Molecular sIgE profiles in infants and young children with peanut sensitization and eczema

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Key words
Peanut – sensitization – eczema – Ara h 1 – Ara h 2 – component-based diagnosis

Abstract

Background: Many children develop a sensitization to peanut in early infancy, even before peanut is introduced in their diet. Sensitization is particularly common in young children with eczema. There have been scant data available to date on the sensitization pattern for specific peanut allergens in this patient group. The aim of this study was to investigate the allergen profile of infants and young children with peanut sensitization and eczema.

Methods: Sera from 53 children aged ≤ 20 months with eczema and sensitization to peanut but who had not yet consumed products containing peanuts were included in the analysis. Sera were analyzed using microarray immunoassay (ImmunoCAP ISAC).

Results: In total, 63 % of peanut-sensitized children showed specific immunoglobulin E (sIgE) against at least one peanut allergen on the microarray. Specific IgE to the 7S globulin Ara h 1 was detected in 40 % of the children, to the 2S albumin Ara h 2 in 30 % and to the 11S globulin Ara h 3 in 23 %. Only one child had sIgE to Arah 8, the homologoue of Bet-v-1. Data on clinical relevance were available for 24 of 53 children: 14 of 24 patients had objective allergic reactions to peanut, while 10 children were peanut-tolerant. The seed storage protein Ara h 2 was not detected on microarray in 43 % (6 of 14) of children with peanut allergy. Two of these six children were mono-sensitized to Ara h 1 and two to Ara h 3, while in three children none of these seed storage proteins was detected.

Discussion: It could be shown that infants and young children with eczema and sensitization to peanut recognize predominantly seed storage proteins from peanut, even before the introduction of peanut into their diet. Sensitization to pollen-related food allergens seems to be rare at this age. At this age not only Ara h 2, but also Ara h 1 seems to be related to clinical relevance.

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Introduction

Peanut allergy is one of the most frequent food allergies in childhood [1]. In general, it endures throughout life and even the smallest quantities of peanut can trigger severe systemic reactions in patients [2]. The prevalence of peanut allergy in children appears to have increased in recent years [3, 4, 5]. The majority of affected children exhibit an allergic reaction after the first oral contact with peanut, and sensitization to peanut can be detected as early on as in infancy [6, 7]. Thus, in addition to the direct consumption of peanut in childhood, other possible sensitization routes are under discussion.

Several peanut allergens have been identified to date, primarily peanut seed storage proteins [8]. A number of studies have shown that, depending on the age and geographic origin of patients, as well as the severity of symptoms, various peanut allergens

Abbreviations

AD	atopic dermatitis
DBPCFC	double-blind placebo-controlled food challenge
FEIA	fluorescence enzyme immunoassay
ISU	standardized units
ISAC	immuno solid-phase allergen chip
ns	not specified
kU/l	kilounits/liter
LTP	lipid transfer protein
OFC	open food challenge
sIgE	specific immunoglobulin E

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play a role [9, 10, 11, 12]. However, there are few data on the sensitization pattern of specific peanut allergens in sensitized infants and young children whose diet does do not yet contain peanut. Therefore, the aim of this study was to investigate by component-based diagnosis, an allergen profile of peanut-sensitized infants and young children with eczema who had not yet consumed products containing peanuts, as well as to assess any its clinical relevance.

Methods

Patients

Sera taken from peanut-sensitized infants and young children during allergy diagnosis at the pneumology/immunology unit of the pediatric clinic at the Charité University Hospital in Berlin between 2007 and 2011 were used for analysis in this study. Patient history, skin status and nutritional status of the child at the time of blood collection were obtained from medical records. Inclusion criteria comprised the following:

- Specific immunoglobulin E (sIgE) to peanut ≥ 0.35 kU/l
- Age: ≤ 20 months
- Eczema [suspected atopic dermatitis (AD)]
- No known introduction of peanut or peanut-containing products in the child's diet

Furthermore, medical records are reviewed for standardized in-patient oral challenges with peanut at a later point in time or whether an objective allergic reaction after an accidental peanut consumption had been reported during an out-patient consultation. Oral challenge test results, reaction dose and objective clinical symptoms were obtained from medical records.

The study was approved by the ethics committee of the Charité Universitätsmedizin, Berlin.

Laboratory investigations

The detection of sIgE to food allergen extracts was performed using the ImmunoCAP fluorescence enzyme immunoassay (FEIA) system (Phadia, Uppsala, Sweden). Next to sIgE to peanut, sIgE to hen's egg, cow's milk, wheat, soy, fish and hazelnut were measured. The detection of sIgE to individual peanut components, other foods and aero-allergens was performed using microarray immunoassay (ImmunoCAP ISAC, Phadia, Uppsala, Sweden) and performed according to the manufacturer's instructions. Results were expressed as in ISAC standardized units (ISU)/l and the cut-off level specified by the manufacturer was 0.3 ISU/l.

