

Food Dependent Exercise-Induced Anaphylaxis. Can we trust the oral food challenge with exercise and acetylsalicylic acid?

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Abstract. Food-dependent exercise-induced anaphylaxis (FDEIA) is an IgE-mediated allergy resulting from the combination of the ingestion of an offending food and physical exercise. According to literature, oral food challenge (OFC) followed by physical exercise (OFCPE) should be considered the diagnostic gold standard. In the absence of adverse reactions, other cofactors should be added (e.g. acetylsalicylic acid, alcohol in adulthood), one at a time. But many other factors increase patient's reactivity. This could reduce the sensitivity of the OFCPE and, consequently, make instructions for patients less reliable. On the other hand, the addition of cofactors not reported by the patient may reduce test specificity. With the help of two exemplary stories, that present opposite outcomes, diagnostic difficulties of FDEIA are discussed.

Key words: Diagnosis; Food allergy; Food-dependent exercise-induced anaphylaxis; Oral Food Challenge

Introduction

Food-dependent exercise-induced anaphylaxis (FDEIA) is a particular type of IgE-mediated food allergy. This condition develops after starting to exercise and in combination with having eaten a causative food, but symptoms are not usually induced by exercise or consuming the causative food alone (1). When FDEIA is suspected, an oral food challenge (OFC) followed by physical exercise (OFCPE) is usually performed. In absence of adverse reactions, other cofactors should be added (e.g. acetylsalicylic acid in pediatric age, and/or alcohol in adulthood), one at a time (from now on, we will identify OFCPE plus acetylsalicylic acid as "augmented OFC"). The foods to be tested should be selected according to the patient's medical history as well as the results of blood and skin prick tests (SPT). SPT using commercial extracts is not accurate enough to diagnose FDEIA. Then, when blood tests and SPT with commercial extracts are negative, prick-to-prick tests (PtP) with suspected foods

should be conducted (1). An OFC as described above is usually used for the diagnosis of FDEIA. However, we believe that this diagnostic process is not always sufficient to confirm or to exclude the diagnosis of FDEIA. We would like to offer a reflection on the usefulness of "augmented OFC". This will be illustrated by the presentation of two real-world exemplary cases. These two stories are illustrative, they are only suitable to support our point of view on augmented OFC.

Written and oral consents from the patients and their parents were obtained, and the study was approved by the local ethical committee.

Case reports

Case report 1. Around 9 pm of a day of October, a 6-year-old girl, already allergic to peach and peanut lipid transfer protein (LTP) (with generalized urticaria and angioedema as symptoms) and with grass rhinitis (2), ate a multiple flours-made pizza (wheat,

corn, sunflower, sesame, linen, rye, barley, oats) dressed with olive oil and cherry tomatoes. Twenty minutes after finishing dinner, she went to play outdoors with other children, doing a moderate physical exercise. The ambient temperature was pleasant, the ambient humidity was not high. The girl was fine and she didn't have to take any medications that day. Five minutes after the beginning of physical exercise, she developed a face erythema and auricles edema, watery rhinorrhea, labial angioedema and moderate stridor. She took cetirizine, the reaction lasted about 1 hour and hoarseness remained for a few more hours. Since then, the girl has no longer eaten that kind of pizza, but she has eaten olive oil, tomato sauce, and wheat in the form of bread, pasta and biscuits. After that evening, and until we met her, she has presented no fever and she has not taken non-steroidal anti-inflammatory drugs. Therefore, she hasn't been exposed to cofactors which could have increased allergic reactivity. Moreover, the girl had very carefully avoided physical exercise. In fact, she was already not allowed to practice physical exercise because of her LTP allergy, even before the October activity, that was an exception. Her parents could not explain the reason for this restrictive prescription they had received from other doctors. In any case, she has never presented any other adverse reaction episodes.

Three months after the adverse reaction, the girl underwent an allergologic evaluation. On that occasion, diagnosis of wheat induced FDEIA (WDEIA) was made, based on a slightly positive PtP with wheat flour (wheal mean diameter = 3 mm) and a specific IgE to Tri a 14 (wheat LTP) = 1.8 kU/ml. Moreover, the extensive elimination of wheat from her diet was suggested. This indication was given because the girl used to eat wheat at least 3 times a day and there was no absolute guarantee that she would avoid exercise every time.

