Infants and toddlers with sensitization to peanut are often co-sensitized to tree nuts

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Abstract

Background Due to changes in dietary habits tree nuts (TN) are consumed in many households and TN allergy appears to be increasing. One risk factor seems to be allergies to other food such as peanuts. The aim of our study was to investigate, how often peanut-sensitized infants and toddlers are co-sensitized to cashew, hazelnut and walnut and to determine the likelihood of its clinical relevance by their 2S albumin-specific (s)IgE. **Methods** Sera of 101 peanut-sensitized children, 5 to 24 months of age (median 16 months) were analyzed regarding sIgE to hazelnut, walnut and cashew and to their 2S-albumins Cor a 14, Jug r 1 and Ana o 3 as well as to Ara h 1 and 2, by using the NOVEOS ^{TM} immunoanalyzer system. **Results** 96% of the peanut-sensitized children were co-sensitized to at least one TN with 94.1% to hazelnut, 87.1% to walnut and 84.2% to cashew. More than half (58.4%) of the children were sensitized to at least one 2S albumin with similar rates for infants and toddlers, 26.7% to all three. Moreover, sensitization rates were similar in peanut allergic and tolerant children. Estimating the likelihood of clinical relevance, 15.8% of all peanut-sensitized children had an at least 90% probability to be hazelnut and/or cashew allergic. **Conclusion** TN sensitization seems to be common among peanut-sensitized infants and toddlers. Many had a high likelihood to be TN allergic. Therefore, it should be considered to determine TN-sIgE in peanut-sensitized children if TN are not consumed so far.

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Background

Due to changes in dietary habits tree nuts (TN) are consumed in many households and TN allergy appears to be increasing. One risk factor seems to be allergies to other food such as peanuts. The aim of our study was to investigate, how often peanut-sensitized infants and toddlers are co-sensitized to cashew, hazelnut and walnut and to determine the likelihood of its clinical relevance by their 2S albumin-specific (s)IgE.

Methods

Sera of 101 peanut-sensitized children, 5 to 24 months of age (median 16 months) were analyzed regarding sIgE to hazelnut, walnut and cashew and to their 2S-albumins Cor a 14, Jug r 1 and Ana o 3 as well as to Ara h 1 and 2, by using the NOVEOS^{TM} immunoanalyzer system.

Results

96% of the peanut-sensitized children were co-sensitized to at least one TN with 94.1% to hazelnut, 87.1% to walnut and 84.2% to cashew. More than half (58.4%) of the children were sensitized to at least one 2S albumin with similar rates for infants and toddlers, 26.7% to all three. Moreover, sensitization rates were similar in peanut allergic and tolerant children. Estimating the likelihood of clinical relevance, 15.8% of all peanut-sensitized children had an at least 90% probability to be hazelnut and/or cashew allergic.

Conclusion

TN sensitization seems to be common among peanut-sensitized infants and toddlers. Many had a high likelihood to be TN allergic. Therefore, it should be considered to determine TN-sIgE in peanut-sensitized children if TN are not consumed so far.

Keywords Tree nut sensitization, infants, toddlers, eczema, peanut sensitization, food allergy

