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Peanuts allergy in atopic dermatitis patients, analysis of sensitization to molecular components

J. Čelakovská^a, J. Bukač^b, R. Vaňková^c, J. Krejsek^c and C. Andrys^c

^aDepartment of Dermatology and Venereology, Faculty Hospital and Medical Faculty of Charles University, Hradec Králové, Czech Republic; ^bDepartment of Medical Biophysics, Medical Faculty of Charles University, Hradec Králové, Czech Republic; ^cDepartment of Clinical Immunology and Allergy, Faculty Hospital and Medical Faculty of Charles University, Hradec Králové, Czech Republic

ABSTRACT

This study aims to evaluate the occurrence of food allergy to peanuts in atopic dermatitis (AD) patients and to analyse the sensitization to molecular components. The complete dermatological and allergological examination including the examination of the sensitization to molecular components with Multiplex ISAC testing was performed. Altogether 100 AD patients were examined – 48 men, 52 women, the average age 40.9 years. The food allergy to peanuts was confirmed in 27% patients; the majority of these patients are sensitized to PR 10 proteins (Ara h 8) and the minority to species-specific storage proteins and to non-specific lipid transfer protein (Ara h 9). In patients suffering from a clinical reaction to peanuts, the significant relation was confirmed to the sensitization to molecular components Aln g 1, Bet v 1, to molecular components of Timothy Phl p 1, 2, 4, 5, 6, 7 and to Mer a 1.

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Peanuts allergy; molecular components; atopic dermatitis

Introduction

Atopic dermatitis (AD) is a chronic intermittent inflammatory skin disease. It was originally regarded as a childhood disorder mediated by an imbalance toward a T-helper-2 response and exaggerated immunoglobulin E (IgE) responses to allergens, but it is now recognized as a lifelong disposition with variable clinical manifestations and expressivity in which defects of the epidermal barrier are central (Weidinger & Novak, 2016). There is increasing evidence from studies in infants that sensitization to food protein can occur across the skin barrier, in particular in the presence of eczematous skin inflammation. Carefully conducted large longitudinal studies amongst adults that take into account skin barrier function and genetics are required (Alduraywish et al., 2016; Manam et al., 2014; Röckmann et al., 2014). Food allergy and other allergic reaction or response encompasses two distinct stages based on the contact of the allergen with the immune system, referred to as the humoral or primary response and the cell-mediated or secondary response (Manam et al., 2014). It is important to recognize

CONTACT Jarmila Čelakovská ✉ jarmila.celakovska@seznam.cz

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that there are a number of other immunologic and non-immunologic reactions that can produce symptoms after exposure to foods or food additives. These reactions include conditions that are considered to be examples of food intolerance and conditions that are considered to be neither food allergy nor food intolerance. Diagnosis of food allergy is based on personal history, measurement of specific IgE (serum-specific IgE level – sIgE, skin prick tests – SPTs), atopy patch tests, challenge tests (open exposure test – OET, double-blind, placebo-controlled food challenge test – DBPCFC). The DBPCFC is considered as the gold standard for diagnosis of food allergies, but it is rarely employed by physicians outside of an academic context (Manam et al., 2014). Many studies reveal the prevalence of allergic diseases; however, most studies analysed a limited period from infancy to later childhood and/or to early adolescence. Adult AD patients show much higher rates of sensitization to foods than healthy individuals, in particular to food proteins cross-reactive with airborne allergens rather than the food allergens that typically predominate amongst children with AD. The incidence of new-onset food allergy in adult AD patients is currently unknown, as are the main routes of sensitization. Patients with established AD who are sensitized to a food protein can show three distinct reaction patterns: noneczematous reactions, isolated AD flares or a combination of both reactions (Alduraywish et al., 2016; Manam et al., 2014; Röckmann et al., 2014). Recent data indicate that peanut allergy is on the rise (Du Toit et al., 2015; Grimshaw et al., 2015; Perkin et al., 2016; Sebei et al., 2013). Peanuts are the seeds of the peanut plant (*Arachis hypogaea*), a member of the legume family (Fabaceae). Peanuts are very rich in nutrients and are one of the basic crops of India, China, the USA and West Africa. Peanuts contain 44–56% of oil and 22–30% of protein (Sebei et al., 2013). Peanut allergy has been well described and widely reported with population prevalence estimates between 1% and 6% (Allen et al., 2006; Clark & Ewan, 2005; Maloney et al., 2008; Osborne et al., 2011; Rona et al., 2007). The processing of peanuts seems to be important in regard to their allergenicity as roasting at high temperatures likely promotes the formation of compact globular protein aggregates that can increase the allergenicity of Ara h 1 and 2 (Vissers et al., 2011). The peanut allergens belong to diverse protein families leading to immunochemical IgE-mediated cross-reactions among different members of the legume families but also other plant foods such as tree nuts (Bublin & Breiteneder, 2014). The identified peanut allergens are shown in Table 1. The at-risk subject is an atopic individual, and risk is heightened for those with AD and/or other food allergies. The main symptoms triggered by peanut ingestion are in general cutaneous (urticaria, erythema and angioedema), gastrointestinal (abdominal pain, vomiting and diarrhoea), respiratory (wheezing and dyspnoea) and cardiovascular (hypotension, arrhythmia and shock). The usual onset of symptoms occurs soon after peanut ingestion (minutes to hours); however, some patients have biphasic reactions, with exacerbations occurring up to 8 h later (Sicherer, 2002). Clinical practice guidelines covering general diagnosis and management of food allergies have recently been published by the EAACI Food Allergy Diagnosis Systematic Review and Guidelines (Matricardi et al., 2016; Soares-Weiser et al., 2014). Progress in laboratory diagnostics of IgE-mediated allergy is the use of component-resolved diagnosis or molecular diagnosis of allergies (Matricardi et al., 2016). This approach has been developed when highly purified or recombinant allergen molecules have become available. These molecules are the allergenic proteins towards which the specific and clinically relevant IgE

