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Letter to the Editor

Food-dependent, exercise-induced anaphylaxis in a patient allergic to peach

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Abstract

Determining the single factor that triggered anaphylactic shock can be challenging. We present an interesting case of a 25-year-old female patient with recurrent anaphylactic reactions developing after eating various foods, particularly in presence of co-factors of allergic reactions. Symptoms occurred after consumption of various kinds of foods – peach, pancakes with cottage cheese and fruit, a meal from a Chinese restaurant – all eaten on other occasions without symptoms. During diagnosis, skin prick tests were negative for all tested allergen extracts (both inhalatory and food) from Allergopharma. Prick by prick tests were positive for the peach – wheal diameter – 6 mm, nectarine – 4 mm (histamine 4 mm, negative control 0 mm). Increased levels of asIgE were found for allergens of peach (0.55 kU/L).Open challenge test with one mid-size peach combined with the physical exercise challenge test was positive. ImmunoCAP ISAC test indicated increased levels of IgE specific for the lipid transfer protein (LTP) for walnut (nJug r 3), peach (Pru p 3), wheat (rTri a 14) and plane tree (rPla a 3). The patient was diagnosed with food-dependent, exercise-induced anaphylaxis associated with an allergy to lipid transport proteins (LTPs).

Keywords

component-resolved diagnosis, exercise challenge test, LTP, peach, Pru p 3

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Introduction

Determining the single factor that triggered anaphylactic shock can be challenging. That is especially true for cases in which anaphylaxis developed in association with a consumed food, and in cooperation with an additional factor, such as physical exercise, alcohol and the use of non-steroidal anti-inflammatory drugs (NSAIDs). In those cases, a patient may not be able to determine which food was the actual source of their symptoms.[1]

The case study

The 25-year old female patient was admitted in September 2017 to the Department and Clinic

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Allergology, Clinical Immunology and Internal Diseases of the Ludwik Rydygier Collegium Medicum in Bydgoszcz, because of recurrent anaphylactic reactions after eating various foods, particularly in presence of co-factors of allergic reactions, such as physical exercise, the use of NSAIDs and menstruation.

Interview revealed a history of hypothyroidism. The patient was on 100 μg of Levothyroxinum natricum for 4 days a week and 112 μg for 3 days a week. She did not use any other medication and was not treated for any other chronic condition. The patient was a full-time student of chemistry. She was slim (height 160 cm, body weight 48 kg, body mass index (BMI) 18.7) and well-groomed. She did not do any sport regularly and in general avoided physical activity. The patient's family history revealed her mother was suffering from atopic bronchial asthma and sinus polyps.

The first anaphylactic reaction in the patient's life occurred on 7 July 2016, after ingesting a peach. Moderate physical exertion (shopping) was associated with a massive facial oedema (particularly eyelids) and dyspnoea resulting from oedema of the lower throat. The patient was menstruating at that time. Because of those symptoms, the patient remained at the Emergency Department of the local hospital for 2 days on observation, and there she received systemic steroids and antihistaminics.

Another reaction occurred in October 2016: the patient ate a roll and possibly also other snacks (she could not precisely recall the menu), and then she carried boxes with her personal belongings, as on that day she was moving to another flat. At that time, the patient was menstruating and had taken NSAIDs (Ibuprofen). Pruritus and oedema of eyelids developed as a result of the physical exercise. She received Prednisone and Rupatadine, and then she was observed in the emergency room (ER) until complete disappearance of her symptoms.

In January 2017, the patient participated in a birthday party where she ate various foods (meat, salads, cakes). After eating a hearty meal, she went dancing. After several minutes of dancing, an anaphylactic reaction developed in the patient, in the form of stomach ache, vomiting and a generalized urticaria and oedema of eyelids. Paramedics were called, and the patient received medication in the emergency room, with a satisfactory effect.

In the beginning of March 2017, a similar reaction occurred after the patient ate pancakes with cottage cheese and fruit, and afterwards went for a vigorous walk. At the end of March 2017, the patient had another anaphylactic reaction, in the form of dyspnoea accompanied by a dry, tiring cough and facial oedema, occurring after eating a meal from a Chinese restaurant, and a vigorous walk.

