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

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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 homologue 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
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 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 who had not yet consumed products containing peanuts, as well as to assess any 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 IgE to food allergen extracts was performed using the ImmunoCAP fluorescence enzyme immunoassay (FEIA) system (Phadia, Uppsala, Sweden). Next to IgE to peanut, IgE to hen’s egg, cow’s milk, wheat, soy, fish and hazelnut were measured. The detection of IgE 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 Table 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 homologue 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 homologue 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 mono-sensitization 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 IgE reactivity to at least two peanut allergens (primarily Ara h 1 and Ara h 2) and were

| Characteristics of the patient collective (n = 53) | Table 1 |
|--------------------------------------------------|---------|
| **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
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 (Table 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 Immuno Cap FEIA, and in six of these 20 children sIgE to at least one peanut allergen component 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 respectively (Table 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.
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

| 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 |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 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 | 1,2 | 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 | – |
| 29 | 13,5 | 2,53 | DBPCFC | 16 | 4 | Urticaria | – |
| 33 | 93 | 11,7 | OFC | 27 | 12 | Urticaria, conjunctivitis | – |
| 35 | k. A. | / | 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 | 1,8/ | Accidental exposure | 15 | k. A. | Urticaria, angioedema, wheezing | Ara h 3 |

**Oral tolerance to peanut**

| Patient | 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 |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 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.
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Ara h 6 and Ara h 9. The allergen spectrum of the ISAC microarray has now been expanded to include pollen-related allergen components, peanut seed storage proteins and ara h 3. In contrast, sensitization to pollen-related allergens (Ara h 2, but also Ara h 1 in particular are clinically relevant in this age group.

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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