Table 1. Peanut allergens, (www.allergen.org, 27 September 2015), (Grimshaw et al., 2015; Weidinger & Novak, 2016).

Allergen	Biochemical name	MW	Heat stability
Ara h 1*	Cupin (vicilin type, 7S globulin)	64	yes
Ara h 2*	Conglutinin (2S albumin)	17	yes
Ara h 3*	Cupin (Legumin type, 11 S globulin, glycinin)	60, 37	yes
Ara h 5	Profilin	15	no
Ara h 6*	Conglutinin (2S albumin)	15	yes
Ara h 7	Conglutinin (2S albumin)	15	yes
Ara h 8*	Pathogenesis related protein PR 10, Bet v 1 family member	17	no
Ara h 9*	Non-specific lipid transfer protein type 1	9.8	yes
Ara h 10	Oleolin	16	yes
Ara h 11	Oleolin	14	yes
Ara h 12	Defensin	8	yes
Ara h 13	Defensin	8	yes
Ara h 14	Oleolin	17.5	yes
Ara h 15	Oleolin	17	yes
Ara h 16	Non-specific lipid transfer protein type 1	8.5	yes
Ara h 17	Non-specific lipid transfer protein type 1	11	yes

Note: Molecular components in ISAC Multiplex testing are shown in extra bold*.

immune response is directed. Molecular diagnosis provides a major step in improving the accuracy of diagnosing IgE-mediated sensitizations in food allergy. The ability to identify and characterize single allergens at a molecular level has added a significant body of understanding as to the mechanism of sensitization to foods. Research into the structural similarity between allergens and the amino acid sequence homology between food allergens also helps to explain cross-reactivity between allergens, which may be clinically relevant or irrelevant. Certain panallergen molecules can indicate broad cross-sensitization and unfold particular pollen-food or plant-food syndromes (Luengo & Cardona, 2014; Matricardi et al., 2016). The introduction of allergen molecules has had a major effect on analytic specificity and allergy diagnosis. They are used in both singleplex ImmunoCAP and multiplex ImmunoCAP ISAC assays. The major advantage of ISAC is the comprehensive IgE pattern obtained with a minute amount of serum (van Hage et al., 2017). ImmunoCAP ISAC (Thermo Fisher), based on 112 different molecular components (both extracted and recombinant), is the most studied and most frequently used molecular diagnostic tool based on a microarray (Melioli et al., 2011). In our previous studies, we evaluated the occurrence of sensitization to food and inhalant allergens in patients suffering from AD; these patients were subjected to skin prick test, atopy patch tests and extract specific IgE to different food and inhalant allergens (Čelakovská et al., 2014; Čelakovská et al., 2015; Čelakovská et al., 2018; Čelakovská & Bukač, 2017).

Aim

The aim of our study is to evaluate the occurrence of food allergy to peanuts and to analyse the results of the examination to molecular components of peanuts in ISAC Multiplex testing.

We evaluate also if there is a significant relation between the occurrence of clinical reaction to peanuts and the sensitization to other molecular components such as Aln g 1, Bet v 1, Art v 1, Alta a 1, Asp f 6, Ole e 1 and Ole e 9, molecular components of

timothy Phl p 1, 2, 4, 5, 6, 11 and pollen – derived panallergens (Lipid transfer proteins – LTPs – Ole e 7, Pla a 3, Art v 3, Profilins – Bet v 2, Phl p 12, Mer a 1, and Polcalcins – Phl p 7, Bet v 4).

Method

Patients and methods

In the period of 2018–2019, 100 patients suffering from AD at the age of 14 years and older were examined. All these patients were examined in the Department of Dermatology, Faculty Hospital Hradec Králové, Charles University, Czech Republic. The diagnosis of AD was made with the Hanifin-Rajka criteria (Hanifin & Rajka, 1980). Exclusion criteria were systemic therapy (cyclosporin, systemic corticoids and biological therapy), pregnancy and breastfeeding. Patients with AD having other systemic diseases were excluded from the study as well. Complete dermatological and allergological examination was performed in patients included in the study. This study was approved by Ethics committee of Faculty Hospital Hradec Králové, Charles University of Prague, Czech Republic.

