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THE ROLE OF COMPONENT-BASED DIAGNOSTICS IN HAZELNUT ALLERGY TESTING

ROLA DIAGNOSTYKI OPARTEJ NA KOMPONENTACH W BADANIU ALERGII NA ORZECHY LASKOWE

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Wkład autorów:
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B. Data collection/entry
zebranie danych
C. Data analysis/statistics
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D. Data interpretation
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F. Literature analysis/search
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Summary

Background. Allergies have become a widespread disease in all parts of the world. Allergic diseases affect nearly 30% of the population in Hungary, of which food allergies account for a significant proportion. In this paper the prevalence of hazelnut allergy was analyzed.
Material and methods. In the present study, the sensitivity to hazelnut, a specific and otherwise healthy food component, was investigated comparing it with the self-reported symptoms of the participants, and Component-Resolved Diagnostic (CRD) method. In the study a total of 229 persons were included, 87 men and 142 women.
Results. Molecular allergy testing showed some serum immunoglobulin E level elevation related to hazelnut in 20 participants of which 1 individual was asymptomatic but CRD positive for hazelnut. There was positivity in 90% of the cases for the component Cor a 1, which is perhaps a consequence of a cross-reaction to the homologous component Bet v 1 of birch pollen. In 10% of cases, sensitization to components of Cor a 8 was found, which may be a consequence of cross-reactivity to the lipid transfer protein (LTP) component of other foods.
Conclusions. Knowledge of hazelnut sensitization may be important for people affected, as avoiding consumption of raw hazelnut may theoretically prevent the development of hazelnut allergy.

Keywords: hazelnut allergy, component-resolved diagnostics, sensitization, allergy, prevention

Streszczenie

Wprowadzenie. Alergie stały się chorobą powszechnie występującą we wszystkich częściach świata. Choroby alergiczne dotykają prawie 30% populacji Węgier, z czego istotny odsetek stanowią alergie pokarmowe. W niniejszym artykule przeanalizowano częstość występowania alergii na orzechy laskowe.
Materiał i metody. W pracy zbadano wrażliwość na orzechy laskowe, specyficzny i skądinąd zdrowy składnik żywności, porównując ją z objawami zgłaszanymi przez uczestników oraz metodą diagnostyki molekularnej, inaczej diagnostyki opartej na komponentach (CRD; ang. *Component-Resolved Diagnostic*). Do badania włączono ogółem 229 osób, w tym 87 mężczyzn i 142 kobiety.
Wyniki. Molekularne testy alergiczne wykazały pewne podwyższenie poziomu immunoglobuliny E w surowicy, związane z orzechami laskowymi, u 20 uczestników, z czego 1 osoba nie miała objawów, ale miała pozytywny wynik CRD dla orzechów laskowych. W 90% przypadków stwierdzono wynik pozytywny w przypadku komponentu Cor a 1, co być może jest konsekwencją reakcji krzyżowej na homologiczny komponent Bet v 1 pyłku brzozy. W 10% przypadków stwierdzono uczulenie na komponenty Cor a 8, które może być konsekwencją reakcji krzyżowej z komponentem białka przenoszącego lipidy (LTP) z innych produktów spożywczych.
Wnioski. Wiedza na temat uczulenia na orzechy laskowe może być ważna dla osób dotkniętych tą chorobą, ponieważ unikanie spożycia surowych orzechów laskowych może teoretycznie zapobiegać rozwojowi alergii na orzechy laskowe.

Słowa kluczowe: alergia na orzechy laskowe, diagnostyka oparta na komponentach, uczulenie, alergia, profilaktyka

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Introduction

Allergies have become a widespread disease in all parts of the world, causing mild to severe and even life-threatening symptoms, which in many cases can significantly reduce the quality of life of the people concerned. In recent decades, the number of allergic patients has doubled in Hungary [1]. In the majority of cases, it is a primary immune response with increased production of immunoglobulin E (IgE). With the development of diagnostic methods, it is nowadays possible to determine the specific IgE (sIgE) produced against the protein subunits that trigger the immune response in an increasing number of components. This has led to the development of Component Resolved Diagnostics (CRD) and its wider application [2].

