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Cross-reactive aeroallergens – the main cause of food allergy

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ABSTRACT

The aim of this study was to identify allergenic cross-reacting allergens in patients with inhalation and food allergy using molecular diagnostics ISAC test. The study group consisted of 50 adult patients. The control group contained 20 healthy people. In the study group 92% patients were found to have the asIgE component responsible for cross-allergy between plant pollens and foods. The presence of asIgE was the most common for the Bet v 1 component. AsIgE was also detected for the component responsible for the presence of a true allergy to 26% patients. A statistically significant frequency of sensitization to 12 cross-reactive components was demonstrated, 10 of them belonged to the PR-10 proteins. An allergy profile of the studied population was created based on the ISAC results. The results of the study suggest that cross-reactions are the main cause of food allergy, and their frequency rises with increased sensitization to inhaled allergens.

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KEYWORDS

Food allergy; cross reactions; panallergens; allergy molecular diagnostics; food allergen components

Introduction

According to data from the European Academy of Allergology and Clinical Immunology (EAACI), 60% of cases of food allergy in adults and children are associated with the coexistence of an inhalation allergy (Werfel et al., 2015). There are two phenomena associated with this: co-sensitization and cross-reactivity. Co-sensitization is defined as the simultaneous occurrence of immunoglobulin E (IgE) for inhaled allergens and for food allergens in one person, and cross-reactivity occurs when an IgE-class antibody originally produced against one allergen combines with a similar allergen but was not originally produced as a result of exposure to the second allergen. The essence of this phenomenon is the occurrence of allergy symptoms without first having to come into contact with the cross-reacting allergen (Piwowarek et al., 2015; Vojtek et al., 2019).

The phenomenon of cross-reactivity was first observed and described in the 1940s by the Swedish researcher Carl Juhlin-Dannfelt (1948). Cross-reactions generally occur

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between plant pollen allergens and plant-derived food allergens belonging to the same protein family. In addition, the occurrence of cross-reactions between unrelated species from the world of plants and animals was observed due to commonly occurring substances with a similar structure, called panallergens. The most important panallergens are lipid transport proteins (LTPs), proteins from the PR-10 family, profilins, tropomyosins, 2S albumins, 7S globulins, parvalbumin, polcalcin, and serum albumins.

The structural similarity of proteins is the main factor determining the occurrence of cross-reactivity. The cross-reaction of IgE antibodies is possible due to analogy in the primary structure – the sequence of amino acids in the polypeptide chain (called linear epitopes) – and in the tertiary structure – the mutual position of the secondary structure elements: alpha helix, beta harmonica and beta turn (known as conformational epitopes). It is commonly believed that the occurrence of cross-reactions is highly probable when the protein sequence homology reaches 70%; whereas, with homology not exceeding 50%, the occurrence of a cross-reaction is unlikely (Ferreira et al., 2004; Hauser et al., 2010).

Other factors determining the occurrence of cross-reactions are time and frequency of exposure and the individual response of the organism to a specific allergen. It has been observed that the longer and more frequent the exposure to a given allergen, the greater the risk of cross-reactivity. A higher production of specific IgE antibodies also increases the risk of cross-reactions (Werfel et al., 2015).

Objective

This study aims to identify allergenic cross-reacting allergens in patients with inhalation and food allergies. The study is based on molecular diagnostics using the ImmunoCap® Immuno-Solid phase Allergy Chip (ISAC) test.

Materials and methods

The study group contained 50 adult patients: 30 women and 20 men, aged 18–74 years (mean age 35.8; median 34; standard deviation [SD] 12.8), diagnosed with an inhalation allergy on the basis of their medical history and positive skin prick tests, who had experienced undesirable effects after consuming food. Patients in the Department and Clinic of Allergology, Clinical Immunology and Internal Medicine of Ludwik Rydygier Collegium Medicum in Bydgoszcz were included in the study.

The control group contained 20 healthy people: 12 women and 8 men, aged 18–62 (mean age 36.3; median 32; SD 12.965), with a negative personal and family history of atopy, no infectious symptoms, and who were not taking any medications.

Participation in the study was voluntary. The subject and methodology were approved by the Bioethics Committee at the Nicolaus Copernicus University in Toruń, Collegium Medicum in Bydgoszcz.

