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Use of *in vitro* and *in vivo* tests in the diagnosis of food-induced anaphylaxis – a case study

Zastosowanie testów *in vitro* i *in vivo* w diagnostyce anafilaksji na pokarmy – opis przypadku

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Abstract

Food allergy is a chronic disease that affects both children and adults. Systemic allergic reactions in children are most commonly caused by foods, especially nuts, milk, and eggs. A conventional diagnostic work-up for allergy typically pinpoints the allergen source, while component-resolved diagnostics is an approach that identifies the allergen molecules responsible for causing anaphylaxis. In some cases, determining the causative agent of anaphylaxis requires the use of various diagnostic tests. In the following paper, we want to highlight the importance of a critical approach to allergy tests results and caution in the diagnosis of idiopathic anaphylaxis. Based on a case report of food-induced anaphylaxis, we discuss the diagnostic methods that can be applied following a negative IgE test result for allergens obtained with a multiplex platform.

Keywords: diagnostics, food allergy, anaphylaxis

Streszczenie

Alergia pokarmowa jest chorobą przewlekłą występującą zarówno u dzieci, jak i u dorosłych. Systemowe reakcje alergiczne u dzieci są najczęściej wywoływane właśnie przez pokarmy, zwłaszcza orzechy, mleko i jaja. Konwencjonalna diagnostyka alergii zwykle pozwala zidentyfikować źródło alergenu, natomiast diagnostyka komponentowa umożliwia identyfikację alergenu odpowiedzialnego za wywołanie anafilaksji. W niektórych przypadkach próba ustalenia czynnika sprawczego anafilaksji wymaga zastosowania różnych testów diagnostycznych. W artykule autorki zwracają uwagę na znaczenie krytycznego podejścia do uzyskiwanych wyników badań i ostrożnego stawiania diagnozy anafilaksji idiopatycznej. Na podstawie opisu przypadku anafilaksji wywołanej przez pokarmy omawiają metody diagnostyczne dostępne 2 otrzymaniu negatywnego wyniku badania IgE dla alergenów na platformie multipleksowej.

Słowa kluczowe: diagnostyka, alergia pokarmowa, anafilaksja

INTRODUCTION

Food allergy is a chronic condition that impacts individuals of all ages. The main triggers of systemic allergic reactions in children include nuts, milk, and eggs. Traditional allergy diagnostics typically enables identification of the allergen source, whereas allergen-component diagnostics allows for pinpointing the specific allergen responsible for inducing anaphylaxis. The ALEX (Allergy Explorer) platform facilitates simultaneous testing for allergen-specific IgE (asIgE) across more than 290 allergen molecules and allergen extracts. Occasionally, efforts to pinpoint the causative agent of anaphylaxis may be unsuccessful.

The present study, based on a case report, aims to discuss the diagnostic methods available after obtaining a negative result for allergen-specific IgE testing for antigenic components on a multiplex platform.

CASE REPORT

A two-year-old girl was referred to the Department of Allergology and Pneumonology following an acute grade II allergic reaction, as per the classification developed by Błażowski et al.[1] (Tab. 1), which occurred following the consumption of vegan ice cream containing ingredients such as cashew paste, coconut extract, and tapioca; with a potential presence of other nuts, soya, and sesame. Approximately 10 minutes after eating the ice cream the girl developed generalised urticaria, mixed-type dyspnoea, and watery nasal discharge. An emergency medical team was called, and the girl was administered 4 mg of dexamethasone intramuscularly. Following the emergency response, she was transferred to the Department of Paediatrics, where the treatment plan comprised systemic glucocorticosteroids (hydrocortisone) and oral antihistamines (cetirizine and hydroxyzine). The child's mother was provided with a written action plan outlining steps to be taken in case of recurrent anaphylaxis, along with an adrenaline auto-injector.

Based on the patient's medical history, she has been experiencing skin lesions consistent with atopic dermatitis (AD) since she was three weeks old. Initially, the condition was severe, but gradual improvement has been noted over time. At the time of admission to the Department, the girl demonstrated good tolerance for fermented dairy products, goat's cheese, and certain types of cow's milk cheese. Out of concern about exacerbating skin lesions, the child was not given any pure milk.