Examination of specific IgE to molecular components

The serum level of the sIgE was measured by the component-resolved diagnosis microarray-based sIgE detection assay ImmunoCAP ISAC (Phadia, Thermo Fisher Scientific, Uppsala, Sweden). ImmunoCAP ISAC is a solid-phase multiple immunoassay which enables to determine 112 different components from 51 allergen sources (Melioli et al., 2011; van Hage et al., 2017). The allergens are applied in triplicates to ensure the test reproducibility. The specific IgE values are presented in arbitrary units called ISAC Standardized Units (measuring range of 0.3–100 ISU-E). The level of specific IgE higher than 0.3 ISU-E was assessed as positive. The level of molecular components in ISU-E was evaluated: <0.3 to negative, 0.3–0.9 low positivity, 0.9–15 moderate positivity, above 15 ISU-E very high positivity (Melioli et al., 2011; van Hage et al., 2017).

Scoring of AD

Severity of AD was scored in agreement with SCORAD (scoring of atopic dermatitis) with the assessment of topography items (affected skin area), intensity criteria and subjective parameters. The severity of AD was evaluated with SCORAD as a mild form to 25 points, as moderate over 25–50 points, as a severe form over 50 points (European Task Force on Atopic Dermatitis, 1993). This examination was performed during one year every two months and the average SCORAD index was calculated.

Anamnestic data

A detailed personal history of possible food allergy was taken in all included patients. The patients indicate whether they suffer from immediate or late adverse food reactions affecting the skin, gastrointestinal tract or respiratory tract, not only after the ingestion of peanuts but also after ingestion of other foods. We recorded previous reactions to

peanut; symptoms; affected organ system, onset and course, cofactors (exercise, NSAID, alcohol). The open exposure test was not performed in patients with the early reaction after the ingestion of peanuts in their history because of anaphylactic reaction danger. All of these patients have been carefully examined and they are always monitored.

Confirmation of food allergy

- (1) The diagnosis of peanuts allergy was confirmed according to the convincing history with the food reactions after peanuts ingestion (gastrointestinal symptoms – oral allergy syndrome, vomiting, cramps, abdominal pain, skin symptoms – pruritus and worsening of AD), together with the positive results of specific IgE to molecular components of peanuts in ISAC Multiplex testing.
- (2) Sensitization to peanuts was confirmed in patients with no clinical reaction after ingestion of peanuts, but with positive results of specific IgE to molecular components of peanuts in ISAC Multiplex testing. It means, that although the positive results of specific IgE to molecular components of peanuts were recorded; these patients are without clinical symptoms. All these patients are informed about the positive results of specific IgE to molecular components of peanuts and they are always monitored.
- (3) Patients with clinical reactions after peanut ingestion without positive results to molecular components in ISAC Multiplex testing were monitored and the relation to the sensitization to molecular components of inhalant allergens was examined.

Statistical analysis

The analysis of the results in the examination of ISAC multiplex testing in patients with food allergy to peanuts was performed. Venn diagram was used to show the positivity to molecular components of peanuts in patients suffering from food allergy to peanuts.

We tested also if there is the significant relation between the occurrence of clinical reactions to peanuts and the sensitization to some molecular components such as Aln g 1, Bet v 1, Art v 1, Alta a 1, Asp f 6, Ole e 1 and Ole e 9, molecular components of timothy Phl p 1, 2, 4, 5, 6, 11 and pollen – derived panallergens (Lipid transfer proteins – LTPs – Ole e 7, Pla a 3, Art v 3, Profilins – Bet v 2, Phl p 12, Mer a 1, and Polcalcins – Phl p 7, Bet v 4). Such a table was evaluated by the usual Chi-squared test. The p – value is displayed in the right-hand column.

Results

Patients

One hundred patients suffering from AD were included in the study – 48 men and 52 women with the average age 40.9 years and with the average SCORAD 39, (s.d.13.1 points). The mild form of AD was recorded in 14 patients (14%), moderate form in 58 patients (58%), severe form in 28 patients (28%); 55 patients (55%) suffer from asthma bronchiale and 78 patients (78%) suffer from rhinitis. The clinical reactions after the ingestion of peanuts according to the history were recorded altogether in 49 patients (49%).

Table 2. The characteristic of patients with AD.

