliadin), but seafood, seeds, grains, nuts, vegetables, milk, eggs, and meat have been implicated (2-6). In the Mediterranean area, sensitization to panallergens, such as lipid transfer proteins (LTP), is quite widespread, so plant-based foods (legumes, nuts, fruit, and vegetables) are often involved in sFDEIA (3-5).

Usually, symptoms occur within an hour of the onset of physical activity, but some cases have been reported 2-6 hours after physical exercise (3-5). Some cofactors have been described as promoters or ampli-

fiers of anaphylactic reaction in FDEIA, such as infections, alcohol, or drugs (particularly aspirin, nonsteroidal anti-inflammatory drugs, and antacids), emotional stress, menstruation, weather conditions (cold temperatures) or concomitant diseases (asthma, mastocytosis) (2-5, 7).

Data on the prevalence of FDEIA are still lacking. However, the estimated prevalence of FDEIA is 0,001% to 0,017% worldwide for all food (8). FDEIA is responsible for 30% to 50% of cases generally attributed to exercise-induced anaphylaxis (EIA) (8, 9). In pediatrics, the FDEIA prevalence rate is 0,06% among primary school students, and 0,017%-0,21% among high school students, mostly males (3, 6, 10,11).

Diagnosis of FDEIA is based on an accurate clinical history collection to investigate the causality between the timing of onset of first signs, the food ingestion, and the physical effort.

Blood and skin prick tests may help the diagnosis of FDEIA only if they are focused on specific candidate allergens according to the clinical history. Among in vitro tests, it could be helpful to consider Tri a 19 ω-5 gliadin-specific IgE and Tri a 14-specific IgE for wheat-related FDEIA, and Pru p 3-specific IgE for LTP-related FDEIA (3-5). Serum tryptase level could be increased, supporting FDEIA diagnosis in doubtful cases (4). In vivo tests, such as prick to prick tests with fresh foods, are more reliable than skin prick tests (SPT) with commercial extracts (3-5). Once clinical history or diagnostic test results are conflicting, it is recommended to conduct an open food-exercise challenge (OFEC) or a double-blind, placebo-controlled, food-exercise challenge (DBPCFEC) which may be performed after 30-60 min after eating the culprit food (3,4,7). In these cases, the suggested physical exercise consists of running on a treadmill or using an ergometer under close observation, trying to reproduce the setting and the features (such as duration or intensity) of the physical strength involved in the previous anaphylactic reaction (3,7). Provocation test can confirm the diagnosis, that cannot be rouled out in case of negativity. Only 70% of provocation tests are positive (12). When the food-exercise challenge fails, but there is a high clinical suspicion of FDEIA, the provocation test can be repeated, adding another trigger, such as aspirin, before eating the causative food (3, 7).

Diagnosis of sFDEIA could be only based on the suggestive clinical history and allergy tests when all of the following criteria are met:

- An anaphylactic reaction is preceded by the ingestion of causative food and occurs during or after a physical exercise.
- Increased levels of specific serum IgE for causative food.
- Both physical exercise and food ingestion induce an allergic reaction.
- No other diagnosis could be made (13).

Differential diagnosis is first based on identifying typical anaphylactic symptoms and signs and includes disorders that may mimic anaphylaxis or exercise-induced anaphylaxis (EIA) (4). Several allergic disorders, such as exercise-induced asthma, EIA, cholinergic urticaria, and cold urticaria, may be triggered by exercise but occur independently of food ingestion (4,14). Mastocytosis, chronic urticaria, hereditary angioedema, cardiovascular disorders, neurological events, and neoplastic disorders (e.g., phaeochromocytoma and medullary carcinoma of the thyroid) may present with one or more symptoms or signs, typically observed during anaphylaxis (4,14,15).

Once the FDEIA diagnosis has been formulated, the patient and his/her caregivers should be trained to prevent other potential episodes, recognize allergy symptoms, and promptly administrate emergency drugs (2-4). Although the most critical advice is to separate exercise from ingestion of the specific causative foods (in sFDEIA) or food in general (in nsFDEIA), respecting at least 4 hours (for a minimum of 4 to 6 hours), it is also recommended the avoidance of such trigger foods one hour after the physical activity (2-4). Furthermore, the management of FDEIA requires a personalized action plan with the patient's generalities, food allergies, concomitant asthma, and the emergency drugs with steps of administration (2-4). The action plan and the emergency drugs such as antihistamines, corticosteroids, beta-2 agonists, and adrenaline auto-injector should always be with the patient (2-4). Among all emergency medications, adrenaline auto-injector is the gold standard for treating moderate to severe anaphylactic reactions in FDEIA (2-4). If diet restrictions are difficult to accept, children with FDEIA should be evaluated on nutritional balance and psychological aspects (4). The course of FDEIA is not known. Some childhood food allergies are overcome

with growth (4); the most recent studies suggest the use of omalizumab in preventing these episodes (2).

