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Title: Influence of age on IgE response in peanut allergic children and adolescents from the Mediterranean area

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ABSTRACT

Background: Peanut allergens are common triggers of food allergy. Analyses of sensitization patterns, relationships with other allergens, clinical symptoms and variation with age are needed. We studied sensitization to Ara h 2, Ara h 9 and Pru p 3 in a peanut allergic children/adolescents, and the relationship with peach and pollen.

Methods: Peanut allergic patients aged between 1 and 20 years old were classified into two groups: A) allergic to peanut only, and B) allergic to peach and peanut. The IgE response was measured to Ara h 2, Ara h 9 and Pru p 3.

Results: Of 964 subjects evaluated, 28% were allergic to peanut. From this group 68% were also sensitized to pollen. Urticaria was the most frequent entity followed by anaphylaxis and OAS. Fifty-eight percent had Ara h 2 and/or Ara h 9 specific IgE. More than half reported symptoms with peanut alone (Group A); 35% to peanut and peach (Group B). We observed significant differences in sex, age, onset of symptoms and sensitization to Artemisia between groups. IgE response to Ara h 2 was more frequent in Group A; Ara h 9 and Pru p 3 in Group B. We observed a decrease in sensitization to Ara h 2 and an increase to Ara h 9 and Pru p 3 with increasing age.

Conclusion: Peanut allergy is frequent in subjects with allergy to plant-foods, with Ara h 2 and Ara h 9 being two important allergens. In younger patients Ara h 2 predominates over Ara h 9. The reverse was observed in older patients. Abbreviations: SSP, seed storage proteins; LTP, lipid transfer proteins; SPT, skin prick test; PR-10, pathogenesis related-10; double-blind-placebo-controlled food challenge (DBPCFC); OAS, oral allergy syndrome.

Key Words: Food allergy, peanut, peach, allergens, sensitization, LTP, SSP

INTRODUCTION

Immediate reactions to food of plant origin are one of the most frequent causes of food allergy, with many cases starting in infancy (1). Peanut allergens are frequently implicated, affecting 1% of the population (2). Several studies have reported an allergy prevalence rate of 0.50%-1.85% in children (3,4). However, more studies need to be undertaken in other populations and with larger age ranges.

The major peanut allergens Ara h 1, Ara h 2 and Ara h 3 (5) are seed storage proteins. Ara h 8 is a pathogenesis-related protein, PR-10 (6); Ara h 9 belongs to the lipid transfer protein (LTP) family, relevant in Mediterranean countries (7,8).

Many plant allergens are panallergens, being responsible for the cross-reactivity between homologous proteins from plant-derived foods and pollens (9,10). In central European countries a strong association exists between pollen sensitisation and food allergy (11,12). This situation differs in the Mediterranean area where sensitization to Pru p 3 (LTP from peach) has been shown to be unrelated to pollen allergies (13,14).

Specific IgE to single molecular allergens may vary with age. Peanut allergen molecular recognition has shown age-related, with Ara h 2 more prevalent in children (15,16) and Ara h 9 in adults (7). Ara h 9 sensitization is mainly due to cross reactivity with Pru p 3, both LTPs (8,17). Reasons for the age-related differences in allergen recognition are complex and cannot be explained in term of allergen exposure and cross-reactivity alone. Detailed studies of how sensitisation patterns occur at different ages in the same population and the relationship with related foods/inhalants are needed. This is particularly relevant in populations where primary sensitization occurs through the oral route such as Mediterranean countries.

We undertook a cross-sectional study in a child/adolescent population to establish the molecular response and sensitization patterns at different ages. Those confirmed allergic to peanut were further studied to verify the role of major peanut and peach allergens in inducing sensitization and symptoms.

MATERIAL AND METHODS

Patients

We evaluated all patients attending our service from 1 to 20 y.o. with a suspected food allergy of plant origin during a two years period. All participants completed a written informed consent and the ethical committee of our institution approved the study.

The allergological evaluation included: clinical history with implementation of an exhaustive questionnaire and skin prick test (SPT). In subjects with unclear history or negative skin tests a double-blind-placebo-controlled food challenge (DBPCFC) was carried out.