-
- 100 patients examined – 48 men, 52 women, the average age 40.9 years
 - the average SCORAD 39 s.d. 13.1 points
 - the positive results in to molecular components in ISAC Multiplex testing – 93 patients (93%)
 - mild form of AD patiens 14 (14%), moderate form of AD patients 58 (58%), severe form of Ad patiens 28 (28%)
 - number of patients with asthma bronchiale – 55 (55%), number of patients with allergic rhinitis – 78 (78%)
 - the anamnestic data about the food reactions to peanuts – 49 patients (49%)
 - the positive results in ISAC Multiplex testing to molecular components of peanuts in 41 patients (41%)
-

From the whole number of patients included in the study (=100 patients, 100%), the positive results to one or more of molecular components of peanuts were recorded in 41 patients (41%). The characteristics of patients are shown in Table 2.

In Table 3, we demonstrate the results of specific IgE to molecular components of peanuts in patients suffering from a clinical reaction to peanuts. From these 49 patients (=100%), the positive results to one or more of molecular components of peanuts were confirmed in 27 patients (45.1%); no positive results to molecular components of peanuts were recorded in 22 patients (44.9%).

The severity of AD and the clinical reactions in patients suffering from a clinical reaction to peanuts (49 patients = 100%) are recorded in Table 4. From these patients, severe form of AD was recorded in 34.7%, moderate form of AD in 42.8% and mild form of 22.5%. The early allergic reactions such as oral allergy syndrome or nausea with abdominal pain were recorded altogether 55.1%, early + late reactions (oral allergy syndrome + pruritus and worsening of AD) were recorded in 44.9% (Table 4).

In Table 5, we demonstrate the results of specific IgE to molecular components of peanuts in the whole group of examined patients (100 patients = 100%) in comparisson to the occurrence of clinical reaction to peanuts. In patients with both clinical reactions to peanuts and the positive result of specific IgE to one or more of molecular components to peanuts we confirmed the food allergy to peanuts. The food allergy to peanuts was confirmed altogether in 27 patients (27%). The clinical symptoms of peanut allergy were recorded as a mild oral allergy syndrome, abdominal pain and pruritus with some new eczematic lesions in patients with positive results to Ara h 8 and Ara h 9. These patients try to eliminate peanuts from the diet, but after accidental ingestion, they observe burning of the oral cavity, itching and worsening of AD also. The clinical symptoms such as oral allergy syndrome and pruritus were recorded in patients with

Table 3. The results of the examination of specific IgE to molecular components of peanuts in ISAC Multiplex testing in patients suffering from clinical reaction to peanuts, 49 patients = 100%.

Clinical reaction to peanuts – 49 patients = 100%	positive results to at least to one of molecular components	negative results to molecular components
	27 (55.1%) patients – food allergy confirmed	22 (44.9%) patients

Table 4. Severity of AD and the anamnestic data about the food reactions to peanuts in AD patients (49 patients = 100%).

Severity of AD		Number of patients	
Reaction to peanuts	mild	11 (22.5%)	
	moderate	21 (42.8%)	
	severe	17 (34.7%)	
	early	27 (55.1%)	
		OAS	22 (44.9%)
		GIT	5 (10.2%)
	early + late	22 (44.9%)	
		OAS	15 (30.6%)
		GIT	7 (14.3%)
		Pruritus	7 (14.3%)
		Worsening of AD	8 (16.3%)

Note: OAS – oral allergy syndrome, GIT – gastrointestinal symptoms (nausea, abdominal pain).

positive results to storage proteins (Ara h 1, Ara h 2, Ara h 3, Ara h 6). All these patients strictly eliminate peanuts from their meal. We show the Venn diagram (areas proportional to frequencies) of positive results to molecular components in patients suffering from peanuts allergy – [Figure 1](#). In this figure, we show the role of species-specific components (Ara h 1, Ara h 2, Ara h 3, Ara h 6) and cross-reactive components (Ara h 8, Ara h 9) in patients with confirmed food allergy to peanuts. Majority of these patients have positive specific IgE to Ara h 8, only a minority of them to Ara h 1, Ara h 2, Ara h 3, Ara h 6.

The overview of patients suffering from a clinical reaction to peanuts is recorded in [Table 6](#).

We show the kind of clinical reaction to peanuts, severity of AD, the level of specific IgE to molecular components of peanuts (ISU – E) in ISAC Multiplex testing. Patients

Table 5. Positive results of specific IgE to molecular components of peanuts in 100 AD patients (100 patients = 100%) in comparison to the occurrence of clinical reaction to peanuts.