A detailed allergology interview and physical examination were performed for all the patients. The ImmunoCap ISAC test was used to demonstrate the presence of antigen-specific IgE (asIgE) for allergen components. The measurement of IgE antibodies in the ImmunoCAP ISAC test is based on the microarray (biochip) method. The ImmunoCAP ISAC test is intended for the semi-quantitative determination of specific IgE

antibodies in serum tested for the presence of allergenic molecules. The ISAC kit contains a solid phase, which is the surface of a glass plate in microarray format with 112 components (43 native and 69 recombinant) adsorbed on it and arranged in triplets. Allergen components bound on the surface of the glass plate react with specific antibodies present in the test serum. Bounded, specific IgE are demonstrated by the addition of fluorescently labelled anti-human IgE. The level of specific IgE antibodies is proportional to the intensity of the measured fluorescence. The results are processed by computer using the Microarray Image Analysis (MIA) program. Antibody levels are presented in ISU-E standardized units (i.e. an ISAC standardized unit for IgE specifically), the values ranging from 0.3 to 100 ISU-E. Results ≥ 0.30 ISU-E are considered positive. The results obtained for asIgE levels are divided into four ranges: 0 (undetectable): < 0.3 ISU-E; 1 (low): 0.3–0.9 ISU-E; 2 (medium/high): 1–14.9 ISU-E; and 3 (very high): ≥ 15 ISU-E.

Results – medical interview

In the study group, the most common allergic diseases were: allergic rhinitis (88% of the patients), bronchial asthma (46%), atopic dermatitis (18%), and chronic urticaria (14%); 46% of the respondents had a positive family history of allergies. Analysis of the data from the medical interviews showed that the occurrence of adverse symptoms was associated with the consumption of 31 different foods. Most of the patients did not tolerate the following: apples (66% of the respondents), hazelnuts (52%), peaches (46%), celery (36%), peanuts (20%), and kiwi (20%). Most of the patients who qualified for the study group reported more than one side effect after eating food, oral allergy syndrome (OAS) being the most common. Anaphylaxis occurred in eight people. The most common combination of symptoms was the presence of OAS with urticaria in 14 of the patients. Detailed data on clinical symptoms are presented in [Table 1](#).

Results of the ImmunoCAP ISAC test

In the study group, asIgEs against at least one allergic component were found in all the patients. In the control group, no asIgEs were detected for the ISAC test components in 17 of the patients (85%).

Table 1. Percentage of people reporting specific undesirable symptoms.

Symptoms of food intolerance	Number of people reporting symptoms	Percentage of people reporting symptoms
Oral allergy syndrome	40	80
Acute urticaria	10	20
Diarrhoea	10	20
Abdominal pain	10	20
Dyspnoea	8	16
Angioedema	6	12
Abdominal gas	6	12
Anaphylaxis	6	12
Exacerbation of atopic dermatitis	6	12
Contact urticaria	4	8
Exacerbation of urticaria	4	8
Dysphagia	2	4
Reflux	2	4
Constipation	1	2

Statistical analysis using a non-parametric Mann-Whitney U test showed a statistically significant difference in the incidence of sensitization to 26 of the 112 components of the ISAC test in the study group compared with the control group. The results are shown in Figure 1.

Of the 112 allergen components of the ISAC ImmunoCAP test, 33 were cross-reacting. In the study group, asIgE was detected for the component responsible for a cross-allergy between pollen and food in 46 of the 50 (92%) patients. Using the test for two structure indices, it was shown that in 92% of the patients in the study group, being allergic to cross-reacting components was statistically significant ($p = .0001$). In the test group, the presence of asIgE was demonstrated for all 33 cross-reactive components of the ISAC test. AsIgE was most often demonstrated for the Bet v 1 component (in 42 patients). The mean ISU-E was calculated for each component, with the highest reported for Bet v 1: 28.5 ISU-E. Statistical analysis using the Mann-Whitney U test showed a statistically significant difference in the incidence of allergy to 12 cross-reactive components in the study group compared with the control group. Of the 12 components for which a statistically significant difference in the frequency of asIgE was demonstrated, 10 belonged to the PR-10 proteins: Bet v 1, Mal d 1, Cor a 1.04, Aln g 1, Cor a 1.01, Ara h 8, Pru p 1, Gly m 4, Api g 1 and Act d 8. There was also a statistically significant difference in the incidence of asIgE for the MUXF 3 and Art v 3 components, which belong to the LTPs. The frequency of specific IgE antibodies for the cross-reactive components belonging to tropomyosin, serum albumin, profilin and thaumatin-like proteins was not statistically significant. Detailed results for the cross-reactive component of the ISAC test are presented in Figure 2.