SPT was performed as recommended (18) using a panel of relevant prevalent allergens including *Dermatophagoides pteronyssinus*, *Phleum*, *Olea*, *Platanus*, *Artemisia*, peach and peanut (ALK-Abelló, Madrid, Spain). SPT was considered positive if the diameter of the wheal was 3 mm greater than that induced by the negative control.

Patients were considered peanut-allergic if they had at least two reactions within the first hour after exposure. In those with only one episode, DBPCFC was performed as described (19). Briefly, 3mg, 10mg, 30mg, 100mg, 300mg, 1g, and 3g of peanut protein were given orally every 30 min. Following PRACTALL criteria, if cutaneous and/or respiratory symptoms or alterations in vital signs appeared, the procedure was stopped and the symptoms were evaluated and treated (19). After the challenge was completed, the patient remained for at least two hours under clinical supervision. We excluded subjects with pathologies such as genetic, autoimmune and metabolic diseases.

Peach allergic patients were diagnosed if they had a clear history of reaction after peach ingestion and positive skin tests and/or peach-specific IgE antibodies. If negative, positive challenge was required for inclusion in the study group.

Serological determination

Specific IgE antibodies to whole peanut and peach extract and allergens Ara h 2, Ara h 9 and Pru p 3 were measured by ImmunoCAP (Phadia, Uppsala, Sweden). A positive result was defined as > 0.35 kUA/l.

Statistical analysis

Quantitative variables are shown as median and interquartile ranges (IR), while qualitative variables are shown as frequencies. Medians were compared between groups using Mann-Whitney or Kruskal-Wallis tests, while χ^2 was used to compare proportions. Differences with a $p < 0.05$ were considered significant.

RESULTS

Characteristics of peanut allergic patients

From the total number of 964 patients allergic to plant foods evaluated, 270 (28%) reported symptoms with peanut, 550 showed tolerance and the remaining 144 subjects had not had previous contact with peanut. Of the 270 patients with reported symptoms, 250 were confirmed as hypersensitive to peanut. Of these, 188 were diagnosed by clinical history and positive skin prick test, 62 by DBPCFC. The remaining 20 cases had good tolerance in spite of reported symptoms after peanut ingestion in their clinical history and were not included. The median age was 9.73 (IR:2-20) and 51% were male. SPT to aeroallergens was positive for 95% of cases, of which 68% were sensitive to pollens. The majority of patients (87%) had other allergic diseases in addition to food allergy. These were atopic dermatitis (62%), rhinoconjunctivitis (67%) and asthma (50%). The most frequently reported clinical entities were urticaria/angioedema in 134 patients (54%), followed by anaphylaxis (dyspnea, wheeze and hypotension) in 63 (25%) and OAS in 53 (21%).

Detailed analysis of these patients showed that 86 were also allergic to peach. The clinical symptoms reported by these patients were: urticaria/angioedema in 48 patients (56%), OAS in 30 (35%), and anaphylaxis in 8 (9%).

Skin prick test results

Eighty-seven percent of patients were prick test positive to peanut. More detailed analysis showed that skin tests were positive to peanut in 88% of patients with anaphylaxis, 79% with urticaria/angioedema and 75% with OAS. Out of the 33 patients with negative SPT, 13 had urticaria/angioedema, 13 OAS and 7 anaphylaxis. Eighty-two percent of peach allergic patients showed positive skin prick test to peach.

Considering pollen allergy, 86% were positive to *Phleum*, 75% to *Olea*, 72% for *Platanus* and 43% for *Artemisia*.

Specific IgE results

Of 250 patients studied, 81% had specific IgE to whole peanut allergen. When we measured specific IgE to peach allergen in patients allergic to both peanut and peach, 83% had specific IgE. The IgE response to peanut allergens showed that Ara h 2 antibodies were detected in 33% of patients and Ara h 9 in 42%. Considering cases with specific IgE to only one allergen, 17% were positive to Ara h 2 and 25% to Ara h 9 only. Out of all peanut allergic patients tested, 58% were positive to at least one allergen.

Of the 217 patients with positive SPT to peanut, 69% showed IgE antibodies and in those with negative SPT (33 cases), 8% had IgE antibodies.