Molecular component	Protein family	Number of patients with positive results of specific IgE to molecular components of peanuts		
		(1) in the whole group (100 patients = 100%)	(2) in patients suffering from clinical reaction to peanuts	(3) in patients without clinical reaction to peanuts
Arah8*	PR 10 protein	38 (38%)	26 (26%)	12 (12%)
Arah9*	Lipid transfer protein (nsLTP)	7 (7%)	4 (4%)	3 (3%)
Arah1	Storage protein, 7S globulin	4 (4%)	4 (4%)	0
Arah3	Storage protein, 11S globulin	4 (4%)	4 (4%)	0
Arah2	Storage protein, 2S albumin	3 (3%)	3 (3%)	0
Arah6	Storage protein, 2S albumin	2 (2%)	2 (2%)	0
Total number of patients		41 (41%)	27 (27%)	14 (14%)
		41 (=100%)*	27 (65.8%) %	14 (34.1%)

Notes: (1) Number of patients with positive results of specific IgE to molecular components of peanuts in the whole group of 100 patients (=100%). (2) The positive results of specific IgE to molecular components of peanuts in patients suffering from clinical reaction to peanuts (food allergy to peanuts is confirmed together with positive results to molecular components). (3) The positive results of specific IgE to molecular components of peanuts in patients without clinical reaction to peanuts (=sensitization). *cross-reactive components. The positive results to one or more of molecular components of peanuts were recorded altogether in 41 (41%) patients; from these patients (41 patients = 100%), the clinical reactions to peanuts were recorded in 27 patients (65.8%), no clinical reactions to peanuts were recorded in 14 patients (34.1%).

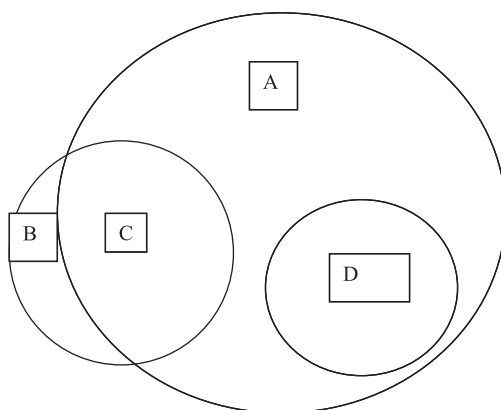


Figure 1. Venn diagram (areas proportional to frequencies) of positive results to molecular components in patients suffering from food allergy to peanuts. A – represents altogether 26 patients with positive results to Ara h 8 (PR 10 protein). B and C represent patients with positivity to storage proteins (Ara h 1, Ara h 2, Ara h 3, Ara h 6) – altogether 8 patients B – 1 patient with the positive results to storage proteins only. C – 7 patients with positivity to both Ara h 8 (PR – 10 protein) and storage protein. D – 4 patients with positivity to both Ara h 9 (nsLTP) and Ara h 8.

with confirmed peanuts allergy (positive anamnestic data and positive results in ISAC Multiplex testing) are shown in extra bold*.

We analysed the data to evaluate, if there is the significant relation between the occurrence of clinical reaction to peanuts and the sensitization to other molecular components in ISAC Multiplex testing. In patients suffering from a clinical reaction to peanuts, the significant relation was confirmed to the sensitization to molecular components Aln g1 (Alder, PR – 10 Protein), Bet v 1 (Birch, PR – 10 Protein), to molecular components of Timothy Phl p 1, 2 (Grass group 1, 2), Phl p 4 (Berberine bridge enzyme), Phl p 5, 6 (Grass group 5, 6), Phl p 7 (Polcalcin) and Mer a 1 (Annual Mercury, profilin) (Table 7).

Discussion

The sense of our study was to show the occurrence of peanuts allergy in AD patients and to analyse the data of ISAC Multiplex examination. The occurrence of peanut allergy in AD is confirmed in 27 patients (27%). In another 22 patients (22%), we recorded the positive anamnestic data about the clinical reaction after peanut ingestion, but these patients had no positive results to molecular components of peanuts in ISAC Multiplex testing; the explanation can be in the fact, that these patients suffer from pollen food syndrome (PFS) and/or other molecular components of peanuts may play the role in these patients. Our results are in agreement with our previous study, where we evaluated the peanuts allergy in 332 AD patients (Čelakovská et al., 2018).

As for the diagnosis of peanut-allergic patients, most people are aware of ingesting peanuts, and thus, the patient history is often quite reliable as for the exposure. In our study, we recorded both early reactions, which appear within minutes up to 2 h after ingesting of peanuts (oral allergy syndrome, abdominal pain, pruritus) and late reactions,

Table 6. The overview of patients suffering from clinical reactions to peanuts.