Results

Patient characteristics

In total, sera from 53 patients were included. The median age of the children at the time of blood collection was 9 months. Details are provided in **Tab. 1**.

At the time of blood collection, 38 children (72 %) were receiving their first solid foods, primarily fruit and vegetable purees, 12 infants (23 %) were still fully breastfed and three (6 %) received exclusively infant formula. Peanut or peanut-containing products had not been knowingly introduced into the child's diet in any child.

The majority of children (87 %) showed a sensitization to at least one other foods in addition to peanut, as detailed in **Table 1**.

Pattern of sensitization

Specific IgE to peanut seed storage proteins nAra h 1, nAra h 2 and nAra h 3, as well as to nAra 8, the Bet-v-1 homologoue in peanut, were measured using microarray.

Specific IgE to at least one of the peanut allergens were detected on the microarray in 33 (62 %) of the 53 sera from peanut-sensitized children investigated (detected using CAP-FEIA) (**Table 2**). All these 33 children were sensitized to at least one peanut seed storage protein. Specific IgE to the 7S globulin Ara h 1 was detected in 40 %, to the 2S albumin Ara h 2 in 30 %, whilst 23 % showed sensitization to the 11S globulin Ara h 3. Only one child demonstrated sIgE to the Bet-v-1 homologoue Ara h 8 and concurrent reactivity to Bet v 1 without having clinical symptoms during pollen season. Aged 20 months, this particular child was the oldest of all patients.

Over 50 % of the children in whom sIgE to peanut were detected on microarray demonstrated a monosensitization to peanut allergen components (**Tab. 2**). Ara h 1, followed by Ara h 2 and Ara h 3 were most commonly detected. These children had a median age of 11.5 (range, 5–17) months. 15 out of 33 children showed sIgE reactivity to at least two peanut allergens (primarily Ara h 1 and Ara h 2) and were

Table 1

Characteristics of the patient collective (n = 53)

Patient characteristics	
Age in months, median (range)	9 (3–20)
Males (%)	34 (64)
sIgE to peanut in kU/l, median (range)	4,01 (0,58–75)
Skin status	
Atopic dermatitis (%)	50 (94)
Suspected atopic dermatitis (%)	3 (6)
Sensitization to other foods (%)	**46 (87)**
Hen's egg, number (%)	42 (79)
Hazelnut, number (%)	37 (70)
Cow's milk, number (%)	34 (64)
Wheat, number (%)	25 (47)
Soy, number (%)	22 (42)
Fish , number (%)	3 (6)

kU/l, kilounits/liter; sIgE, specific immunoglobulin E

Table 2

Sensitization pattern in 53 peanut-sensitized children measured using ImmunoCAP ISAC (Phadia, Uppsala, Sweden)

Allergen components	Sensitization pattern								Number of sensitized patients
	Poly-sensitization					Mono-sensitization			
nAra h 1	X		X	X		X			21 (40 %)
nAra h 2	X	X	X		X		X		16 (30 %)
nAra h 3	X	X		X	X			X	12 (23 %)
nAra h 8		X							1 (2 %)
Number of sensitized patients	1 (2 %)	1 (2 %)	8 (15 %)	4 (8 %)	1 (2 %)	8 (15 %)	5 (9 %)	5 (9 %)	
Number of sensitized patients	2 (4 %)		13 (25 %)			18 (34 %)			33 (63 %)*

[a]*Number of all patients sensitized to at least one allergen component*

Table 3

Sensitization patterns in 53 peanut-sensitized children depending on infant nutrition to date

	Infant formula (n = 3)	Fully breastfed (n = 12)	First solid foods (n = 38)
sIgE to Ara h 1	2 (77 %)	5 (42 %)	14 (37 %)
sIgE to Ara h 2	1 (33 %)	2 (17 %)	14 (37 %)
sIgE to Ara h 3	0	1 (8 %)	10 (26 %)
sIgE to Ara h 8	0	0	1 (3 %)
sIgE to no allergen components	1 (33 %)	5 (42 %)	14 (37 %)
Polysensitization	1 (33 %)	1 (8 %)	13 (34 %)

sIgE, specific immunoglobulin E

therefore poly-sensitized. These children had a median age of 12 (range, 5–17) months. Only two patients (median age, 18 months) showed a sensitization to three peanut allergens.