The proportion of patients with specific IgE to Ara h 2 and Ara h 9 was similar for patients with anaphylaxis and urticaria. For OAS, a significant higher proportion ($p=0.028$) of patients showed IgE to Ara h 9 (54%) compared to Ara h 2 (25%).

Comparison between peanut allergic patients with tolerance to peach and patients allergic to both peanut and peach.

We compared patients with allergy to peanut but tolerant to peach (Group A, N=162) with those allergic to peanut and peach (Group B, N=86) (Table 1). Group A patients were younger with symptoms appearing earlier than in Group B. The overall pollen sensitization in Group A was lower than in Group B, but if we analyzed this response considering the pollens individually we detected that *Phleum*, *Olea* and *Platanus* sensitisation was similar between both groups, however the percentage of *Artemisia* sensitisation was significant higher ($p=0.021$) in Group B. Significant differences were observed for median age and age at symptom onset, gender, peach specific IgE and pollen sensitisation.

When we compared clinical entities, anaphylaxis appeared in 27% of the cases in Group A and in 14% of Group B ($p=0.021$), urticaria/angioedema was similar for both (56% in Group A and 51% in Group B) and OAS was more common in Group B (32%) compared to Group A (14%) ($p=0.018$). The most prevalent entity in both groups was urticaria/angioedema ($p=0.005$ and $p=0.008$, respectively) (Figure 1).

Considering sIgE response to molecular allergens, we observed that the number of patients with IgE to Ara h 9 and Pru p 3 was higher in Group B ($p=0.025$ and $p=0.038$, respectively). Within Group A, Ara h 2 was the most frequent allergen, although this did not reach statistical significance. Within Group B, Ara h 9 and Pru p 3 IgE was significantly more prevalent than Ara h 2 ($p=0.032$ and $p=0.041$, respectively) (Figure 2).

When we considered all allergens together, positive cases for Ara h 2 were the most frequent ($p=0.042$) for Group A, followed by the combination of Ara h 2, Ara h 9 and Pru p 3. On the other hand, for cases with allergy to both peanut and peach, the highest number of positive results corresponded to the combination of Ara h 9 and Pru p 3 ($p=0.022$) only; few cases were found that were positive to Ara h 2 only (Table 2).

IgE recognition of peanut and peach allergens according to age

We grouped patients by age intervals of 5 years from youngest to oldest in order to evaluate the IgE response to Ara h 2, Ara h 9 and Pru p 3. Values of sIgE for Ara h 2 decreased with increasing age (Figure 3A), whilst values for Ara h 9 and Pru p 3 increased (Figure 3B, 3C).

DISCUSSION

We have performed a cross-sectional study in a large group of children and adolescents with plant-foods allergy. More than a quarter of patients reported symptoms with peanut as published (16). We also confirmed association with other allergic diseases such as atopic dermatitis and asthma (20).

Plant-food allergy is highly associated with pollen allergy (9,10). Over half of the patients were sensitized to *Phleum*, *Olea* and *Platanus* pollens. Whether this association is related to cross-reactivity or represents a clinical property of atopic patients is a matter of speculation, however all these pollens contain panallergens with similar structures to peanut and peach proteins, such as profilins, PR-10 and LTPs. We observed a strong association between patients allergic to both peanut and peach and *Artemisia*, suggesting cross-reactivity across LTP proteins (21,22).

Considering clinical manifestations, urticaria/angioedema was the most frequent entity followed by anaphylaxis and OAS. These findings are similar to those reported by Pedrosa et al. (15).

The diagnosis of peanut allergy was largely based on an unequivocal history of several episodes after ingestion of peanut. We found SPT positivity to peanut in 87% of patients, with 81% having IgE antibodies. Similar results have been reported previously (23). For patients with anaphylaxis, 88% were SPT positive, and 72% had detectable IgE antibodies to peanut allergens. For urticaria/angioedema, 79% were SPT positive and 64% had detectable IgE antibodies. For patients with OAS, 75% had positive SPT and 77% detectable IgE antibodies. Interestingly, we detected IgE antibodies to purified allergens for 8% of the cases that had a negative SPT to peanut. This may be due to a low concentration of the relevant allergen in the whole extract used for SPT as reported (24).