Patient	Severity	Reaction	Ara h 1	Ara h 2	Ara h 3	Ara h 6	Ara h 8	Ara h 9
1	Mild	Early						
2*	Severe	Early + late					0.5	
3*	Severe	Early + late		17.0			17.0	
4*	Severe	Early + late					1.2	
5*	Mild	Early					8.3	
6	Mild	Early						
7	Moderate	Early + late						
8	Moderate	Early + late						
9	Moderate	Early						
10*	Moderate	Early					1.2	
11*	Mild	Early					1.4	
12*	Moderate	Early + late					8.6	
13*	Moderate	Early + late					25.0	2.3
14*	Severe	Early + late					2.4	0.8
15*	Moderate	Early + late					3.2	
16*	Severe	Early					0.4	
17	Moderate	Early						
18*	Severe	Early	0.4				24.0	
19*	Severe	Early					1.6	
20*	Severe	Early	22,0				19.0	
21*	Severe	Early	7.0	17.0		11.0	14.0	
22*	Moderate	Early + late					11.0	
23*	Moderate	Early + late					16.0	
24	Severe	Early + late						
25*	Mild	Early					6.7	0.8
26*	Moderate	Early					0.4	
27	Moderate	Early + late						
28	Moderate	Early + late						
29	Mild	Early						
30*	Severe	Early + late			0.6		0.5	
31*	Severe	Early + late			1.1		10.0	
32	Moderate	Early						
33	Severe	Early + late						
34*	Mild	Early					0.8	
35	Severe	Early						
36	Severe	Early						
37*	Moderate	Early			0.9		11.0	1.2
38	Moderate	Early + late						
39	Moderate	Early						
40	Moderate	Early + late						
41	Mild	Early						
42	Severe	Early						
43*	Mild	Early					0.6	
44*	Moderate	Early					4.6	
45	Moderate	Early + late						
46*	Severe	Early + late					2.1	
47	Mild	Early						
48	Mild	Early						
49*	Moderate	Early + late	12.0	10.0	17.0	9.0		

Notes: Clinical reaction to peanuts, severity of AD, the results of the ISAC Multiplex testing – the level of specific IgE to molecular components of peanuts (ISU – E) in ISAC Multiplex testing. The positive results to molecular components of peanuts in ISAC Multiplex testing were recorded in 27 patients (55.1%) – shown extra bold*, no positive results were recorded in 22 patients (44.9%). **Early reaction** – reactions within minutes up to two hours after the ingestion of peanuts; oral allergy syndrome, abdominal pain, pruritus were recorded in patients with clinical reaction to peanuts. **Late reaction** – eczematous, late-type reactions, as flare-ups of typical eczematous lesions occurring within hours to two days after ingestion of peanuts; pruritus and worsening of atopic dermatitis were recorded in patients with clinical reaction to peanuts.

eczematous, which appear as flare-ups of typical eczematous lesions occurring within hours to two days after ingestion of peanuts. All of these patients have been carefully examined and they are always monitored. Majority of patients with the clinical reactions

Table 7. The relation between the occurrence of clinical reaction to peanuts and the sensitization to molecular components in ISAC Multiplex testing.

Molecular components – number of patients with positive results in the whole group of 100 patients	Nnumber of patients with positive results to molecular components		<i>p</i> – value
	Clinical reaction to peanuts no 51 patients = 100 %	Clinical reaction to peanuts yes 49 patients = 100 %	
Aln g 1–43 patients	16 (31.4%)	27 (55.1%)	.017*
Bet v 1–57	22 (43.1%)	35 (71.4%)	.004*
Art v 1–29	13 (25.5%)	16 (32.7%)	.43
Alt a 1–29	11 (21.6%)	18 (36.7%)	.095
Asp f 6–21	8 (15.7%)	13 (26.5%)	.183
Ole e 9–17	5 (9.8%)	12 (24.5%)	.051
Ole e 1–14	5 (9.8%)	9 (18.4%)	.217
Phl p 1–61	25 (49.0%)	36 (73.5%)	.012*
Phl p 2–39	14 (27.5%)	25 (51.0%)	.016*
Phl p 4–52	19 (37.3%)	33 (67.3%)	.003*
Phl p 5–43	17 (33.3%)	26 (53.1%)	.046*
Phl p 6–42	15 (29.4%)	27 (55.1%)	.009*
Phl p 11–20	7 (13.7%)	13 (26.5%)	.11
Ole e 7 – 1	1 (2.0%)	0 (0.0%)	.325
Pla a 3–5	1 (2.0%)	4 (8.2%)	.155
Art v 3–5	1 (2.0%)	4 (8.2%)	.155
Bet v 2–9	2 (3.9%)	7 (14.3%)	.07
Phl p 12 – 3	0 (0.0%)	3 (6.1%)	.073
Mer a 1–13	3 (5.9%)	10 (20.4%)	.031*
Phl p 7 – 7	1 (2.0%)	6 (12.2%)	.044*
Bet v 4 – 4	1 (2.0%)	3 (6.1%)	.288

Notes: In patients suffering from clinical reactin to peanuts, the significant relation was confirmed to sensitization to molecular components Aln g1 (Alder, PR – 10 Protein), Bet v 1 (Birch, PR – 10 protein), Phl p1 (Beta expansin, Timothy), Phl p 2 (Grass group 2, Timothy), Phl p 4 (CCD bearing protein, Berberine bridge enzyme, Timothy), Phl p 5 (Grass group 5, Timothy), Phl p 6 (Grass group 6, Timothy), Phl p 7 (Polcalcin, Timothy) and Mer a 1 (Annual Mercury, Profilin). The significant relation is marked extra bold.*

after peanuts ingestion eliminate peanuts from meals. They suffer from exacerbations of AD, but the main triggering factors are aeroallergens and stress.