Because of AD, the child remained on an egg-free diet which also excluded soya, red fruits and vegetables, potatoes, fish, nuts, garlic, and seafood. No diagnostic allergy testing had been performed. The girl did not take any medications on a chronic basis. There was a positive family history of atopic diseases (mother: AD; father: allergic rhinitis, allergy to grass pollen). In the home environment, exposure to animal allergens (dog) was identified. There was no passive exposure to tobacco smoke.

On admission to the Department, the patient's general condition was evaluated as good. Abnormalities on physical examination included dry skin with pronounced follicular keratosis, discrete papules in the joint flexures, and epidermal exfoliation on the fingers. Laboratory tests indicated a borderline decrease in the complement C4 level (0.119 g/L) and an elevated level of total IgE (117.8 IU/mL). The levels of other immunoglobulin (IgA, IgM, IgG), complement component C3, transaminases, creatinine, and fasting blood glucose were within the reference values. The peripheral blood count showed no significant abnormalities. Acute inflammatory markers were low, and serum

System / Severity of anaphylaxis	Skin, mucous membranes	Gastrointestinal	Upper respiratory	Lower respiratory	Central nervous system	Cardiovascular
Systemic allergic reaction Grade I	• Urticaria • Pruritus (skin, lips, nose, eyes) • Erythema • Angioedema (not laryngeal)	• Oral/palatal itching/ tingling • Nausea • Salivation	• Nasal discharge • Sudden sneezing • Itchy throat			
Grade II		• Crampy abdominal pain • Sudden vomiting • Diarrhoea	• Feeling of difficult breathing • Hoarseness	• Sudden repetitive cough • Chest tightness • Mild to moderate bronchospasm	• Sudden change in behaviour or activity level • Dizziness • Presyncope	
Grade III			• Tongue swelling • Throat tightness • Difficulty swelling, odynophagia • Stridor	• Severe broncho-spasm (not responding or worsening despite treatment)	• Confusion • Somnolence • Feeling of impending doom	• Sudden relevant hypotension • Pale and floppy child • Short episode of collapse (syncope)
Grade IV				• Respiratory failure	• Loss of consciousness	• Cardiovascular failure • Cardiac arrest

Tab. 1. Four-point scale for assessing the severity of systemic allergic reactions and anaphylaxis according to Błażowski et al.[1]

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vitamin D_3 levels were suboptimal (27.17 ng/mL). Serum tryptase levels were within the normal limits (4.29 μg/L).
During the hospital stay, the levels of IgE specific to allergen molecules and extracts were evaluated using the ALEX multiplex platform. Medium asIgE sensitisation were observed for the major and minor dog allergens (Can f 1, Can f 4), low asIgE sensitisation for the major birch pollen allergen (Bet v 1), medium asIgE sensitisation for the minor birch pollen allergen (Bet v 6), and low asIgE sensitisation for the minor house dust mite allergen (Der p 10). Regarding tropomyosin allergens, low asIgE sensitisation were recorded for storage mites (*Blomia tropicalis*, Blo t 10), American cockroach (Per a 7), nematodes (Ani s 3), and shrimp (Pen m 1). In addition, low asIgE sensitisation were found for the following allergens: crab (Chi spp.), mealworm (Ten m), garlic (All s), and egg white (Gal d white). However, there was no evidence of allergy to nuts. With no evident cause identified for the patient's systemic reaction, the ingredients of the ice cream that triggered the symptoms were reviewed again, leading to the decision to expand the diagnostic approach to include a food-specific IgE panel, IgE panel targeting the allergenic components of peanuts, and IgE determination for specific allergens using a singleplex assay (cashew nut – Ana o 3, peanut – Ara h 1, hazelnut – Cor a 8, rice – extract, sesame – extract). ImmunoCAP testing confirmed the presence of asIgE for the component of Ana o 3 of cashew nut (4.65 kU/L) and sesame extract (0.79 kU/L). In the food panel, only hazelnut extract showed a low asIgE sensitisation (0.44 kU/L), while the other tested allergens were classified as negative. The results of prick-to-prick tests were positive for cashew nut (3 × 4 mm) and ambiguous for peanut (2 × 1 mm).
In the reported patient, despite a relatively clear medical history, identifying the cause of anaphylaxis required a series of diagnostic tests.