Regarding the sensitization profile to peanut allergens, we found that 42% of patients had IgE to Ara h 9, and 25% of the patients were monosensitized to this allergen.

A third of all patients recognized Ara h 2 and 17% were monosensitized. Our results are in line with a recent study from Calamelli (25) but are lower than those of Vereda et al (8). More than half (58%) of all patients had IgE antibodies to at least one allergen. Although Ara h 2 has been implicated in other populations (15,16,26), Ara h 9 was the most prevalent here and appears to play an important role in peanut allergy in the Mediterranean area (7).

Our work revealed an age dependent sensitization pattern in peanut allergic patients, with the youngest group of children more frequently sensitised to Ara h 2: 40% at 1-5 years, followed by 32% at 6-10 years decreasing to 16% in the oldest group. The opposite pattern was found for Ara h 9: 20% had sIgE in the 1-5 year group, increasing to 60% in the oldest group. Similar results have been described in a recent study carried out in a pediatric population (25, 27). It seems that a loss of sensitisation to Ara h 2 occurs with increasing age, whilst awareness of LTP is gradually beginning. The presence of members of the LTP family in many species may represent a maintenance dose of the allergen for these individuals. However, the absence of cross reactivity between 2S albumins due to the high difference in the primary structure of these proteins may lead to a reduction in the maintenance of allergy to Ara h 2 (28).

Regarding the relationship between clinical symptoms and the pattern of allergen recognition, fewer patients with OAS had IgE to Ara h 2 than to Ara h 9. However, we did not find any differences for anaphylaxis or urticaria/angioedema. Our data agree with previous studies where the severity of clinical reactions was not shown to be correlated with the presence of specific IgE to any of the peanut allergens (15). However it has recently been described that high levels of IgE to Ara h 2 are indicative of the severity of the clinical response in North America and European populations (8,27,29).

The association of peach and peanut allergy is high in the Mediterranean region, due to LTP cross-reactivity (30). However this relation is less marked in other countries (8). Our cases could be divided into two groups: patients allergic to peanut (Group A), and patients allergic to peanut and peach (Group B). Almost one third of the peanut allergic patients belonged to Group B. Symptoms with peach often appeared before peanut allergy. This may be due a primary sensitization to peach LTP, Pru p 3, as previously reported by our group in an adult population (17). Sensitization to pollen was higher in patients allergic to peanut and peach than in those only allergic to peanut, especially for *Artemisia*. This could be due to cross-reactivity between pollen and food as described previously (22,31).

Analysis of the sensitization pattern confirmed that allergen recognition differed between groups. In Group A, Ara h 2 was higher than Ara h 9 or Pru p 3 (peanut and peach LTPs). In Group B, Ara h 9 and Pru p 3 were significantly higher. These findings agree with other studies (7,16,26). However, only 22% of LTP positive cases from Group A had systemic reactions (anaphylaxis and urticaria/angioedema) and from Group B only 12% of positive cases to Ara h 2 had systemic reactions.

In 10% of cases in Group A, the subject had IgE antibodies to Ara h 2 and Ara h 9. Because these subjects developed symptoms to peanut only and tolerated peach, we conclude that Ara h 2 or a further peanut allergen was eliciting the symptoms.

For some cases in Group B, specific IgE was detected for Ara h 9 but not Pru p 3, indicating that Ara h 9 can be the primary sensitizing agent. Ara h 9 has been described as the primary sensitizer in adults (17).

In summary, in this study we:

- Have presented the largest study of children and adolescents with peanut allergy to date.
- Have performed a cross-sectional study that included child and adolescent populations to establish a possible age dependency in molecular response and sensitization patterns.
- Have provided evidence that suggests that the sensitization profile is related to sensitivity to other foods and pollen.
- Have provided evidence that indicates that at very early ages patients may show sensitivity to peanut and peach allergens with variation in the pattern of recognition over time.
- Have shown that the predominating allergen differs according to age, from Ara h 2 for younger children, to Ara h 9 and Pru p 3 for older children and adolescents.
- Did not detect association between clinical symptoms and the pattern of allergen recognition

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Table 1. Comparison of demographic and clinical characteristics of patients with allergy to peanut and tolerance to peach (Group A) and patients with allergy to peanut and peach (Group B). Significant differences ($P<0.05$) are indicated in bold.