We may summarize, that patients with the positive results to molecular components of peanuts and with clinical reactions to peanuts are in majority sensitized to PR 10 proteins (Ara h 8); the positivity to species-specific storage proteins (Ara h 1 and / or Ara h 2 and /or Ara h 3 and /or Ara h 6) was recorded only in minority of patients with clinical reaction to peanuts. Only 1 patient had a positive result to species-specific protein Ara h 1, Ara h 2, Ara h 3, Ara h 6, but negative to Ara h 8. The positive results to nsLTP were confirmed in minority of patients with clinical reaction to peanuts also. Sensitization to peanuts (= no clinical reactions to peanut, but the positive results of specific IgE to molecular components Ara h 8 and Ara h 9) were recorded in 14% of patients included in the study; in majority of these patients we recorded the positivity to Bet v 1 and Phl p 1 according to the results in ISAC Multiplex testing.

In the whole group of patients, we analysed the data to evaluate, if there is a significant relation between the occurrence of clinical reaction to peanuts and the positive results of specific IgE to other molecular components of inhalant allergens. In these patients, we confirmed a significantly higher occurrence of positive specific IgE to Aln g1 (Alder, PR – 10 Protein), Bet v 1 (Birch, PR – 10 Protein), to molecular components of Timothy Phl p 1, 2 (Grass group 1, 2) Phl p 4 (Berberine bridge enzyme) Phl p 5, 6 (Grass group 5, 6), Phl p 7 (Polcalcin) and Mer a 1 (Annual Mercury, profilin).

Depending on the geographic and climatic region and vegetation, allergenic plants are characteristic for certain areas and the pollen concentrations of various plant species depending on the phenophase of each single species and most of all on the climatic and meteorological conditions of a certain area. Based on data from the nearest phenological station Běleč nad Orlicí (241 m above sea level, 50°12' N, 15°56' E), which is located in the immediate vicinity of Hradec Králové (East Bohemia region in Czech Republic), the following species are present from important pollen allergens: owing to the sandy substrate, white birch (*Betula pendula*) and wood pine (*Pinus sylvestris*) predominate, as well as common hazel (*Corylus avellana*). There is also abundant sticky alder (*Alnus glutinosa*), willow (*Salix caprea*), hornbeam (*Carpinus betulus*), summer oak (*Quercus robur*), spruce (*Picea excelsa*), deciduous larch (*Larix decidua*), Heartworm (*Tilia cordata*) and grasses such as (*Dactylis glomerata*) and (*Alopecurus pratensis*). Birch and other related trees of the families Betulaceae and Fagaceae (alder, hazel, oak, hornbeam, chestnut, and beech) constitute the birch homologous group. This grouping is primarily based on the extensive IgE cross-reactivity of allergen homologues to the major birch allergen Bet v 1. Furthermore, many plant food allergens contain homologues to Bet v 1, meaning that the majority of patients with birch pollen allergy suffer from secondary PFS (Matricardi et al., 2016).

Irrelevant sensitization to peanuts seems to be especially high in subjects with coexisting pollen allergy, whereas clinically relevant sensitization is much higher in children with AD (Matricardi et al., 2016). In an Australian study, it has been shown that infants with AD were 11 times more likely to develop a peanut allergy than infants without AD (Martin et al., 2015). Screening a non-selected cohort of 13,100 German children of the general population aged 3–17 years demonstrated that almost 11% of the children were sensitized to peanuts (Niggemann et al., 2011). However, this high prevalence of peanut sensitization predominantly results from cross-reactivity to pollen and does not reflect the rate of primary peanut allergy. In a multicenter, multinational study on the prevalence of sensitizations to foods in adults in Europe (EuroPrevall) (Burney et al., 2014), peanut extract sensitization rates showed high variability between 0.5% and 7.2%; the prevalence of IgE sensitization to seed storage proteins of peanut showed lower rates (Ballmer-Weber et al., 2015). Data from the multicenter study on children and adults (EuroPrevall) indicate that allergic subjects possess allergen specific IgE to seed storage proteins, only if the allergy manifested before the age of 14 years (Ballmer-Weber et al., 2015).

In patients with clinically relevant peanut allergy, it has been shown that 76–96% of peanut-allergic children and adolescents in the USA and Central and northern Europe possess specific IgE to Ara h 2 and Ara h 6, compared with only 42% in Spain (Codreanu et al., 2011; Vereda et al., 2011). The sensitization rates for Ara h 1 are between 63% and 80% and for Ara h 3 somewhat lower, whereas the rate for Ara h 7 is only 43% (Codreanu et al., 2011; Vereda et al., 2011). Ara h 9 is considered a secondary food allergen, particularly, in Mediterranean countries. This secondary sensitization/ cross-reaction is probably due to other nsLTPs (e.g. Pru p 3 in peach) (Codreanu et al., 2011; Vereda et al., 2011). The prevalence of sensitization to Ara h 10/11 and Ara h 14/15 is not known and likely affects only a small number of peanut-allergic patients. The fact that oleosins may be underrepresented or absent in aqueous peanut extracts represents a diagnostic

gap hampering the identification of affected patients (Aalberse et al., 2013; Romano et al., 2012; Trendelenburg et al., 2014).