DISCUSSION

Food allergy affects both children and adults. It occurs with a frequency of 3–8% in the child population and 1–3% in the adult population. Food-induced anaphylaxis is the most prevalent form of anaphylaxis in children, accounting for 30–50% of all cases[2,3]. The primary triggers of food-induced anaphylaxis in the population of Polish children (0–18 years old) are allergens found in cow's milk, peanuts, chicken eggs, tree nuts, and grains[3]. The leading causes of fatal anaphylaxis include peanuts and tree nuts[2].
As of now, there is no universally agreed-upon definition of anaphylaxis. According to the Polish Society of Allergology, anaphylaxis is a severe, potentially life-threatening, generalised or systemic hypersensitivity reaction[4]. The clinical criteria for food-induced anaphylaxis published by the World Allergy Organization (WOA) are the following:

1. acute onset of the disease developing after exposure to the food allergen, including skin/mucosal tissue symptoms (generalised hives, erythema, itching, angioedema) and symptoms from one or more of the following systems: respiratory (shortness of breath, bronchospasm, swelling in the throat/larynx), cardiovascular (decrease in blood pressure, dysfunctions associated with the decrease in central nervous system tissue perfusion), gastrointestinal (persistent vomiting and/or severe crampy abdominal pain)

or

2. any sudden onset of hypotension and/or sudden obstruction of the lower and/or upper respiratory tract that occurred after exposure to a food allergen, regardless of the presence of skin symptoms[5,6].

There are various scales designed to assess the severity of anaphylaxis, some of which vary considerably. The most commonly used scales are those developed by Mueller (1966)[7], Ring and Messmer (1977)[8], Sampson (2003)[9], Muraro et al. (2007)[10], and Cox et al. (2017)[11]. The severity of anaphylaxis plays a crucial role in determining the appropriate medical intervention; however, it is important to note that the scales used for severity assessment may not be entirely comparable (Tab. 2).
The most recently proposed 4-item scale, featuring a 2-item decision-making model for adrenaline administration, was developed by a collaborative effort between physicians from the Department of Allergology and Pneumonology in Rabka-Zdrój and physicians from the Department of Paediatric Pneumonology, 3rd Division of Paediatrics, Medical University of Lodz (2021). The scale is based on the natural history of food-induced systemic reactions in children (Tab. 1)[12].
The primary objective of diagnostic allergy tests is to confirm sensitisation to the allergen responsible for triggering allergic symptoms. It also involves identifying strategies for avoiding exposure to that allergen and assessing patient eligibility for specific immunotherapy.
Allergy diagnostics comprises both *in vivo* tests, such as skin prick testing (SPT), prick-to-prick tests with native allergens, and intranasal, intraocular, and oral challenge tests, as well as *in vitro* tests including allergen-specific IgE assays, molecular diagnostics, basophil activation test, and mast cell activation test[12].
Component-resolved diagnostics (CRD) is based on multiplex (e.g. ALEX2, ImmunoCAP, ISAC) or singleplex (ImmunoCAP) tests. Multiplex testing allows simultaneous determination of asIgE for several hundred allergenic source materials and allergenic components. This is especially important in patients with polyvalent allergies, where multiple allergens may be involved. Unlike the diagnostic methods based on allergen extracts, CRD enables the identification and quantification of asIgE for individual allergen molecules. This approach provides a more precise understanding of the specific allergen responsible for triggering the patient's clinical symptoms[13,14].

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System	Clinical symptoms	Mueller, 1966[7]	Ring and Messmer, 1977[8]	Sampson, 2003[9]	Muraro et al., 2007[10]	Cox et al., 2017[11]
Skin	Angioedema	II	I	II	I	I
	Generalised urticaria	I	I	II	I	I
Digestive	Itching of the mouth	None	None	I	I	I
	Nausea	II	II	II	I	I
	Crampy abdominal pain	II	II	None	II	II
	Persistent vomiting	II	III	III	II	II
	Diarrhoea	None	III	IV	II	II
Respiratory	Nasal symptoms	None	II	II	I	I
	Itching of the throat	None	None	III	I	I
	Hoarseness	III	II	IV	II	None
	Swelling of the upper airways	III	III	IV	II	None
	Stridor	None	None	IV	II	IV
	Chest tightness/shortness of breath	III	II	IV	II	III
	Mild/moderate wheezing	II	III	IV	II	III
	Severe bronchospasm of the lower airways	III	III	IV	III	IV
	Acute respiratory failure	IV	IV	V	III	V
Cardiovascular	Sudden relevant hypotension	IV	II	V	III	V
	Pale and floppy child	None	None	None	None	None
	Syncope	IV	None	None	III	V
	Acute cardiovascular failure	IV	IV	V	III	V