Using this method, it is possible to identify patients sensitized to a particular component, which may help to identify more effective therapy. Different allergies usually show age differences. Primary food allergy is more common among young children, while pollen sensitization predominates in adults. Cross-reactivity of allergens may result in the development of the so-called oral allergy syndrome (OAS) [1,3,4]. In such cases, cross-reactivity is caused by a response to similar IgE epitopes [3]. In OAS, the symptoms are usually milder, characterized by skin symptoms (urticaria) and oral discomfort, but systemic reactions (asthma, anaphylaxis) may occur in rare cases [1,3,5-8]. The development of such pollen-food cross-allergies is also common in hazelnut-allergic patients. The (major) component Bet v 1 of birch pollen, which belongs to the pathogenesis-related protein (PR-10) family of stress proteins, is primarily responsible for the development of OAS in hazelnut allergy [1].

Both hazelnut (*Corylus avellana*) and birch (*Betula pendula*) are taxonomically members of the beech order (*Fagales*), within which they belong to the birch family (*Betulaceae*) [9]. For this reason, the Betv1 component of birch and the Cor a1 component of hazelnut share 80% similarity in their amino acid sequence [10]. This explains why in northern and central Europe, Asia and North America, the cross-reactive hazelnut allergy caused by Bet v 1 sensitization is predicted by elevated sIgE levels against the component of hazelnut Cor a 1 (PR-10 type). Cross-reactive pollen allergy as a result of pollen sensitization is prevalent in adults, with a small number of cases in children [1,10-13].

PR-10 proteins are mostly heat- and pH-labile, so the consumption of hazelnuts in raw form is the main source of OAS symptoms, whereas the consumption of hazelnuts in cooked or roasted form does not usually trigger symptoms [13,14]. In birch-endemic areas, OAS can also typically develop to other food components of the PR-10 family besides hazelnuts. Most commonly, cross-reactive sensitization to PR-10 components of apples (Mal d 1), strawberries (Fra a 1), peanuts (Ara h 8), celery (Api g 1), and carrots (Dau c 1) is observed, often accompanied by symptoms [3,10,14,15]. A minor component of birch pollen is Bet v 2, which belongs to the profilin family. Rarely, this component also induces OAS with profilin-type food components. In the case of hazelnut, the component Cor a 2 belongs to the profilin family, although milder symptoms are also typically seen in this case [8,14,16]. In Mediterranean areas of Europe (Spain, Italy, Greece), sensitization to the lipid transfer protein (LTP) component Cor a 8 of hazelnut is typical, mainly as a cross-reaction to the LTP component Pru p 3 of peach [14,17-19]. The onset of true hazelnut food allergy is predominantly seen in children under 6 years of age, usually with more severe and even life-threatening symptoms [1,3,17,20]. In this case, the heat-stable and indigestible components of the storage proteins of hazelnuts (Cor a 9, Cor a 14) may cause severe reactions [8,12,14,16,21-23]. According to a study by Sándor Sipka, hazelnut allergy was observed in 13.8% of children under 1 year of age in the Debrecen area (Hungary), and in only 1.6% of children aged 1-6 years. Peanut allergy was also present in both age groups. Adults had no symptoms when eating hazelnuts and only 11 of the 1,526 subjects reported symptoms for peanuts. However, birch was not among the most common pollen allergens in the studied population [1]. The prevalence of hazelnut food allergy in Europe is around 9.3% [24] and 10.8% in the USA [4]. Several studies have shown that the degree of sensitization to Cor a 9, but especially to Cor a 14, is positively correlated with the severity of symptoms following hazelnut consumption [8,21-23].

The significance of CRD is demonstrated by the fact that the detection of sIgE elevations against specific components provides a better assessment of the severity of hazelnut allergy, although the method alone is not sufficient for a definitive diagnosis. In all cases, it is necessary to know the medical history and to perform in vivo tests (skin prick test, prick-to-prick test, oral provocation test) in addition to CRD [3,12,13,16,17,19,21,22,25].

The aim of this study was to investigate the characteristics of allergy symptoms of people living in the county capital and its surrounding area in the northern region of Hungary using a new method (CRD). In this paper, the prevalence of hazelnut allergy among the participants was analyzed.

Material and methods

Participants and ethics

The participants in the study were volunteers recruited by special invitation via email. The invitation was sent by email to all employees of the University of Miskolc. Those who applied for the study and agreed to participate in the research were included. The individuals included in the study were informed orally and in writing about the purpose of the study and its possible outcome. After having received all this information, the participants completed a consent form.

The study was performed among the citizens of the University of Miskolc with the permission of the Regional Research Ethics Committee (permission number IG-117-24/2020), in accordance with the legislation in force and the World Medical Association Declaration of Helsinki.