In April 2017, the patient experienced oedema of eyelids and dyspnoea after eating sweet pancakes. At that time, the patient was menstruating and had taken NSAIDs (Ibuprofen).

Another reaction occurred in May 2017 – after eating cookies with nuts and raisins and physical exertion. The patient experienced dyspnoea and facial oedema. As previously, at that time, the patient was menstruating and was taking Ibuprofen. In June, August and September 2017, Chinese food triggered dyspnoea, oedema of eyelids and generalized urticaria. Since July 2016, the patient has been carrying a rescue set (adrenaline, steroids and antihistaminics) to be used in case of another anaphylactic reaction.

Despite the recurrent anaphylactic reactions described above, the patient kept on eating peach and other fruit, Chinese food, various pancakes and bread. Reactions were not repeatedly associated with particular foods, and a detailed interview indicated that these were always associated with various co-factors (mostly physical exertion, but also menstruation and NSAIDs). Patient used NSAIDs (Ibuprofen) on many occasions without any symptoms.

Diagnostics

At the time of admission to the Department and Clinic of Allergology, Clinical Immunology and Internal Diseases, the patient strongly denied any pathological symptoms. Physical examination revealed nothing abnormal. Basic laboratory investigations (blood cell count, creatinine, sodium, potassium, CRP, TSH, transaminases) revealed nothing abnormal.

The patient was subjected to detailed allergy diagnostics. Skin prick tests (SPT) with extracts of common inhalatory allergens (birch, alder, hazel, mugwort, ragweed, grass, house dust mites, moulds, animal fur) and food allergens (chicken egg, cow's milk, cocoa, tomatoes, carp, apple, banana, strawberries, rye flour, wheat flour, peanuts, hazelnut, walnut, celery, pork, poultry, citrus fruits) were performed using the Allergopharma kit. Prick by prick tests were also performed with a

fresh peach, nectarine, white grape, apple, pear and wheat-rye bread.

The level of IgE against allergens of peach, wheat flour, peanuts, hazelnuts and a mix of spices was also determined using the ImmunoCAP method (Thermo Fisher Scientific Phadia). The patient was also subjected to spirometry with the bronchial challenge test with histamine. The patient gave informed, signed consent to participation in this study and to the publication of this case report. SPT were negative for all tested allergen extracts (both inhalatory and food) from Allergopharma.

Prick by prick tests were positive for the peach – wheal diameter – 6 mm, nectarine – 4 mm (histamine 4 mm, negative control 0 mm). Increased levels of asIgE were found for allergens of peach (0.55 kU/L). For other tested allergens, those levels were <0.35 kU/L.

A blood sample was taken from the patient in order to expand the diagnostics by testing the level of IgE specific for allergen components using the semi-quantitative method - the ImmunoCAP ISAC micro-assay test. Those results were pending during the patient's hospitalization.

The patient was informed about the diagnosis – hypersensitivity to peach and nectarine. The patient was not satisfied with the diagnosis. She kept claiming the absence of correlation between her symptoms and the consumption of peach, nectarine and Chinese food.

Following an explanation of further available diagnostic options, and after obtaining the patient's informed consent, we decided to perform a physical exertion challenge test – first with no allergens and then after consumption of one, mid-size peach.

The physical exertion challenge test was performed in two phases of motor activity with increasing loads. The procedure was performed twice, with a 24-h interval between individual trials.

In the first phase of the challenge, a warm-up on a bicycle ergometer was carried out for 10 min, raising the heart rate to 120 beats per minute after 4 min of exercise. The actual physical exercise challenge was performed on a treadmill with continuous monitoring of the heartbeat rate, at 80%–90% of maximal heart rate (HR max) for 10 min, as described in other research.[2]

The first physical exercise challenge test was performed on an empty stomach. No adverse effects were observed.