The relationship between the ISAC test results for cross-reactive components and gender was also investigated. Statistical analysis using Pearson's Chi-square test

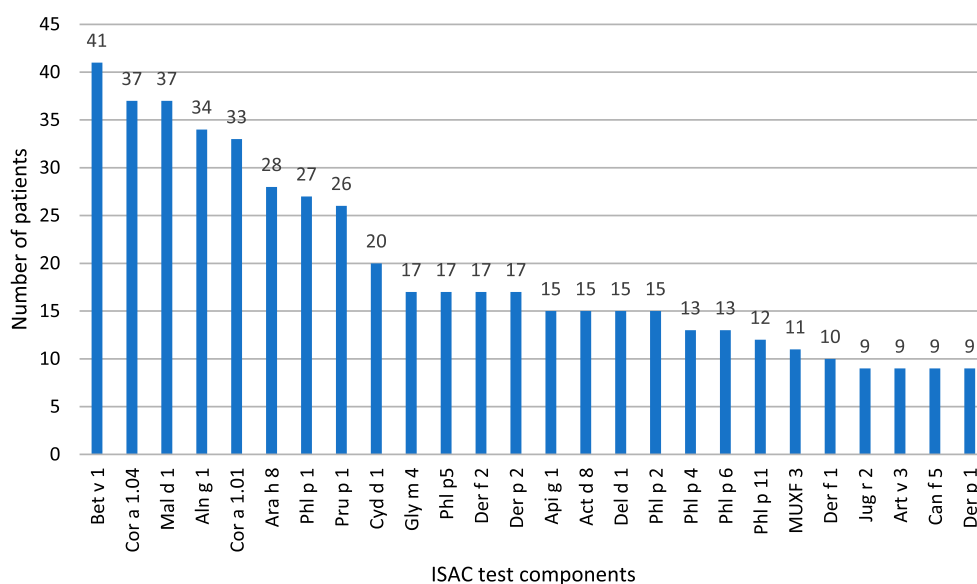


Figure 1. Components for which a statistically significant frequency of specific IgE was demonstrated in the study group compared with the control group.

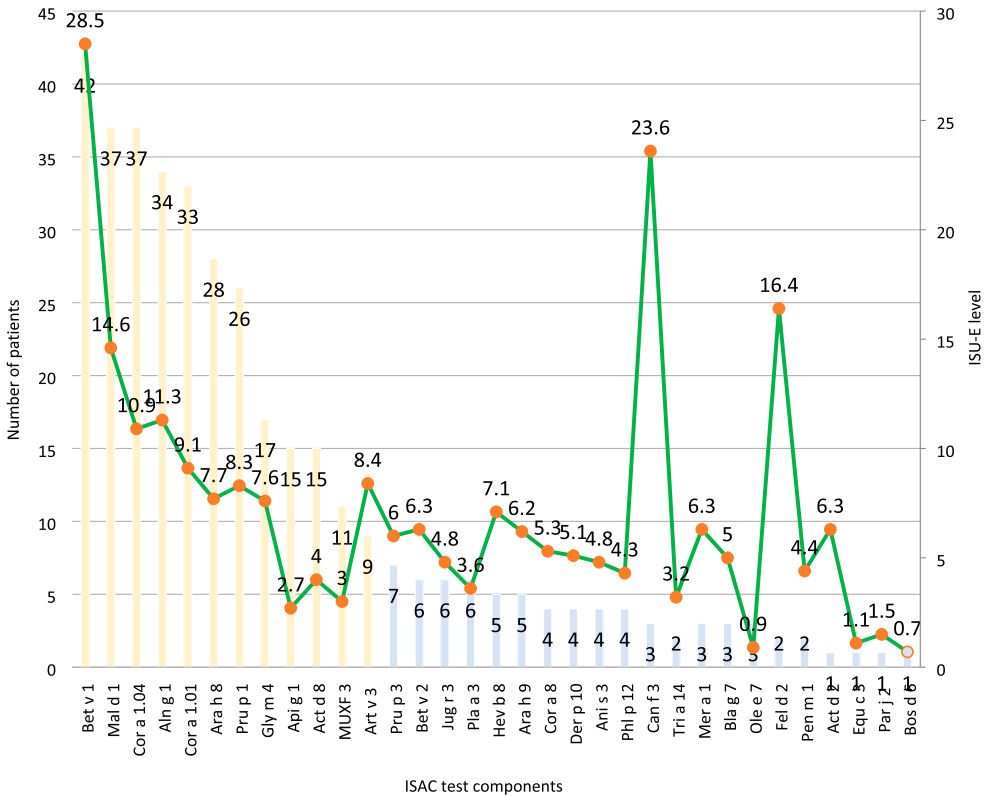


Figure 2. Cross-reacting component frequency, mean ISU-E and statistical significance of the frequency of specific IgE in the study group compared with the control group.