Abbreviations

DBPCFC Double-blind Placebo Controlled Food Challenge

HEAP Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants

IgE Immunoglobulin E

OFC Oral Food Challenge

Background

IgE-mediated food allergy affects up to 8% of infants and children in industrialized countries and often starts early in infancy (1). Especially infants with eczema are at high risk for developing food allergies and it is the current understanding that sensitization occurs via the cutaneous route due to an impaired skin barrier function (2, 3). Accordingly, a high peanut consumption in the household has been shown to be a possible risk factor for developing peanut allergy in infancy (4). Moreover, we demonstrated that food proteins, such as peanut and hen's egg can be found not only in the eating area, but also in bed dust and increase with consumption, further supporting the hypothesis of cutaneous sensitization (5, 6). Therefore, German S3-guidelines on allergy prevention recommend that peanut allergy should first be ruled out in infants with moderate to severe atopic dermatitis, before introducing peanut into the infant´s diet for preventive purposes (7). What about other food allergens such as tree nuts? It has been shown that infants with eczema are at risk for multiple food sensitizations (8). During the last decades, nutrition across Western countries has changed substantially as for example vegan and plant-based diets have become a growing trend (9). Tree nuts, such as cashews, hazelnuts and walnuts are a nutritional mainstay of plant-based diets (10). Moreover, plant-based alternatives for milk and milk-products often contain tree nuts and such products are gaining in popularity among consumers (11). These changes in dietary habits may lead to a wider spread of tree nut allergens in households, increasing the risk for cutaneous exposure in infants. Moreover, tree nuts are very potent allergens, as evidenced by having caused up to 21% of all fatal anaphylaxis cases among children between 1992 and 2018 in the United Kingdom (12). Among tree nuts, hazelnut, cashew and walnut are the most common triggers inducing anaphylaxis in children in Europe (13). Regarding the clinical reactivity, sensitization to 2S albumins of peanut and tree nuts have been shown to be associated with severe allergic reactions (14). Ana o 3, the 2S albumin of cashew, discriminates between allergic and tolerant children better than cashew-specific IgE and probability curves for Ana o 3-specific IgE have been calculated, a 95% probability could be estimated at 2.0 kU/l (15). Similarly, the 2S albumin of hazelnut, Cor a 14, estimates the probability for a positive clinical reaction, with a 90% probability for hazelnut allergy at 47.8 kU/l (16). Concerning walnut, the 2S albumin Jug r 1 has been shown most accurate for estimating the risk for clinical relevant walnut allergy (17). There are hints, that individuals with peanut allergy have a higher likelihood of being allergic to tree nuts compared to the general population (18, 19). Therefore, the question comes up what to recommend in a peanut-allergic child: To eat, to screen, or to avoid as it has been recently discussed in this journal (20)? To date, there are scarce data on the sensitization patterns to tree nuts in very young infants and children with peanut sensitization. Therefore, the aim of this study was to investigate, how often peanut-sensitized infants and toddlers are sensitized to cashew, hazelnut and walnut and their seed storage proteins, which might be associated with a high risk for clinical reactivity. We hope to add some important information to this discussion.

Methods

Study design and population

The study cohort consists of infants and toddlers who were referred to our clinic with suspected peanut allergy. Some patients underwent an oral food challenge (OFC) for routine diagnostics between 2007 and 2020. Patient history, atopic comorbidities, OFC test results and objective clinical symptoms were obtained from the ongoing EFA (Eczema and Food Allergy) registry. Blood was collected from all patients in the frame of routine diagnostics. Inclusion criteria for the analysis of co-sensitization was age [?] 2 years and specific IgE (sIgE) to peanut [?] 0.1 kU/l. Parents provided written informed consent. The study was approved by the ethics committee of the Charite Universitatsmedizin, Berlin.

Study procedures: oral food challenges

OFCs were performed either in an open (6.2%) or double-blind, placebo-controlled (93.8%) manner (DBPCFC) by trained staff following the PRACTALL criteria (21). Allergens were blinded in a food matrix (e.g. apple sauce) and fed in seven increasing doses (amounts equal to 3 mg, 10 mg, 30 mg, 100 mg, 300

mg, 1 g and 3 g of peanut protein) over 30-minutes intervals under clinical supervision. A positive challenge outcome was defined by objective clinical reactions (e.g. urticaria/angioedema, vomiting, wheezing/stridor, rhinitis/conjunctivitis and/or a decrease in blood pressure). After completion of all 7 titration steps without the occurrence of any kind of objective allergic reaction, patients received a subsequent cumulative dose of 4.5 g of peanut on the following day, proving clinical tolerance in case of no objective symptoms.

Laboratory investigations

The detection of sIgE to peanut, hazelnut, walnut and cashew and to their respective 2S albumins Ara h 2, Cor a 14, Jug r 1, Ana o 3 as well as to the 7S vicilin-like globulin Ara h 1, was performed by using the NOVEOS^{TM} immunoanalyzer (Garden Grove, California, USA). Sensitization was defined as specific IgE [?] 0.1 kU/l.