We reported three cases of FDEIA in children followed at our Pediatric Allergy Unit. The parents provided written informed consent.

Case 1

A 12-year-old boy with no previous history of atopy or food allergy and no taking drugs, presented to our Emergency Department (ED) for generalized urticarial rash, and sudden dysphonia occurred a few minutes after a soccer match. Clinical examination revealed no neurological or cardiovascular impairment or wheezing; vital signs were normal. Medical history revealed that the child consumed packed classic chips with lemongrass iced tea (both previously eaten) one hour before the exercise. His clinical signs resolved after the administration of intramuscular (IM) adrenaline. The patient was hospitalized for 48 hours with no rebound symptoms.

Investigations

Complete blood count and other biochemical values were in range. Serum tryptase was slightly upper limits (7,4 μg/L; normal values 0-7 μg/L). Specific serum IgE and molecular diagnostic tests. (ImmunoCAP®) were positive to grass pollen (Phl p 1 and Phl p 5b >100 KUA/L), ragweed, and birch. Potato-specific IgEs were elevated (16,9 KUA/L) while Tri a 19, Tri a 14, and Pru p 3 were negative. The main pan-allergens profilins, Phl p 12, Pru p 4, Hev b8, and Bet v2, were also positive.
The prick-to-prick test with white potato was positive (9 mm for raw potato and 3 mm for cooked potato).

Management

The adrenaline auto-injector and a personalized emergency action plan were prescribed. Although we stressed the importance of avoiding potatoes 4-6 hours before and 1 hour after physical activity, a new anaphylactic episode occurred with the same symptoms while the patient was playing soccer. The child ate fried potatoes in fast food three hours before the match.

Case 2

Patient two is a 14-year-old girl born in El Salvador with a previous uncertain food allergic reaction, characterized by urticaria after eating pasta with tomato and sausage sauce containing black pepper and never investigated before. Following that episode, the girl always carries with her antihistamines. The patient was referred to our ED for generalized urticaria, abdominal pain, diarrhea, and weakness that occurred 30 minutes after eating margherita pizza (previously eaten) at school. Vital signs were normal, including blood pressure. She was successfully treated with IM adrenaline and intravenous (IV) fluids. A careful history revealed that the patient walked for 10 minutes to school after eating her pizza. She was hospitalized for 48 hours with no rebound reaction.

Investigations

Blood tests were normal. Serum tryptase was elevated (19,2 μg/L; normal values 0-7 μg/L). Total serum IgEs were 468 UI/ml (normal value < 200 UI/ml). Specific serum IgEs were positive for dust mites, grass pollen, ragweed, pellitory, birch, and other flowering trees. Molecular diagnostic investigations (ImmunoCAP®) revealed sensitization to Tri a 19 (11,40 KUA/L) and gliadin (5,99 KUA/L), while Tri a 14 was negative (0,01 KUA/L). The prick-to-prick with tomato and sausage sauce was negative. The prick-to-prick with black and white pepper was both positive.

Management

The patient was discharged with adrenaline auto-injector and a personalized emergency action plan. According to the clinical history and diagnostic tests, we did not perform the OFEC. We recommended avoiding wheat products before physical activity, including low-intensity activity. A spices-free diet was recommended too.

Case 3

Case three is a 14-year-old girl with no previous history of allergic diseases, referred to our ED for ab-

dominal pain, generalized urticaria, swelling of the lips, sickness, and diarrhea that occurred ten minutes after a volleyball training. Ten minutes before the physical activity, the patient ate an organic cereal bar, also made with red fruits (cherries 4,6%, blueberries 6,1% and blackberries 2,3%), nuts (almonds 7,7%), and peanuts (25,3%), that she previously tolerated. She had her menstrual period and supplemented iron and folate. Symptoms resolved after the administration of IM adrenaline.

M.I. was hospitalized for 48 hours with no rebound reaction.

Investigations

Serum tryptase was normal (4,4 μg/L; normal values 0-7 μg/L). Total serum IgEs were 1482 UI/ml (normal values < 200 UI/ml). Serum specific IgE were positive for peanuts (52,50 KUA/L), almonds (5,96 KUA/L), and cherries (7,23 KUA/L). Molecular

ImmunoCAP assay revealed a sensitization to Ara h 9 (25,7 KUA/L), Pru p 3 (13 KUA/L), Jug r 3 (8,84 KUA/L), Cor a 8 (1,59 KUA/L), and Mal d3 (15,70 KUA/L). Tri a 14 LTP was also positive (6,09 KUA/L). The ImmunoCAP assay also showed high values for Phl p 1 (>100 KUA/L) and for Phl p 5b (97 KUA/L) and a mild sensitization to profilins such as Pru p 4 (6,01 KUA/L) and Bet v 2 (3,82 KUA/L).