Tab. 2. Main differences between the available grading scales for the severity of anaphylaxis along with the classification of symptoms[1]

The singleplex (ImmunoCAP) method yields quantitative results. In contrast to methods relying on multiplex platforms, it is more precise, but it involves the testing of individual allergens.

CRD allows the identification of primary sensitisation and assessment of potential cross-reactions. Determining the affiliation of individual components to different allergen families (e.g. profilins, PR-10 proteins) indicates specific features of the allergen, which helps with the assessment of sensitivity to heat treatment or digestion, among other factors. Additionally, it offers an opportunity to estimate the risk of a systemic allergic reaction. The most anaphylactogenic proteins are allergens classified within the category of storage proteins. Confirming the presence of asIgE for a particular allergen family indicates the potential severity of an allergic reaction but does not predict it with absolute certainty[15]. Positive values obtained do not always correspond directly to the occurrence of a clinical response.

CRD carries no risk of systemic reactions and requires no discontinuation of antihistamines or cooperation from the patient. However, like any test, it has its limitations. Multiplex tests are susceptible to producing false-negative results in individuals with low total IgE levels. Also, variability in results is observed between different CRD methods when testing for the same allergens. There is a possibility of interference between IgE and other immunoglobulin isotypes, primarily within the IgG. Because of its high cost and limited availability, the World Allergy Organization recognises CRD as a third-line approach to diagnostic management[15].

In the presented case, asIgE testing for allergen components on a multiplex platform did not confirm nut allergy. It was necessary to measure the asIgE levels using the single testing method, which found positive results for cashew nut and sesame extract allergens.

Skin prick testing (SPT) is known for its high accessibility and relatively low cost. The disadvantages of SPT include the requirement for patient cooperation, which can be challenging, especially in infants and young children. In addition, antihistamines need to be stopped prior to skin prick testing[12]. Among the indisputable advantages, it is highlighted that SPT demonstrates high sensitivity and specificity for inhalant allergens (80–97% and 70–95%, respectively). For food allergens, however, both sensitivity and specificity are noticeably lower (30–90% and 20–60%, respectively)[16]. SPT results reflect skin reactivity and serve as a marker of sensitization in other target organs, including the eyes, nose, lungs, and intestines[16]. Upon introducing allergens into the skin, the allergen interacts with specific IgE bound to cutaneous mast cells. The interaction leads to the degranulation of mast cells, releasing histamine and other mediators, which ultimately leads to a visible "wheal-and-flare" reaction.

SPT should be performed to the volar surface of the forearm, at least 2–3 cm from the wrist and the antecubital fossa. In infants, where cooperation is limited and the forearm area is much smaller, tests can be performed on the skin of the back. It is important to note that the skin on the back is more sensitive, potentially leading to more pronounced reactions. A wheal of 3 mm or greater (compared to the negative control) is considered a positive skin prick test.

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Pseudopods are not included in the measurements, but may be marked separately; however their significance is unknown[16].

While there are no strict age limits for SPT, it is worth noting that skin reactions are often diminished in the very young and the elderly, which can make result interpretation challenging in these age groups. Also, infants often show larger flares and smaller wheals.

The absence of certain allergen molecules, such as oleosins, in commercial nut extracts poses a risk of obtaining false-negative results in SPT[17]. Furthermore, for many source allergens, commercial extracts are not available. Then, **prick-to-prick** tests can be more effective in detecting hypersensitivity to food allergens. Research has demonstrated that tests using native allergens yield positive results more frequently (over 80%) than tests with commercial allergens (40%). The level of agreement between a positive prick test result and a positive oral food challenge result was found to be 58.8% for commercial extracts and 91.7% for native allergens[18]. For peanuts, SPT has demonstrated low sensitivity with commercial extracts (3–35%) compared to prick-to-prick tests (50–100%)[19].