Measures

Personal data and disease information were recorded by filling in a self-report questionnaire. The questionnaire contained 38 questions and assessed the participants' quality-of-life status in relation to allergic complaints. The participants provided demographic and lifestyle data, as well as about existing diseases, possible symptoms and their frequency. The participants also answered questions about their self-assessed health status, any chronic illnesses in the family and any known allergies.

Molecular allergology tests were performed on native blood samples in the Laboratory of the Faculty of Health Sciences between February 2020 and June 2021. BD Vacuainer sterile blood collection tubes were used to draw whole blood after centrifugation (5 min, 1700 rcf). Serum samples were stored at -80°C until processing. For sample analysis, an ALEX^2 Allergy Explorer kit (MacroArrayDX, Vienna, Austria) was used. The testing protocol followed the manufacturer's protocol. Microarray cassettes were measured with Image Xplorer (MacroArrayDX, Vienna, Austria) and evaluated using Raptor v1.5.4.16 software. Total IgE and different allergen-specific IgE antibodies were quantitated from each participant's sample. Data analysis was performed using Microsoft Excel (Microsoft, USA).

Results

In the study, a total of 229 persons were included. The average age of the participants was 45 years (SD=11.81). 87 men and 142 women participated in the total study.

Participants were divided into two groups according to the symptoms indicated in the self-report questionnaire. Of the respondents, 174 experienced allergic symptoms at some time of the year, while 55 were asymptomatic. Molecular allergy testing revealed some hazelnut-related elevation of sIgE levels in 20 participants. The sex ratio in this group was male:female = 1:1. According to the self-reported questionnaire, not everyone reported symptoms of allergies. Among the hazelnut-sensitized participants, 1 person belonged to the asymptomatic group and 9 persons had mild or severe symptoms, mainly respiratory (rhinitis, runny

nose, cough, asphyxia) and/or eye irritation (watering, itching). Two cases also reported a previous history of laryngeal edema, the etiology and progression of which is unknown. Among the 20 sensitized subjects, different proportions of different hazelnut molecular allergens were present (Table 1).

Table 1. Distribution of molecular allergens in hazelnut

Molecular allergen sensitization	All asymptomatic cases n=55	All symptomatic cases n=174
Hazelnut pollen Cor a 1.0103 (n/%)	1/1.82	13/7.47
Hazelnut food Cor a 1.0401 (n/%)	1/1.82	13/7.47
Hazelnut food Cor a 8 (n/%)	0	2/1.15
Hazelnut food Cor a 9, 11, 14 (n/%)	0	0

Typically, sensitization to the labile protein of the Cor a 1, PR-10 family was observed for both pollen (Cor a 1.0103) and food (Cor a 1.0401) components. Birch pollen sensitization (to Bet v 1 or Bet v 2 components) was observed in 18 cases. Component Bet v 1 was detected in 16 cases, while Bet v 2 was positive in 5 cases, of which 3 cases were also positive for component Bet v 1. Cor a 8, a lipid transfer protein, was detected in 2 patients. In these two cases, no sensitization to other hazelnut allergens was observed. No positive results were obtained for the storage protein components (Cor a 9, Cor a 14) in any of the cases.

The presence of sensitization to other food components resulting from cross-reactions are presented in Table 2. In the CRD method the RAST scale had an interval of 0-4. The upper limit of RAST grade 0 was 0.3 kUA/L. Samples above this value were considered positive. In most cases, in addition to Bet v 1 pollen, pollen sensitization for Cor a 1.0103 is present and among the molecular allergenic components appearing as a result of PR-10 cross-reaction that can be related to hazelnut, the Cor a 1.040 component was present in 16 people. In addition, sensitization to other food components is also demonstrated in different severities: strawberry (Fra a 1+3 mix) in 10 participants, apple (Mal d 1) in 11 participants, peanut (Ara h 8) in 3 participants, celery (Api g 1) in 5 participants, carrot (Dau c / Dau c 1) in 5 participants.

Table 2. RAST classes of other sensitivities observed in hazelnut-sensitized cases