Management

The patient was discharged with an adrenaline autoinjector and a personalized emergency action plan. The OFEC was not conducted considering the diagnostic test and clinical history. The patient was advised not to eat peanuts, nuts, red fruits, peach, apple, and wheat 4-6 hours before and 1 hour later performing physical exercise.

Discussion

In all three cases, the association between exercise-induced symptoms and the diagnostic test results confirmed the diagnosis of sFDEIA.

Patient 1 was sensitized to potatoes, profilins, and many aeroallergens. Thus, under environmental conditions, the ingestion of potato three hours before and one hour after the exercise impairs the reaction. Although in our geographic area, the most common sensitizations in FDEIA cases involve LTP (especially Pru p 3), wheat components, and other foods, including fruits and vegetables (3,5). In Italy, 78% of sFDEIA patients show specific IgE to the LTP of peach Pru p 3 (5). Potato allergy is uncommon, especially as unique sensitization. After exposure to raw potatoes, adverse reactions are mainly described in pollen food allergy syndrome (PFAS). PFAS is due to the cross-reactivity between the major pollen allergen and related heat-labile proteins. The major cross-reactive potato protein is probably patatin (Sol t 1), also contained in other plants of the Solanaceae family (18, 19). It is well known that Bet v 1 homologs are present in potatoes, too (16). Furthermore, potato is one of the foods implicated in the latex-fruit syndrome (17).

Systemic symptoms, including anaphylaxis, have been previously described in atopic young children after ingesting cooked potatoes. In our Country, white potato is one of the first solid foods introduced at the beginning of weaning and is also associated with food-protein induced enterocolitis (FPIES) (16,19, 20, 21). Cases of FDEIA induced by potatoes are reported in the adult population (18).

Our case is one of the few described in childhood. The patient's allergic reaction was the tip of an iceberg, allowing us to facilitate safe management and discover pollinosis unknown before.

The second case represents the most typical features of wheat-dependent exercise-induced anaphylaxis (WDEIA). The patient was sensitized to the most critical wheat allergen Tri a 19 ω-5 gliadin, and her symptoms were induced by mild and short-term physical activity (13, 23, 24).

In patients with FDEIA, the most common food trigger is wheat, particularly its main component Tri a 19 ω-5 gliadin (13,23,24). A single-center experience recruiting patients diagnosed with FDEIA reveals that the culprit food was wheat in 46% of cases (6). Pediatric reports showed that the average interval between the onset of symptoms and the exercise is approximately 22 minutes (6). Recent studies also reported that several patients with WDEIA and sensitization to ω-5 gliadin developed symptoms without physical exercise (13). Therefore, physical activity is not a strictly nec-

essary condition to trigger the allergic reaction; thus, it could be defined as an enhancement factor for the clinical expression of an underlying wheat allergy (13).

The third case report underlines that FDEIA may occur in patients with multiple food sensitizations, including LTP. Results of an Italian study suggested that specific IgE to the LTP might have a crucial role in sFDEIA. Pru p 3 is positive in most subjects (5). Our patient was sensitized to Ara h 9, Pru p 3, Jug r 3, Cor a 8, Mal d3, and Tri a 14, a condition attributable to LTP syndrome (22). LTPs show high cross-reactivity and are found in plants and foods. In sensitized patients, different clinical allergic manifestations such as reaction to the ingestion of vegetables, fruits, nuts, or cereals are common (5, 22). Allergic reactions can also occur during the menstrual period in many patients, which is considered an additional enhancement factor. In literature, cases of FDEIA following the intake of nuts and peanuts are also reported (9,23). An Italian study suggested considering Tri a 14 as the causative trigger of FDEIA when serum-specific IgEs to ω-5 gliadin are negative (24).

Conclusion

All foods could potentially be associated with FDEIA differing by Country. Grains and cereals, seafood, nuts, cow's milk, fruits, vegetables, fish, and meat are mainly involved. Potato is a widespread ingredient in the diet and is generally considered a safe food. However, potato allergy has been reported in a few pediatric cases only. We firstly reported a case of exercise-induced anaphylaxis in a child who ate fried potatoes a few hours later. The second case concerns the typical presentation of WDEIA, while the third case is an example of FDEIA associated with LTP sensitization as frequently occurs in the Mediterranean area.

Although considered a rare allergic reaction, FDEIA is often an underdiagnosed life-threatening event.

Prevention includes avoiding causative food in combination with exercise and the prescription of emergency drugs (25,26). FDEIA should be suspected when the causality link between symptoms, food ingestion, exercise associated with one or more foods ingestion), and diagnostic tests could support the diagnosis. Provocation tests should be considered once the clinical history and diagnostic test are conflicting.

Conflict of Interest: All author declares that they do not have commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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