	SYMPTOMS TO PEANUT AND TOLERANCE TO PEACH (N=162)	SYMPTOMS TO PEANUT AND PEACH (N=86)	P
Age, median (IR)	8.64 (2-20)	11.95 (2-20)	0.043
Age at onset of symptoms, median (IR)	5.62 (1-17)	Peanut: 8.29 (1-19) Peach: 6.58 (1-19)	0.006
Sex, % Male	57	37	0.031
Caucasian, %	87	91	0.517
Specific IgE, % Peanut whole extract Peach whole extract	78 59	91 89	0.142 0.004
Atopy, %	93	84	0.316
Sensitization to pollen, % <i>Phleum</i> <i>Olea</i> <i>Platanus</i> <i>Artemisia</i>	63 93 70 73 33	84 82 82 81 62	0.016 0.156 0.301 0.760 0.021
Associated Allergic Diseases, %	86	88	0.674

Table 2. Comparison of percentages of positive cases to single or to combinations of allergens Ara h 2, Ara h 9 and Pru p 3 for patients with symptoms to peanut and tolerance to peach (Group A) and patients with symptoms to peanut and peach (Group B). Significant differences ($P<0.05$) are indicated in bold.

	SYMPTOMS TO PEANUT AND TOLERANCE TO PEACH (N=162)	SYMPTOMS TO PEANUT AND PEACH (N=86)	p
Ara h 2	16%	7%	0.042
Ara h 9	0%	7%	0.482
Pru p 3	2%	2%	0.566
Ara h 9 + Pru p 3	12%	35%	0.022
Ara h 2 + Ara h 9	1%	2%	1
Ara h 2 + Pru p 3	1%	0%	1
Ara h 2 + Ara h 9 + Pru p 3	16%	16%	0.333

FIGURE LEGENDS

Figure 1.- Differences between patients with peanut allergy and peach tolerance (Group A : N=162) and patients with allergy to peanut and peach (Group B : N=86) in clinical entities. $P<0.05$ represents a significant difference.

Figure 2.- Differences between patients with peanut allergy and peach tolerance (Group A : N=162) and patients with allergy to peanut and peach (Group B : N=86) in specific allergens (Ara h 2, Ara h 9 and Pru p 3) (B). $P<0.05$ represents a significant difference.

Figure 3.- Percentage of positive cases showing specific IgE (A,B,C) to peanut and peach allergens (Ara h 2, Ara h 9 and Pru p 3) in all patients, grouped by age intervals of 5 years from youngest to oldest. $P<0.05$ represents a significant difference.

FIGURE 1

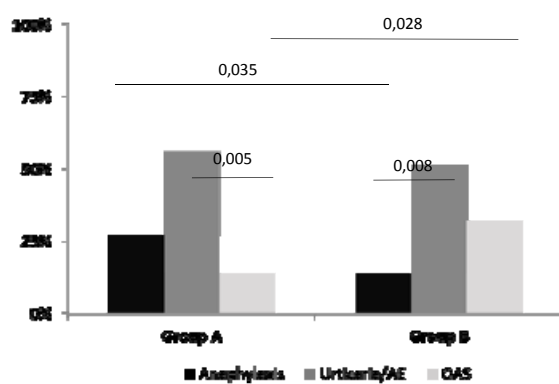


FIGURE 2

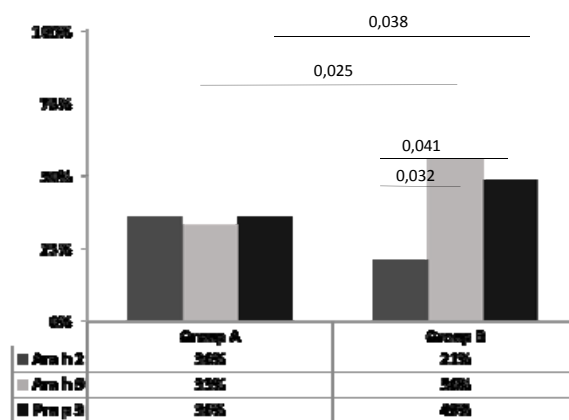


FIGURE 3