Molecular allergens/ Cases	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Birch pollen Bet v 1	2	1	0	3	0	2	4	4	4	4	3	2	3	4	2	3	3	1	0	0
Birch pollen Bet v 2	0	1	2	0	1	0	0	0	4	0	2	0	0	0	0	0	0	0	0	0
Hazelnut pollen Cor a 1.0103	1	1	1	1	0	2	4	0	4	2	2	2	3	4	1	2	2	0	0	0
Hazelnut Cor a 1.0401	1	0	0	1	1	2	4	4	2	3	2	1	2	4	1	2	2	0	0	2
Hazelnut Cor a 8	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***1***	***3***	***0***
Strawberry Fra a 1+3 mix	1	0	0	1	0	1	2	4	0	2	0	0	2	4	0	2	0	0	2	0
Apple Mal d 1	0	1	0	1	0	1	0	4	1	3	2	0	2	3	0	2	0	0	0	0
Apple Mal d 3	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***1***	***2***	***0***
Peanut Ara h 8	0	0	0	0	0	0	3	2	0	0	0	0	0	2	0	0	0	0	0	0
Peanut Ara h 9	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***2***	***0***
Celery Api g 1	0	0	0	0	0	0	2	2	2	3	0	0	0	2	0	0	0	0	0	0
Carrot Dau c / Dau c 1	0	0	0	0	0	0	0	2	2	2	0	1	0	2	0	0	0	0	0	0
Peach Pru p 3	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***0***	***2***	***0***

The Bet v 2 profilin component may also cause a cross-reaction, but the method did not allow the measurement of the profilin component of hazelnut Cor a 2. However, in all Bet v 2 sensitized cases, we also found a slight increase in sIgE levels for the profilin component of melon Cuc m 2. The Cor a 8 lipid transfer protein component showed an increase in sIgE in 2 cases, but only in one case was a sensitization to other LTP

components found (apple Mal d 3, peanut Ara h 9, peach Pru p 3), but this was not associated with any pollen sensitization.

Discussion

The participants in our study were adults. Polysensitivity was characteristic, which was found to be associated with cross-reactive positivity for several different food allergens, which may even lead to OAS. It is known from the literature that pollen sensitization and associated OAS are more common among women in the adult population [3]. However, in the hazelnut-sensitized group focused on in this article, the proportion of men and women was equal. In 90% of the group, no OAS symptoms associated with hazelnut consumption were experienced. Only 2 subjects reported laryngeal edema suggestive of food allergy (cases 5 and 9). Sensitization to the PR-10 component of birch Bet v 1 occurred in 90% of the samples tested, and in 45% of the cases it was associated with the PR-10 component of hazelnut pollen Cor 1.0103. Among the cross-reactive hazelnut food allergens that can be associated with the Bet v 1 component, Cor a 1.0401 showed an increase in sIgE levels in 16 cases, but no pollen sensitization was measured in 1 case (case 20). Hazelnut sensitization is probably not relevant here. In the other case (case 5), total IgE levels were only 20 kUA/L, but we found a slight increase in sIgE not for Bet v 1 but for the birch Bet v 2 profilin minor component, as well as for Timothy grass Phl p12 and the cantaloupe Cuc m 2 profilin components. The profilin component of hazelnut Cor a 2 was not measurable in the present study; despite this, based on a review of the literature [14], it is likely that the present case was a cross-reaction induced by the profilin group, which also caused symptoms. In the other cases, we observed PR-10-type cross-reactive sensitization of hazelnuts and other foods to the Bet v 1 component, which is consistent with the literature [1,3,10,14,15]. We observed an increase in sIgE levels for the Cor a 8 LTP-type component in 2 cases (18 and 19 cases). In both cases sensitization to other LTP-type food allergens was present, suggesting a cross-reaction to LTP, which may occur without pollen sensitization [3,14]. Sensitization of the Cor a 8 component is typical for the Mediterranean region [14,17-19]. No positive results were found for the hazelnut Cor a 9, Cor a 11, Cor a 14 components, which is in correlation with the literature. [1,3,10,12,13] The test was limited by the fact that the chip – although it contains many more antigens than a conventional allergy test – only contains the more significant protein components that often trigger allergies, not all possible components. In some cases, mainly polysensitized, it would have been useful to test additional components. In particular, due to the high costs, only 1 test per individual was performed. Participants with a positive CRD result were advised to see a specialist, but their follow-up was no longer part of the study, so we have no information on their further treatment.

Conclusions

In the present study, we compared the participants' self-reported symptoms with the sIgE results obtained by the precision CRD method, with a special focus on hazelnut allergy. Bet v 1 pollen-induced hazelnut Cor a 1 cross-reactivity was found in 90% of the cases studied when the results of the CRD tests were analyzed. In 10% of the cases, we found sensitization to the LTP component of Cor a 8 associated with cross-reactivity to the LTP component of other foods. In conclusion, although CRD alone is not sufficient to establish a definitive diagnosis of hazelnut allergy, it is an increasingly indispensable component of the allergological diagnostic tools both in the recognition and risk stratification and in the indication and efficacy of possible immunotherapy.

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