Children who had not yet received solid foods at the time of blood collection primarily demonstrated a mono-sensitization to Ara h 1 (**Tab. 3**). In cases where solid foods had already been introduced, children showed increasingly sIgE to various allergen components, most commonly Ara h 2. Of the 53 children with peanut sensitization (detected using CAP-FEIA), 20 children (38 %) showed no reactivity to the four peanut allergen components on the microarray. Five of these 20 children had sIgE to peanut <1 kU/l measured using ImmunoCap FEIA, and in six of these 20 children sIgE to at least one peanut allergen component on the microarray was detected at a level just below the manufacturer's specified cut-off level (values between 0.2 and 0.3 ISU/l).

Clinical relevance

Data on the clinical relevance of peanut sensitization were available for 24 of the 53 patients (45 %) (**Table 4**). The median age of children at the time of oral food challenges was 17 months. In total 13 children (54 %) had objective clinical symptoms during oral food challenge, whereas 10 children (42 %) produced no response. Since patient 40 underwent a food challenge at an external clinic, no further details were available. Patient 12 had a clear allergic reaction after the consumption of peanut puffs, therefore no food challenge was performed in this child. More than one organ system was affected upon allergic reaction in eight children (57 %), in five of these children (29 %) the respiratory tract was involved.

Approximately only half of the 14 children (57 %) with clinically relevant peanut sensitization and none of the eight peanut-tolerant children showed sIgE reactivity to the seed storage protein Ara h 2 on the microarray. Sensitization to the seed storage protein Ara h 1 was found in eight children with peanut allergy (57 %), but also in three children with oral tolerance to peanut (30 %). 50 % of children with peanut allergy had sIgE to at least two seed storage proteins. Three children with peanut allergy were monosensitized, whereby one child was sensitized to Ara h 1, Ara h 2 and Ara h 3 repectively (**Tab. 4**) Sera from 50 % of the children with oral tolerance to peanut, as well as 21 % of children with peanut allergy, tested negative for sIgE to the relevant peanut allergen components on the microarray.

Table 4

Data on clinical relevance and comparison of specific IgE to peanut allergen components

Patient n = 24	Total IgE (kU/l)	Specific IgE to peanut (kU/l), ImmunoCAP	Peanut challenge	Age (months)	Reaction dose (gram)	Objective symptoms	sIgE to peanut allergen components, microarray
Clinically relevant peanut allergy							
3	27,5	44,4	DBPCFC	40	1,2	Urticaria, vomiting, breathing difficulties	Ara h 1, Ara h 2
4	4,5	3,65	DBPCFC	21	12	Vomiting	Ara h 1, Ara h 2
6	25,5	1,82	DBPCFC	15	0,4	Urticaria	Ara h 1, Ara h 2
7	111	0,87	DBPCFC	21	12	Urticaria	–
21		1,34	DBPCFC	24	4	Urticaria, eyelid swelling, rhinoconjunctivitis	Ara h 2
29	13,5	2,53	DBPCFC	16	4	Urticaria	
33	93	11,7	OFC	27	12	Urticaria, conjunctivitis	
35	k. A.	75	DBPCFC	16	1,2	Urticaria	
36	68,5	24,6	DBPCFC	15	1,2	Rhinoconjunctivitis, sneezing, coughing	
37	> 100	12,6	DBPCFC	34	0,12	Urticaria, coughing, wheezing	
40	69,2	1,56	k. A.	k. A.	k. A.	ns	–
44	k. A.	29,9	DBPCFC	22	1,2	Urticaria, vomiting	Ara h 2, Ara h 3, Ara h 8
49	k. A	9,33	DBPCFC	11	4	Urticaria, fatigue	Ara h 1
12	9,93	1,87	Accidental exposure	15	k. A.	Urticaria, angioedema, wheezing	Ara h 3
Oral tolerance to peanut							
9	362	4,39	OFC	17	–	–	–
15	300	19,4	DBPCFC	12	–	–	Ara h 1
17	6848	50,9	OFC	12	–	–	Ara h 1, Ara h 3
20	k. A.	2,69	OFC	17	–	–	–
27	>100	46,7	DBPCFC	11	–	–	Ara h 3
30	244	1,56	DBPCFC	17	–	–	-
34	67,2	3,52	DBPCFC	19	–	–	Ara h 3
41	70,8	3,44	DBPCFC	10	–	–	–
45	k. A.	1,6	DBPCFC	17	–	–	–
50	46,5	2	DBPCFC	11	–	–	Ara h 1

DBPCFC, double-blind placebo-controlled food challenge; IgE, immunoglobulin E; ns, not specified; kU/l, kilounits/liter; OFC, open food challenge

Discussion

The present study demonstrates that infants and young children with eczema show primarily a sensitization to the peanut seed storage proteins. These seed storage proteins belong to the major peanut allergens [8]. Compared with pollen-related peanut allergens, seed storage proteins are resistant to heat and digestive enzymes and are associated with particularly severe allergic reactions [13, 14, 15]. Specific IgE to the 7S globulin Ara h 1 was most commonly detected in the children (40 %), and many children demonstrated mono-sensitization to peanut allergen components (34 %). A broader sensitization pattern emerged upon introduction of solid foods and with increasing age.