Statistical Analysis

All statistical analyses were performed using R version 4.2.0 (R Core Team 2022). Categorical data are shown as absolute and relative frequencies; continuous data are expressed as median and range. To test if there were significant differences in sensitization patterns between patients that were allergic or tolerant to peanut, chi-squared tests were used (key basic assumptions of the test were not fulfilled regarding sensitization to hazelnut and walnut). Wilcoxon tests were performed to analyze if there were significant differences in sIgE levels between peanut-allergic and peanut-tolerant patients. P-Values were adjusted using the Bonferroni adjustment. A p-value of < 0.05 was considered to indicate a significant difference. In order to determine the probability for a positive hazelnut food challenge by Cor a 14-sIgE and for a positive cashew food challenge by Ana o 3-sIgE for each patient, probability curves by Beyer et al. and Lange et al. were utilized (15, 16). Since there is no probability curve available for walnut, the individual risk for a positive OFC with walnut could not be estimated.

Results

Patient characteristics

In total, sera from 101 peanut-sensitized patients (peanut-sIgE [?] 0.1 kU/l) were analyzed. The median age of the patients at the time of blood drawing was 16 months (range: 5-24 months). 26 patients (25.7%) were [?] 12 months of age. Nearly all patients (98%) suffered from eczema. A high proportion was sensitized to Ara h 1 (83.2%) and Ara h 2 (70.3%). Of 81 (80.2%) patients undergoing an OFC with peanut, 33 (40.7%) showed objective symptoms of an immediate type allergic reaction and were therefore proven to be allergic. Details on patient characteristics are provided in table 1.

Pattern of sensitization

Specific IgE [?] 0.1 kU/l to at least one tree nut was detected in 96.0% (n=97) of the peanut-sensitized infants and toddlers. Most children were sensitized to hazelnut (n=95; 94.1%; sIgE median 1.21 kU/l; range, 0.11-101 kU/l), followed by walnut (n=88; 87.1%; sIgE median 0.87 kU/l; range, 0.10-101 kU/l) and cashew (n=85; 84.2%; sIgE median 0.97 kU/l; range, 0.10-101 kU/l) (Figure 1). More than half (59/101; 58.4%) were sensitized to at least one 2S albumin with 42 patients (41.6%) were sensitized to Cor a 14 (median, 0.39 kU/l; range, 0.10-101 kU/l) and Jug r 1 (median, 0.41 kU/l; range, 0.10-101 kU/l), while 40 patients (39.6%) were sensitized to Ana o 3 (median, 0.46 kU/l; range, 0.10-101 kU/l) (Figure 1). We detected sIgE [?] 0.1 kU/l to all three tree nuts in 80.2% (n=81) and to all of the corresponding 2S albumins in 26.7% (n=27) of the children. Of the participants aged [?]12 months 88.5% (n=23) were sensitized to at least one tree nut, 46.2% (n=12) to at least one 2S albumin and 34.6% (n=9) to all three 2S albumins (data are not shown).

Sensitization pattern in patients with peanut allergy or tolerance

In 81 (80.2%) of the 101 peanut-sensitized children OFCs have been performed in order to determine their clinical reactivity. Their characteristics are shown in Table S1. As expected, peanut-allergic patients had significantly higher levels of peanut- and Ara h 2-sIgE (Table S1). We observed no significant difference

between peanut-allergic (n=33) and peanut-tolerant (n=48) children regarding their sensitization to tree nuts (Figure 2, Table S1).

Clinical reactivity to tree nuts according to probability curves

Clinical reactivity to hazelnut and cashew was estimated according to probability curves for Cor a 14- and Ana o 3-sIgE, respectively, as published in the literature (15, 16). As shown in Figure 3, five of the 101 peanut-sensitized infants and toddlers (5.0%) would have reacted with 90% probability to hazelnut and 14 (13.9%) to cashew. In total, 15.8% (n=16) of all peanut-sensitized children had an at least 90% predicted probability to be allergic to hazelnut and/or cashew. Of these, 18.8% (n=3) were known to be allergic to peanut, 75.0% (n=12) were clinical tolerant and for one the clinical relevance was not known (data not shown). Moreover, 13.9% (n=14) of the 101 infants and toddlers would have an $>$ 50% probability to be hazelnut and 23.8% (n=24) to be cashew allergic (Figure 3).