Griffiths et al. compared the sensitivity and specificity of SPT, ImmunoCAP, and the multiplex-based diagnostic approach in patients with nut allergy. Sensitivity was 71% for ImmunoCAP, 65% for ISAC, and 56% for SPT[19,20]. SPT combined with ImmunoCAP was not found to improve the sensitivity of diagnosis compared to ImmunoCAP alone (70% vs. 71%), but it increased sensitivity compared to the diagnosis based solely on SPT (70% vs. 56%)[19]. It is important to highlight that in patients with cashew nut allergy a positive asIgE result for the main allergen, Ana o 3 (albumin 2S), correlates with a positive outcome of oral food challenge[20,21]. Analysis of the aetiology of anaphylaxis in a group of children (aged 0–18 years) hospitalised in the Department of Allergology and Pneumonology of the Institute of Tuberculosis and Lung Diseases in Rabka-Zdrój showed that nuts (peanuts, cashews, walnuts, hazelnuts) and sesame accounted for 33% of all anaphylactic reactions[3]; among American children, cashew nuts were identified as the primary cause of food-induced anaphylaxis[21,22]. Błażowski et al. demonstrated that sensitisation (particularly the monovalent type) to the Ana o 3 cashew nut allergen was linked to a higher risk of severe anaphylaxis and more prevalent cardiovascular symptoms, classified as grade IV and V according to Cox et al.[22,23].

In the presented case, prick-to-prick tests were conducted, confirming the patient's allergy to cashew nuts.

Another valuable diagnostic tool for anaphylaxis is the evaluation of serum tryptase levels between 30 and 120 minutes after the onset of the anaphylactic reaction. Comparing this value with the baseline tryptase level, assessed at least 24 hours after the resolution of all anaphylaxis symptoms, can provide important insights. An elevation in tryptase level by 20% + 2 ng/mL during the reaction is regarded as confirmation of anaphylaxis. At the same time, the lack of tryptase elevation does not exclude anaphylaxis. Elevated peak tryptase levels are typically observed in allergic reactions triggered by anaesthetics, intravenous drugs, and insect venoms. In contrast, food-induced anaphylactic reactions are associated with lower tryptase levels[23,24].

The gold standard for the diagnosis of IgE-mediated food allergy is oral food challenge (OFC). The test is performed by physician in the hospital setting. However, in patients with a history of food-induced anaphylaxis, OFC may be contraindicated for safety reasons[25]. To enhance the safety of OFC, it is advisable to determine asIgE levels for relevant allergenic molecules of the source allergen using CRD methods.

In some cases of anaphylaxis, OFC is substituted with the mast cell activation test (MAT) or basophil activation test (BAT). MAT/BAT is performed when the results of skin prick tests and specific IgE assays are inconclusive. MAT evaluates the activation of mast cells derived from precursor cells of healthy donors. These mast cells are subsequently passively sensitised with antibodies from the patient's serum after exposure to the allergen. Conversely, BAT evaluates the expression of surface antigens of basophils following incubation with a particular allergen. BAT and MAT exhibit high specificity, but their diagnostic efficacy is allergen-specific and requires validation for various allergens and in specific patient populations[25,26].

CONCLUSIONS

Since anaphylaxis is a potentially life-threatening reaction, it is crucially important to identify the triggering factor. The leading cause of anaphylaxis in children is food. Identifying the factor responsible for the systemic reaction enables the formulation of appropriate dietary recommendations. Key elements in the diagnosis of anaphylaxis involve comprehensive history taking and a thorough review of test results correlated with patient history. The most accurate test for confirming an allergy to food antigens is the allergen component test. In some patients, verifying IgE-mediated food allergies involves documenting specific IgE via SPT and/or determining allergen-specific IgE antibodies. If the suspected allergen is not confirmed, it is advisable to explore additional diagnostic methods, as different tests exhibit varying sensitivity and specificity.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contributions

Original concept of study: JBM, ACD. Writing of manuscript: JBM, ACD, PJ. Critical review of manuscript: ACD, PJ. Final approval of manuscript: ABM, PJ.

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