Two months later, the girl was admitted to our pediatric allergy clinic. PtP showed positive results for flour mix (wheal mean diameter = 12 mm), wheat (wheal mean diameter = 7 mm), corn (wheal mean diameter = 7 mm), sunflower seeds (wheal mean diameter = 8 mm), linen (wheal mean diameter = 8 mm). She gradually ingested 200 grams of the multi-flours pizza without presenting any adverse reaction and she was fine even an hour after the end of ingestion. The

girl then performed a step test for 10 minutes and had no adverse reactions within 4 hours. After 15 days she returned to the hospital and performed the following sequence: a) she took 10 mg/kg of acetylsalicylic acid (ASA); b) thirty minutes after taking ASA, she ate 200 grams of multi-flours pizza; d) thirty minutes after the end of the ingestion of pizza, she did a physical exercise (free run for 10 minutes). At the end of the physical exercise, the girl presented dry cough and watery rhinorrhea, then throat constriction and nasal obstruction. After 2 minutes, wheezing was appreciated at pulmonary auscultation and finally palpebral angioedema and conjunctival edema also appeared.

Case report 2. On a May evening an 11-years-old boy, suffering from allergic rhinitis with sensitivity to olive pollen, had dinner at home with pasta, mussels and prawns. The ambient temperature was pleasant, it was not very hot and there was not too much humidity. He had played football before and after dinner in the backyard. While he was playing football after dinner, he presented abdominal pain and nasal obstruction, and after two minutes he also presented bilateral palpebral angioedema. In the previous months, the boy had often eaten molluscs (including mussels), coelenterates and crustaceans, but he had never made physical exercise neither immediately before nor immediately after eating them. Moreover, he had never taken non-steroidal anti-inflammatory drugs and he had never had signs of illness on the same occasions. After that episode in May, the boy has eaten crayfish and squids without adverse reactions. He has also made physical exercise several times and he has not presented similar episodes anymore.

The boy was admitted to our pediatric allergy clinic seven months after his adverse reaction. SPT with commercial extract of mollusc was positive (wheal mean diameter = 3 mm) and PtP with raw mussel (wheal mean diameter = 10 mm) and cooked mussel (wheal mean diameter = 9 mm) were positive too. SPTs were negative for crustacean, cuttlefish, dermatophagoides pteronyssinus, blattella, anisakis. PtP for both raw and cooked prawn, cuttlefish and clam were also negative. Assay of specific IgE in serum of the patient showed 0.01 kU/mL for rDer p10 Tropomyosin and 0.01 kU/mL for rPen a 1 Tropomyosin.

Then the boy underwent an incremental OFC with cooked mussels up to the total cumulative dose of 100 grams of mussels, three times the quantity he had ingested during the adverse reaction in May. And he presented no adverse reactions within the next 3 hours after the last dose. The boy underwent a second OFC a week later: he ate 100 grams of cooked mussels all at once and he immediately made a strenuous physical exercise (step test for 10 minutes). And he did not present any adverse reaction. The boy underwent a third OFC two weeks later: he took 10 mg/kg of ASA thirty minutes after he had eaten 100 grams of cooked mussels. After other thirty minutes he made a strenuous physical exercise (step test for 10 minutes) and he did not present adverse reactions.

Concerns on diagnosis of FDEIA

In our opinion, the main problem for the diagnosis of FDEIA is summarized by the words of Asaumi et al (1): “We should confirm definitive diagnosis ... and then we should carry out provocation tests. However, reproducibility of these tests is not always high because environmental and individual condition influences it.” Therefore, the problematic point is the low reproducibility of the OFC, even if followed by exercise (OFCPE). For example, we don't think we can safely say the boy of case no. 2 does not have a FDEIA caused by mussels. We don't think we can safely say to him that he can eat mussels and then go to play football with friends.

Asaumi et al (1, 3) state that if an OFC with the culprit food, preceded by the assumption of ASA and followed by physical exercise, results negative (ie passed, that is without adverse reactions), then the diagnosis of FDEIA can be excluded. However, Asaumi et al (1) also remind us that, in addition to physical exercise and ASA, other nonsteroidal anti-inflammatory drugs may also be augmenting factors. As well as other medications (angiotensin-converting enzyme inhibitors, beta-blockers, antacids, and cannabis), weather (cold and hot temperatures) (4), general conditions (hyperthermia, infections, fatigue, stress, and menstruation), and bathing have also been reported as augmenting factors for FDEIA. Furthermore, Christensen et al

(5) add that exercise test may be influenced by the type of exercise, environmental conditions, even by hour of the day, health conditions (infections, allergies, drugs) and, at least for adults, by the ingestion of alcohol. Mast cell disorder and environmental allergens must be considered as other augmenting factors for FDEIA (6).

In addition, Christensen et al (5) reported that, even in the absence of any cofactor (including physical exercise), the adverse reaction can be elicited in 55% of patients with suspected FDEIA only by increasing the amount of culprit food (gluten in this case) far above the usual one. In short, FDEIA is a high-threshold allergy, and a lot of cofactors, perhaps many of them still unknown, may be able to lower this threshold, in a completely unpredictable way. Brockow et al (7) proposed that FDEIA should be renamed “augmentation factor-triggered food allergy”.

Finally, there is great variability among patients in terms of the amount of food, vigor and duration of exercise, and additional augmenting factors needed to reproduce symptoms (8).