Discussion

We were able to show that peanut-sensitized infants and toddlers are often co-sensitized to tree nuts and their 2S albumins. Regarding co-existing tree nut allergy among peanut-allergic children several observational studies have been conducted. In the population-based Australian HealthNuts study cohort of 5,276 participants, 27% (95% CI: 16.1%, 39.7%) of children with peanut allergy at the age of one year had tree nut allergy at 6 years of age (19). The authors of the SchoolNuts study, a cohort of 9816 school children aged 10–14 years, reported that tree nut allergy co-existed in 41.5% of peanut-allergic children (18). Moreover, our data indicates that even very young peanut-sensitized children below 2 years of age may frequently be sensitized to tree nuts and their seed storage proteins. Calculating the likelihood of clinical relevance, we could show that many of these infants and toddlers would present allergic symptoms.

Almost all of the children included in our analysis (98%) suffered from eczema, which is known to be a major risk factor for sensitization and the development of food allergy (3). In the HEAP study, we observed that 65% of infants with eczema were sensitized to hen's egg at the early age of 4 to 6 months compared to only 9% of sensitized infants without eczema (22). It seems that low-dose concentrations of food allergens in the environment, for example in house dust, can penetrate a disrupted skin barrier, ultimately leading to Th2-response and IgE production (2). In this context, results from the PreventADALL birth cohort showed that a high transepidermal water loss, a marker for impaired skin barrier function, is able to predict sensitization at 6 months of age with 61.7% sensitivity and 78.1% specificity (8). Moreover, we have observed that food allergens like peanut and hen's egg proteins can be detected in house dust and that they even can be found in the infant's bed after consumption in the eating area (5, 6). These findings reflect the dual-allergen-hypothesis proposing that an early cutaneous exposure to allergens in children with eczema occurring before the first oral intake enhances the risk for sensitization but also allergy to these foods (2). Thus, Martin et al. demonstrated that infants with eczema had an 11 times higher risk to develop peanut allergy and were 6 times more likely to have hen's egg allergy by the age of 12 months compared to infants without eczema (23). Finally, a recently published meta-analysis concluded that the overall prevalence of challenge-proven food allergy among patients with eczema is 40%, whereby the association between eczema and food allergy was stronger in children (3). In our study, peanut-allergic as well as peanut-tolerant patients were at equal risk to be sensitized to tree nuts and its seed storage proteins, highlighting that eczema itself is a major risk factor for the sensitization to food allergens.

Even though the household consumption of tree nuts of the families taking part in our study is unknown, tree nuts in general are becoming more present in many households and are highly potent allergens (11, 13). In principal, experts tending to argue against pre-emptive testing of additional allergens (24). Nevertheless, our analysis has revealed that peanut-sensitized infants and young children were already sensitized to the 2S albumins of tree nuts to a high extent. Being sensitized to 2S albumins is associated with allergic reactions (14). More than 15% of our peanut-sensitized infants and toddlers were very likely to be allergic to hazelnut and/or cashew and 32.7% had a more than 50% probability, according to probability curves outlined in literature (15, 16). Given these findings, it should be considered to test peanut-sensitized infants

and toddlers also for sensitization to tree nuts if tree nuts are not already part of their diet. This might become more relevant if specific recommendations not only for the prevention of peanut but also tree nut allergy will come into place. So far it has been shown in the LEAP trial that the early introduction of peanut significantly reduces the risk for developing peanut allergy (25). Therefore, international guidelines suggest introducing peanuts into the infant's diet in an age-appropriate form as part of complementary feeding in order to prevent peanut allergy in infants and young children in populations where there is a high prevalence of peanut allergy. As Germany is not a country with high prevalence of peanut allergy our S3 guideline states that introduction and regular consumption of peanuts in an age-appropriate form may be considered in infants with atopic dermatitis living in families with regular peanut consumption, however, peanut allergy should first be ruled out, especially in infants with moderate to severe atopic dermatitis (7) as it had been performed in the LEAP trial (25). Due to a lack of interventional trials, so far, no specific recommendations for tree nuts have been formulated. However, in the HealthNuts study, none of the children who consumed cashew by the age of 12 months developed cashew allergy (0%; 95% CI, 0%-2.6%), compared with 3.6% (95% CI, 2.9%-4.4%) of those that had not eaten cashew by one year of age (26). Nevertheless, further randomized-controlled trials are needed to observe the effectiveness regarding allergy prevention and safety of an early introduction of tree nuts into the infant's diet.