To date there are no further data on the sensitization pattern in patients in this age group. School-age patients with manifest peanut allergy predominantly show sIgE to Ara h 2 and Ara h 6 [16, 17, 18, 19]. The Bet-v-1 homologous peanut allergen Ara h 8 is one of the most frequently detected allergens in adults and children with pollen-related peanut allergy [11]. Also in Germany, the high prevalence of peanut sensitization in children aged between three and 17 years appears to be due to cross-reactivity to grasses and birch pollen [20]. On the other hand, sensitization to these aeroallergens is rare in infants and young children.

It remains unclear which alternative route for sensitization underlies early sensitization to peanut. Primary sensitization as a result of exposure in the uterus and via breast milk could be one possibility [21, 22, 23]. Cross-sensitization between homologous peanut proteins and other legumes or tree nuts is a further possibility. [24, 25]. In total, 70 % of our patients showed a sensitization to hazelnut and 42 % to soy, even though these foods are usually introduced in the child's diet at a later time. Another possible route for peanut sensitization might be via skin exposure. This hypothesis, which

is currently under discussion, appears to play a role particularly in children with AD due to the impaired skin barrier function [26, 27, 28], and we recently showed that peanut proteins can be detected in German households, particularly in bed dust [29].

No peanut allergens could be identified on microarray in approximately one third of children with peanut sensitization (sIgE to peanut ≥ 0.35 kU/l measured using ImmunoCap). The same was observed in other studies investigating patients with peanut or hazelnut sensitization [12, 30, 31]. One possible explanation for this could lie in the low sensitivity of the microarray assay in terms of detecting lower sIgE concentrations in serum samples compared with the ImmunoCAP assay [31, 32]. On the other hand, the range of the four allergens spotted on the microarray (Ara h 1, Ara h 2, Ara h 3 and Ara h 8) does not cover the complete allergen profile of the peanut. It is possible that sIgE to other peanut allergens [the S2 albumins Ara h 6 and Ara h 7, the lipid transfer protein (LTP) Ara h 9, the profilin Ara h 5 or the oleosin/seed storage proteins) could have been detected. However, sensitization to peanut LTP is predominantly relevant in patients in the Mediterranean region [33]. The S2 albumin Ara h 6 appears to play a crucial role in children with peanut allergy [16, 19]. The allergen spectrum of the ISAC microarray has now been expanded to include Ara h 6 and Ara h 9.

Peanut seed storage proteins are associated with severe allergic reactions. Ara h 2 in particular appears to correlate best with the clinical relevance of peanut allergy [9]. Due to the young age of our patient collective, data on clinical relevance were available for approximately only 50 % of patients. In contrast to previous studies, sIgE to the seed storage protein Ara h 2 was not detected in 43 % of children with clinically relevant peanut allergy. Nevertheless, the sensitization pattern in children with oral tolerance to peanut differed notably from that of patients with peanut allergy: far fewer peanut allergens were detected (primarily mono-sensitization) and Ara h 2 was not detected in any child with oral tolerance. It has already been shown that the detection of various IgE epitopes is associated with clinical relevance [34, 35].

Conclusion

It has been shown that peanut-sensitized infants and young children with eczema primarily show sIgE to peanut seed storage proteins; sIgE to Ara h 1 was most frequently detected, followed by Ara h 2 and Ara h 3. In contrast, sensitization to pollen-related peanut allergens (Ara h 8) does not appear to play a role in this patient group. Compared with pollen-related allergen components, peanut seed storage proteins are resistant to heat and digestive enzymes and appear to be closely associated with severe systemic reactions. Interestingly, it would appear that not only Ara h 2, but also Ara h 1 in particular are clinically relevant in this age group.

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Conflict of interest

The authors Valérie Trendelenburg, Alexander Rohrbach, Gabriele Schulz and Veronika Schwarz state that there are no conflicts of interest. Kirsten Beyer has received consulting or speaker's fees from Danone, MedaPharma, ALK, Novartis, Unilever, Allergopharma, MedUpdate, HAL, Hipp, Mead Johnson, ECARF Institute, Infectopharm and funding from the European Union, German Research Foundation, ThermoFisher, Danone, DST, FAAN and the Foundation for the Treatment of peanut allergy.

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