showed that sensitization to the Bet v 1 allergen ($p = .009$) was related to gender. AsIgE for Bet v 1 was detected in 19 of the 20 men in the study group, and asIgE for Bet v 1 was detected in 22 of the 30 women in the group. Sensitization to the remaining cross-reacting components of the ISAC test was not gender dependent. The relationship between the ISAC test results for a cross-reactive component and age was also assessed and no statistically significant relationship was found. Of the 112 allergen components of the ISAC ImmunoCAP test, 28 were species-specific food allergen components. In the study group, asIgE was detected in 13 of the 50 (26%) patients for the component responsible for a true food allergy. Statistical analysis showed a statistically significant difference in the incidence of sensitization only for the Jug r 2 component. Detailed results of the species-specific food allergen components of the ISAC test are presented in [Figure 3](#).

Discussion

According to EAACI data from 2014, the main causes of food allergy are food products containing allergens: cow's milk, eggs, wheat, soybeans, peanuts, tree nuts, fish, and crustaceans. The incidence of an allergic reaction to a given food varies with age and geography (Muraro et al., 2014). The majority of the patients in our study group did not tolerate the following: apples (66% of the respondents), hazelnuts (52%), peaches (46%), celery

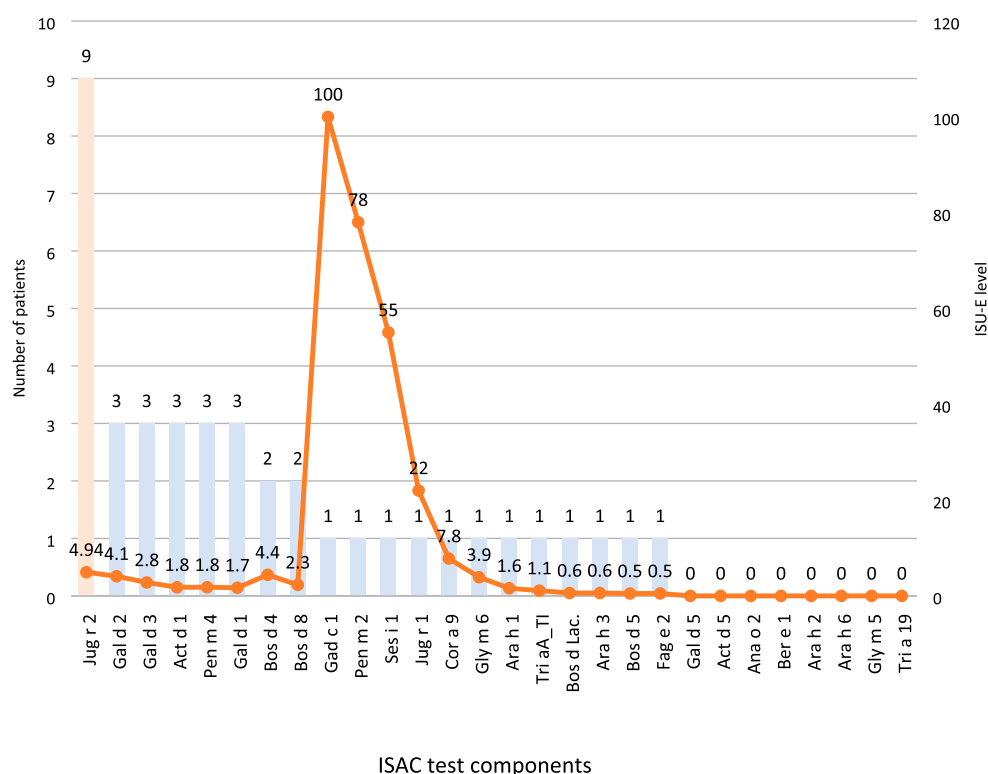


Figure 3. Species-specific food allergen components: frequency of occurrence, mean ISU-E and statistical significance of the frequency of specific IgE in the study group compared with the control group.

(36%), kiwi (20), and carrots (18%). The allergenic food profile was associated with cross-reactivity with PR-10 proteins. Sensitization to the main birch allergen, Bet v 1, was found in 84% of the patients examined.