Limitations of our study have to be mentioned. As this was a retrospective analysis of stored serum samples, we had no data on the clinical relevance of the tree nut sensitization. Therefore clinical reactivity could only be estimated using probability curves published in literature.

In conclusion our study demonstrates that a very high proportion of peanut-sensitized infants and toddlers are already co-sensitized to tree nuts with a high likelihood of clinical relevance in many of them. These findings should be considered for future strategies in screening, diagnostics and the prevention of tree nut allergy in children.

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Impact statement

Sensitization to hazelnut, cashew and walnut seems to be common among peanut-sensitized infants and toddlers. They also seem to be frequently sensitized to the corresponding tree nut 2S albumins, what might be associated with clinical reactivity to these tree nuts. Based on our findings, it should be considered to test peanut-sensitized infants and toddlers also for sensitization to tree nuts if these have not been introduced into the diet so far.

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Tables

TABLE 1: Characteristics of the study population

	All n=101	**Hazelnut sensitized n=95**	**Walnut sensitized n=88**	**Cashew sensitized n=85**
Gender male^{+} (n (%))	68 (71.6)	67 (72.8)	65 (74.7)	62 (72.9)
Age in months, median (range)	16 (5-24)	16 (5-24)	16 (5-24)	16 (5-24)
Eczema (n (%))	99 (98.0)	93 (97.9)	86 (97.9)	83 (97.7)
sIgE to peanut in kU/l, median (range)	1.23 (0.10-75.93)	1.17 (0.10-75.93)	1.08 (0.10-75.93)	1.23 (0.10-75.93)
sIgE to Ara h 1 (n (%))	84 (83.2)	81 (85.3)	75 (85.2)	74 (87.1)
sIgE to Ara h 1 in kU/l, median (range)	0.38 (0.10-12.64)	0.4 (0.10-12.64)	0.43 (0.10-12.64)	0.40 (0.10-12.64)
sIgE to Ara h 2 (n (%))	71 (70.3)	67 (70.5)	60 (68.2)	60 (70.6)
sIgE to Ara h 2 in kU/l, median (range)	0.98 (0.10-43.94)	0.8 (0.10-43.94)	0.69 (0.10-43.94)	0.78 (0.10-43.94)
OFC-challenge proven peanut allergy^{++} (n (%))	33 (40.7)	31 (39.2)	26 (35.6)	27 (38.03)
kU/l, kilounits/liter; sIgE, specific immunoglobulin E $^{+}$data from n=95 $^{++}$data from n=81	**kU/l, kilounits/liter; sIgE, specific immunoglobulin E $^{+}$data from n=95 $^{++}$data from n=81**	**kU/l, kilounits/liter; sIgE, specific immunoglobulin E $^{+}$data from n=95 $^{++}$data from n=81**	**kU/l, kilounits/liter; sIgE, specific immunoglobulin E $^{+}$data from n=95 $^{++}$data from n=81**	**kU/l, kilounits/liter; sIgE, specific immunoglobulin E $^{+}$data from n=95 $^{++}$data from n=81**

Figure Legends

FIGURE 1: Figure 1 shows the proportion of peanut-sensitized patients (n=101) being sensitized (specific

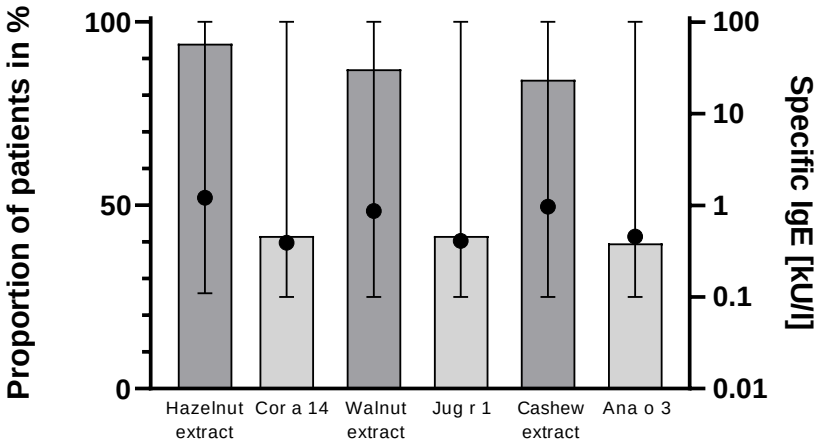
IgE [?] 0.1 kU/l) to hazelnut, walnut and cashew and to their corresponding 2S albumins Cor a 14, Ana o 3 and Jug r 1 as well as median and range of the corresponding specific IgE levels.