Until now, Ara h 2- and Ara h 6-specific IgE demonstrate the best association with systemic reactions to peanut based on controlled oral challenges (Kukkonen et al., 2015). To predict a positive peanut challenge with 95% probability, Ara h 2-specific IgE had extensively been tested in controlled studies with different designs involving oral food challenges to a variable degree (Klemans et al., 2013a, 2013b). Predictive values from <1 to 42 kUA/l demonstrate the broad range and subsequent limitations to use predefined cutoffs (Ara h 2-specific IgE) for the ultimate prediction of clinically relevant reactions to peanut (Beyer et al., 2015; Klemans et al., 2013a, 2013b; Lange et al., 2014). Measurement of peanut- and Ara h 2-specific IgE plays an essential role in case of suspected primary peanut allergy. Elevated peanut- and Ara h 2-specific IgE and a clearly positive patient history are highly suggestive of a clinically relevant allergy; oral challenge is often not needed (Matricardi et al., 2016). In general, the measurement of Ara h 1- and Ara h 3-specific IgE is often not necessary, as there is high cross-reactivity between these seed storage proteins (Bublin et al., 2013) and mono-sensitizations to Ara h 1 and/or 3 are rare. In doubt, an oral food challenge test can clarify cases of negative or low IgE to Ara h 2. If no specific IgE to any seed storage protein can be identified, a clinically relevant peanut allergy is unlikely, although it cannot be ruled out completely in the presence of sufficient clinical suspicion (diagnostic gap due to, e.g. oleosins (Ara h 10/11, 14/15) and defensins Ara h 12/13) (Petersen et al., 2015; Schwager et al., 2015).

The retrospective analyses by Breuer et al. have shown that the patient's history of food-related eczema does not have a high diagnostic importance (2004). We realise this fact, but the worsening of AD was recorded in these patients repeatedly in their history during 6–8 h after the ingestion of peanuts. The most common symptom described in our study was oral allergy syndrome. This syndrome is defined as the symptoms of IgE-mediated immediate allergy localized in the oral mucosa. Another term used for this syndrome is pollen-food allergy; the patient is sensitized with pollen via the airways and exhibits an allergic reaction to food antigens with a structural similarity to the pollen (class 2 food allergy) (Breiteneder & Ebner, 2000). In the Mittag et al.'s study, the authors sought the occurrence of peanut allergy in patients allergic to birch pollen. The patients with peanut and birch pollen allergy and a positive double-blind, placebo-controlled food challenge result to peanut were investigated for IgE reactivity to birch pollen and purified peanut allergens and cross-reactivity between birch and peanut. During the double-blind placebo-controlled food challenge with peanuts, all patients experienced symptoms in the oral cavity, progressing to more severe symptoms in 40% of patients. They concluded in this study that peanut allergy might be mediated in a subgroup of patients by means of a cross-reaction of Bet v 1 with the homologous peanut allergen Ara h 8 (Mittag et al., 2004).

The latest findings showed that early sustained consumption of peanut products was associated with a substantial and significant decrease in the development of peanut allergy in high-risk infants. Conversely, peanut avoidance was associated with a greater frequency of clinical peanut allergy than peanut consumption was. It raises questions about the usefulness of deliberate avoidance of peanuts as a strategy to prevent allergy (Du Toit et al., 2015).

Conclusion

The peanuts allergy was confirmed in 27% AD patients. In majority of these patients, we confirmed positive results of specific IgE to PR 10 proteins Ara h 8 and in minority to species-specific storage proteins (Ara h 1 and / or Ara h 2 and /or Ara h 3 and /or Ara h 6) and to non-specific lipid transfer protein Ara h 9. The clinical symptoms of peanut allergy were recorded as a mild oral allergy syndrome, abdominal pain and pruritus with some new eczematic lesions in patients with positive results to cross-reactive molecular components; oral allergy syndrome and pruritus were recorded in patients with positive results to storage proteins. No clinical reaction to peanuts, but positive results of specific IgE to cross-reactive components of peanuts were recorded in another 14% of patients. We confirmed a significantly higher occurrence of positive specific IgE to Aln g1, Bet v 1 (PR – 10 Protein), to molecular components of Timothy Phl p 1, 2 (Grass group 1, 2), Phl p 4 (Berberine bridge enzyme), Phl p 5, 6 (Grass group 5, 6), Phl p 7 (Polcalcin) and to Mer a 1 (Annual Mercury, profilin) in patients suffering from clinical symptoms after peanuts ingestion.

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