AsIgE was detected for the component responsible for a cross-allergy between pollen and food in 92% of the patients in the studied population. A statistically significant frequency of sensitization to 12 cross-reactive components was demonstrated in the study group compared with the control group. Ten of the 12 components belonged to PR-10 proteins, and the presence of asIgE for the Art v 3 component, which belongs to the LTPs, was also found. Birch pollen is one of the most common causes of IgE-mediated allergy in the countries of Central and Northern Europe and in North America, and 70% of birch pollen allergy patients experience hypersensitivity reactions as a result of IgE cross-reactions with food sources. The main birch allergen, Bet v 1, is the precursor and the most important allergen of allergy to proteins from the PR-10 family. These are thermo – and enzyme-labile proteins and, clinically, cross-reactions with Bet v 1 are most often manifested by OAS (Biedermann et al., 2019). In our study group, 41 people (82%) had specific antibodies to proteins from the PR-10 family and this was the most common allergenic panallergen: ISU-E range 0.4–100; mean ISU-E 12.37. A similar frequency of allergy to Bet v 1 homologues was shown in Faber et al.'s study (79%) (Faber et al., 2017). In patients with asIgE detected against PR-10 components,

the majority reported symptoms of OAS (38/41; 92.7%). Almost identical results of 91.5% were obtained in Tolkki et al.'s study (2013).

LTPs are the most common cause of food-induced allergy in adults in the Mediterranean basin. Peach fruit, an important dietary component in Mediterranean countries, is the most common cause and precursor of LTP-related allergy (Pru p 3 protein). An allergy to LTPs is manifested clinically by severe anaphylactic reaction or milder allergic reactions, such as skin lesions, gastrointestinal symptoms and OAS (Wawrzęczyk et al., 2020). In our study group, 12 patients (24%) had specific antibodies to LTPs: ISU-E range 0.3–34; mean ISU-E 5.26. A similar incidence of LTP allergy was reported by Faber et al., who detected LTP allergy in 24.6% of their respondents (Faber et al., 2017). A different incidence of LTP allergy was demonstrated by Nucera et al., who found an incidence of allergy of 84.1% (Nucera et al., 2015). The differences in results can be explained by the place of residence of the respondents: Poland and Belgium (Faber et al., 2017) and Italy (Nucera et al., 2015) are associated with a different diet as well as with pollinosis to other allergens. AsIgE against Art v 3 was detected in nine of the subjects, and was the only LTP component for which statistical significance was found ($p = .044$); asIgE was detected for Pru p 3, Jug r 3, and Pla a 3 in six subjects; asIgE for Ara h 9 was detected in five patients; and asIgE for Cor a 8 in four patients. The data obtained in the study were different from Pascal et al.'s results, in which allergy to Pru p 3 was the most common (Pascal et al., 2012). Gao et al. obtained similar results in respect of LTP allergy to those in this study. Their study was conducted in China, where peach is not a frequently eaten food, but mugwort is high in pollen. AsIgE against Art v 3 was detected in 60% of their respondents (Gao et al., 2013). The results of the present study and the studies by Gao et al. (2013) and Pascal et al. (2012) suggest that there may be two routes of sensitization to LTPs. The first route occurs in Mediterranean countries, in which the cause and precursor of allergy to LTPs is the peach protein Pru p 3 (an important component of the diet). The second route occurs in countries in which peach is not an important component of the diet but there is a high concentration of mugwort pollen, the cause and precursor of LTP allergy being the mugwort Art v 3 component. García-Sellés et al. (2002) and Lombardero et al. (2004) also discussed two possible mechanisms of allergy to LTPs. In the current study group, asIgE was detected in 13 of the 50 (26%) patients for the component responsible for a true food allergy. AsIgE was most often demonstrated for the Jug r 2 component, which belongs to the plant storage proteins (SPs). A statistically significant sensitization was found ($p = .044$) in nine people. Plant SPs are widespread in monocotyledonous and dicotyledonous plants, and are deposited in the seeds and used as a source of the building blocks used during germination. Symptoms associated with an allergy to SPs are severe systemic reactions (Wawrzęczyk et al., 2019). In the study group, allergy to plant SPs was found in 10 people. In 90% of them, asIgE was detected for the walnut allergen Jug r 2. The research data indicate that Jug r 2 is a precursor and the most important allergen of sensitization to SPs. In their study, Archila et al. discuss the dominant role of the Jug r 2 protein in allergy to SPs (Archila et al., 2015).

Conclusions

The results of analysis of ISAC test results were used to create an allergy profile of the studied population. It was shown that the frequency of sensitization to 26 of the 112

components of the ISAC test was statistically significant. In the test group, the allergenic cross-reacting allergens were Bet v 1 and Art v 3 homologues belonging to the LTPs. The only species-specific food allergen for which a statistical significance of the frequency of sensitization was demonstrated was Jug r 2. The results of the study suggest that cross-reactions are the main cause of food allergy and that their frequency rises with increased sensitization to inhalation allergens.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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