On the next day, the oral food challenge test was performed: the patient ate one mid-size peach on an empty stomach, in an intensive allergological monitoring room, while seated. She ate both pulp and peel, just like she used to do at home. No direct adverse effects were observed within 1 h. Then the patient once again did the physical exercise challenge test. The treadmill test was concluded with no adverse effects, but 10 min after the end of the physical exercise the patient reported lacrimation and itching of eyelids and conjunctiva, followed by intensive lacrimation, reddening of the face and oedema of eyelids. The patient was administered Dexamethasone 8 mg iv and Clemastinum 2 mg iv. Despite the medication, urticarial blisters developed on the skin of the patient's trunk, along with a dry cough and wheezing. Physical examination revealed a steady heart rate of 90 bpm, arterial blood pressure of 100/70 mmHg and single wheezing over lung fields. The patient was administered 0.5 mg adrenaline as an intramuscular injection, which resulted in rapid disappearance of all ailments. On the following day, the patient was discharged home, with the following diagnosis: food-dependent, exercise-induced anaphylaxis (FDEIA).

Three weeks later, the results of the ImmunoCAP ISAC test were available. The test indicated increased levels of IgE specific for the lipid transfer protein (LTP) for walnut (nJug r 3), peach (Pru p 3), wheat (rTri a 14), plane tree (rPla a 3) – Table 1. No asIgE against other allergen components available in the ImmunoCAP ISAC test was found.

Discussion

FDEIA is often described in Japanese population and, in Japan, the most common cause of this form of systemic reaction is wheat omega-5-gliadyn Tri a 19. Due to the fact that exercise-induced anaphylaxis in this population is often wheat dependent; another name was proposed for this syndrome – wheat-dependent, exercise-induced anaphylaxis (WDEIA). Although WDEIA is the most important manifestation of allergy to Tri a 19, sensitization can manifest itself also with symptoms of mild urticaria or anaphylaxis without exercise.[1,3]

Omega-5-gliadyn is one of the allergen components included in ImmunoCAP ISAC micro-array assay and the level was not elevated in the case of the described patient. The patient had elevated

Table 1. ImmunoCAP ISAC test results.

Allergen source	Allergen component	Family of proteins	The level of specific IgE (ISU-E)
Walnut	nJug r 3	Lipid transfer protein (LTP)	1.3
Peach	rPru p 3	Lipid transfer protein (LTP)	0.8
Wheat	rTri a 14	Lipid transfer protein (LTP)	0.5
Plane tree	rPla a 3	Lipid transfer protein (LTP)	0.6

Results of other allergens included in the ImmunoCAP ISAC test were negative.

levels of wheat LTPs (rTri a 14), as well as LTP from other allergen sources (peach, walnut, plane tree). Peach Pru p 3 allergy is considered an immunological marker of LTP allergy and for this reason, the exercise provocation test after peach consumption was performed.[4,5]

In differential diagnosis, a NSAIDs allergy was taken into account. The patient used NSAIDs (ibuprofen) many times without any symptoms. She often used ibuprofen before physical exercise and found no correlation with symptoms. Because of positive results obtained with the exercise challenge with peach, we decided against performing an exercise challenge with NSAIDs.

One of the limitations of differential diagnosis in this case is the lack of baseline tryptase level. Elevated tryptase level is one of the minor criteria of mastocytosis. In an interesting work by Aberer et al.,[6] more than 50% of patients with non-mastocytosis diseases, such as urticaria and angioedema, drug or anaphylactic reactions repeatedly had tryptase levels higher than 20 μg/L. In a very interesting study published in 2018, Dua et al analysed clinical utility of tryptase in peanut allergies. Patients underwent up to four peanut challenges and one placebo challenge each. Tryptase was measured serially on challenge days both before (baseline) and during the challenge. The procedure was performed in total in 160 reactive (9% anaphylaxis) and 45 nonreactive (placebo) challenges in 50 adults aged 18–39 years. When compared with baseline levels, a rise of tryptase level was observed in 100 of 160 (62.5%) reactions and 0 of 45 placebo challenges. The median rise (95% confidence interval (CI)) for all reactions was 25% (13.3%–33.3%) and 70.8% (33.3%–300%) during anaphylaxis. According to authors, a serum tryptase measurement is valuable in food allergic reactions and correlates with symptom severity.[7]