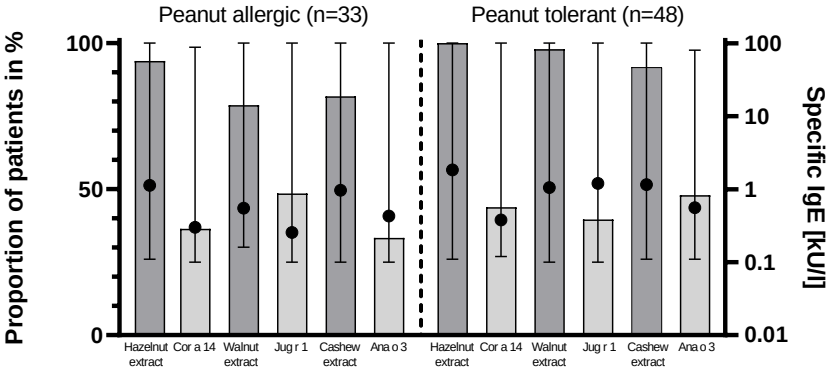
FIGURE 2: Figure 2 shows the proportion of peanut allergic and peanut tolerant patients being sensitized (specific IgE [?] 0.1 kU/l) to hazelnut, walnut and cashew and to their corresponding 2S albumins Cor a 14, Ana o 3 and Jug r 1 as well as median and range of the corresponding specific IgE levels (clinical relevance of peanut sensitization was known in 81 out of 101 patients).

FIGURE 3: Predicted values for an allergic reaction to hazelnut (A) and cashew (B) for each patient. Values were estimated according to the patient´s individual Cor a 14-sIgE and Ana o 3-sIgE values. Those were compared to a given probability for a positive OFC outcome at a certain sIgE value outlined in the prediction curves for Cor a 14 by Beyer et al. (16) and for Ana o 3 by Lange et al (15), respectively.

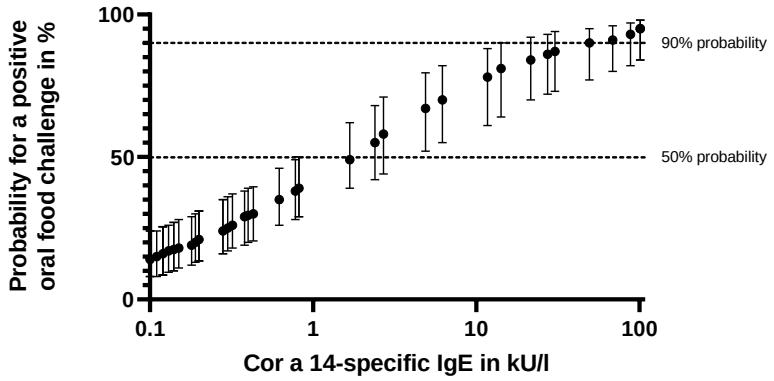
Author Contributions

Lara Meixner: Investigation (equal); formal analysis (lead); validation (equal); writing – original draft (lead); writing – review and editing (equal). Stephanie Heller: Investigation (equal); validation (equal); writing – review and editing (equal). Friederike Bluhme: Investigation (equal); writing – review and editing (equal). Valerie Trendelenburg: Investigation (equal); writing – review and editing (equal). Birgit Kalb: Conceptualization (equal); formal analysis (supporting); writing – original draft (supporting); writing – review and editing (equal); funding acquisition (equal); supervision (equal). Kirsten Beyer: Conceptualization (equal); formal analysis (supporting); writing – review and editing (lead); funding acquisition (equal); supervision (equal).





A



B