Therefore, the augmented OFC (i.e., ASA plus OFCPE), suggested by Asaumi et al (1), might not have 100% sensitivity. It may be possible that, if one day the boy of the case no. 2 ate mussels, then went to play football on a particularly hot and wet day, and was also incubating a flu syndrome (all plausibly achievable events), he could have an allergic reaction, maybe even a serious one. Perhaps the boy of the case no. 2 is suffering from an allergy with a very high threshold, and more than 3 factors (i.e. the ones we tested: ASA, mussels and exercise) are necessary to him to present adverse reactions. The concept of “summation anaphylaxis” was well described by Wong et al (9), it is a phenomenon where accumulation of many factors results in symptoms of anaphylaxis.

But there is also the flip side. We're not sure that the girl of the case no.1 is suffering from FDEIA in the traditional way. We're not sure that we have to tell her to avoid exercise for 4 hours after eating wheat. Asaumi et al (1), recalling the case reports by Matsukara et al (10), remind as some patients experience symptoms after eating causative foods and taking ASA without exercising. The term ‘food-dependent salicylate-induced anaphylaxis’ was used in a report of such

cases. Therefore, in the case no.1, ASA could be the only cofactor determining the adverse reaction during OFC. The girl should undergo an OFC only with the ASA and with the wheat, or rather with each of the flours of that multi-flours pizza without exercising. This could be a very complicated diagnostic process for the child and for her parents, who in fact refused it. In any case, in the first OFCPE the girl of the case no.1 presented no adverse reactions. Then we introduced a third factor that was not present on the evening of the critical episode, that is ASA, and she presented an anaphylaxis. We think that the augmented OFC (OFCPE + ASA) lacks specificity because it can cause an adverse reaction even in patients who are not affected by an FDEIA in the traditional sense of the term, where the cofactor needed is only exercise. We might think the girl of the case no. 1 can run and play even after eating wheat as long as she does not simultaneously take ASA and more generally anti-inflammatory drugs.

Since “to reproduce the reaction under similar environmental, physical, and dietary conditions to the index case” is only “ideal”, as suggested by Foong et al (11), researchers meant to supply to the impossibility of an exact reproduction, adding other cofactors to physical exercise after ingestion of culprit food, such as ASA, or alcohol in adults (12) or greatly increased amount of food to administer (5). But they are all cofactors that are not present in the history that patients tell us, at least not always: the girl of the case no.1 and the boy of the case no. 2 had not taken ASA when they presented critical episodes that raised the suspicion of FDEIA. We might consider their inclusion in a diagnostic OFC as an “artificial” reduction of the threshold, an addition that reduces the specificity of OFCPE.

Anne Feldweg, strengthening our doubts about the impossibility of an accurate diagnosis of FDEIA, suggests that in the most of cases the diagnosis of FDEIA is made clinically, largely based on historical details of events surrounding the episodes. Feldweg lists the following criteria (6):

- Signs and symptoms consistent with anaphylaxis that occurred during (or within an hour of) exercise but only when exercise was preceded by food ingestion.

- No other diagnosis that explains the clinical presentation.
- If a specific food is implicated, there should be evidence of specific IgE to the implicated food, either by skin testing or by food-specific IgE immunoassays and no symptoms on ingestion of that food in the absence of exertion and no symptoms if exercise occurs without ingestion of that food, although there may be rare exceptions (patients may report isolated incidences when symptoms occurred at rest in the presence of other augmenting factors, such as illness).

According to the criteria above, the diagnosis of FDEIA for both children of the case no.1 and no. 2 would be certain only based on the history and the outcome of the allergometric tests.

Conclusions

OFCPE can be considered diagnostic only in case of positivity. If it is negative (ie passed), we cannot be sure, we should add a second cofactor (i.e., ASA, augmented OFC). And in case the augmented OFC is still passed, we should add a third cofactor, and then a fourth, a fifth, etc. We can only stop when the augmented OFC causes an adverse reaction, i.e. failed. Until that moment, we will always have the doubt of not having recreated the ideal conditions to make the adverse reaction happen.

“A standardized model for food challenges with the addition of different co-factors has not yet been developed”, write again in 2019 Christensen et al (5). And until it is developed, we think that, in case of a suggestive history for FDEIA plus a positive SPT, it is useless to perform an OFCPE or an augmented OFC. In doing so, we’ll have to accept some false FDEIA diagnosis. But that, at least in our opinion, is inevitable.

Conflicts of interest: Each author declares that he or she has no 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.

Abbreviations: ASA = acetylsalicylic acid; FDEIA = Food-dependent exercise-induced anaphylaxis; LTP = lipid transfer protein; OFC = oral food challenge; PtP = prick-to-prick; SPT = skin prick test; WDEIA = wheat-induced FDEIA

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