Although the allergen provocation challenge, in the form of a double-blind placebo-controlled food challenge, is considered a gold standard in diagnosis of food allergy, it is performed rarely. In many cases, it is necessary to establish the diagnosis. The type of the challenge test (open, single-blind, double-blind) and the place where it is to be performed should be decided on a case-by-case basis. Special caution should be taken with patients at risk of anaphylaxis.[8] Selecting patients who are most likely to benefit from a given challenge are of great importance. There are several indications favouring a provocation testing, including sensitization in the absence of a clear history of clinical reactions, clinical history of reactions without sensitization, introduction of highly allergenic foods in sensitized or documenting resolution of food allergy.[9] An exercise challenge after provocation with food is a procedure typically used to diagnose FDEIA. Usually, an exercise challenge test is performed according to the Bruce protocol, designed for cardiac testing.[10] Due to the fact that there are still no specific guidelines on how to perform this specific form of challenge, many authors modify the procedure as they see fit. The specificity and sensitivity remain controversial. In another of our studies, despite the fact that the interview and immunological results indicated that the patient suffers from FDEIA due to tomato sensitization, the provocation test was negative.[2] An interesting article was published in 2017 by Gaillard et al. concerning patients with WDEIA. According to Gaillard et al.,[11] the WDEIA challenge test with gluten followed by exercise provocation might be less effective in inducing symptoms of anaphylaxis than a challenge test with gluten followed by alcohol or NSAIDs. Brockow et al. performed provocation tests in 34 patients with history of WDEIA and elevated level of ω 5-gliadine; their aim was to induce objective symptoms by provocation with wheat allergen alone and in combination with exercise, NSAIDs or alcohol. Brockow et al.[12] proved that physical exercise is not necessary to induce

symptoms, but that NSAIDs and alcohol are important co-factors of WDEIA.

In the case of our patient sensitization to peach LTP was proven, but the history of clinical reactions was not clear, mainly because a co-factor was required to induce reaction. For a given diagnostic method, the patient's preferences were also taken into account – before the provocation challenge it was unclear to the patient that in fact LTP allergy might be the cause of their symptoms. The procedure in the described case was not risk free, but resulted in a diagnosis that was clear and convincing both for the patient and physicians.

On the basis of the overall clinical presentation and the obtained results, the patient was diagnosed with FDEIA associated with an allergy to lipid transport proteins (LTPs). LTP are vegetable panallergens, regarded to be typical food allergens. They belong to the superfamily of prolamins. Their presence was described in numerous foods of plant origin, particularly those associated with the *Rosacea* family, such as peach (Pru p 3), apple (Mal d 3) and pear (Pyr c 3). Other well-known examples of food allergens that are lipid transport proteins include Cor a 8 (hazelnut, belonging to the family *Corylaceae*), Jug r 3 (walnut, from the family *Juglandaceae*) and many others.[13, 14]

Symptoms occurring after ingestion of foods containing LTP may be highly variable, from mild oral complaints to a severe systemic anaphylactic reactions. Heterogeneous reactions may occur in a single patient.[15]

Lipid transport proteins are largely resistant to high temperature and digestion in the alimentary tract. It was demonstrated that LTP could be found in cooked apples, peach juice and jam, in vine and in beer. Importantly, a much higher level of LTP is observed in peel, compared to fruit pulp. Approximately 1/3 of patients tolerate peeled fruits and vegetables; however, even in that group, the anaphylactic reaction is possible with a co-factor present (physical effort, alcohol, menstruation, NSAIDs, infection).[16–18]

The levels of LTP may differ for fruits and vegetables of the same species. Sancho et al. found that the LTP level depended on ripeness, conditions of growing and storage. For example, the level of LTP in an apple (Mal d 3) drops gradually in the course of 5 months, in storage in modified atmosphere (16% O_2 + 5% CO_2 filled to 100% with N_2 at 2°C).[8, 19]

Some patients react only to a peach, apple or other representatives of the *Rosaceae* family. In such cases, the presence of asIgE Pru p 3 from peach in the blood serum is considered to be an immunological marker. Other patients react to foods from various and non-related sources, for example, with walnuts and hazelnuts. These are considered to be a type associated with an allergy to LTP of mugwort – Art v 3.[4,18]

In 2011, Asero et al. studied 100 patients allergic to peach. The aim of their study was to assess levels of IgE against fruit and vegetable allergens other than peach, and of intensity of corresponding clinical symptoms (including organ reactions). It turned out that the level of IgE was not a universal tool for predicting the intensity of allergic reactions.[20]

In 2012, Pascal et al. published an interesting paper on the LTP syndrome in 45 patients. The authors found no correlation between the levels of IgE against nsLTP (non-specific lipid transfer protein) and severity of pathological symptoms. In that group, allergies were most commonly associated with peach, walnut and hazelnut, peanuts and green peas. Symptoms were variable from OAS (oral allergy syndrome), urticaria, contact dermatitis, alimentary disorders, to anaphylaxis. In 40% of patients, symptoms developed only in when co-factors were present.[21]

Asero et al.[22] looked for fruits and vegetables safe for patients with the LTP syndrome. Their analysis seems to indicate a relatively low risk of cross-reactions with allergens of carrot, potato, banana and melon.

In the case of the discussed patient, mildly elevated concentrations of IgE specific for LTP from various sources, as well as the variable course of reactions, heterogeneous symptoms and co-participation of co-factors in the release of symptoms indicated that an allergy to LTP was the source of recurrent anaphylactic reactions. Low concentrations of LTP-specific IgE from various sources do not exclude an LTP allergy.[23]

The described case is extremely interesting due to the relatively rare form of FDEIA, and the typical understanding of an allergy to the LTP of peach. This case also indicates the circumstances in which provocative tests are justified, while presenting potential threats resulting from that diagnostic approach.

At discharge, we explained the nature of the LTP allergy and the unpredictable course of reactions to

the patient. She was also informed which foods may potentially trigger reactions. The patient was also recommended to avoid physical exercise 2 h before and 4 h after the ingestion of a potential allergens. Eating peeled fruits and vegetables was recommended. She was recommended to avoid situations that may promote the occurrence of allergic reactions (i.e. co-factors, such as alcohol, NSAIDs, psychological stress and the above-mentioned physical exercise), particularly if she had consumed, or would eat, a potentially sensitizing dish within a window of a few hours. Due to the risk of anaphylaxis associated with the possibility of cross-reactions with LTP in vegetables and fruits, she was recommended to carry a rescue kit containing antihistaminics, oral steroids and an autosyringe with adrenaline.

The described patient might benefit from LTP immunotherapy. Although still considered experimental and not available commercially, food-specific immunotherapy (SIT) with non-specific peach LTP Pru p 3 is found effective both clinically and in immunological research. Gomez F. et al. in 2017 published a 1 year observation of 36 patients treated with sublingual immunotherapy (SLIT) to Pru p 3 and 12 non-treated, all of them after systemic reactions. After 1 year of SLIT, authors observed that the weal area in SPT significantly decreased for the peach threshold, and in peanut SPT weal. What is more, the authors observed immunological changes (a significant decrease in sIgE and a parallel increase in sIgG4, sIgG4/sIgE, as well as basophil reactivity for both Pru p 3 and Ara h 9). This has lead them to conclude that after 1 year of SLIT Pru p 3 patients benefit not only with a lessening of their peach allergy, but also allergies to other related foods responsible for systemic reactions.[24] In this group, successful Pru p 3-enriched-SLIT is linked to an important immunosuppression of allergen-specific effector T cells, potentially due to an increase of allergen-specific Treg cells.[25]

An interesting research, based on a Pru p 3-sensitized mice model, was published in 2018 by Rodriguez et al. The authors assessed the effects of SIT with reduced and alkylated (R/A) Pru p 3 (a hypoallergenic folding variant), compared to native Pru p 3.

SCIT with Pru p 3, but not with R/A Pru p 3, significantly suppressed anaphylaxis after a Pru p 3 challenge; SCIT with Pru p 3 did not suppress Pru p 3-specific IgE and IgG1 production, but enhanced IgG2a production. In contrast, SCIT with R/A Pru p 3 suppressed IgE and IgG1 production, but enhanced IgG2a production only moderately.[26]

Anaphylaxis may be a highly complex phenomenon, posing a significant diagnostic challenge. The role of co-factors in inducing an anaphylactic reaction in patients allergic to lipid transport proteins should be highlighted. Symptomatic and non-pharmacological treatment (e.g. eating peeled vegetables) is necessary to increase the quality of life and improve safety of affected patients. Positive results of researches on Pru p 3 immunotherapy in treatment of LTP allergy give hope for new possibilities of treatment available for patients in the near future.

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