

CORRESPONDENCE

Long-term prognostic value of component-resolved diagnosis in infants and toddlers with peanut allergy

DOI:10.1111/pai.12216

To the Editor,

The interest in component-resolved diagnosis has been growing significantly in the last decade. In peanut allergy, storage proteins Ara h 1 (7S-vicilin), Ara h 2 (2S-albumin), and Ara h 3 (11S-globulin) have been designated as primary sensitizers to peanut in susceptible individuals (1–3). Among available peanut molecular components, Ara h 2 is clinically the most important one (2, 3). Ara h 9 is a non-specific lipid transfer protein (nsLTP) and has been shown to be a dominant allergen, both in terms of prevalence and severity, in south European populations (2, 4). Ara h 8 (peanut PR-10 protein), Ara h 5 (profilin), and CCD are cross-reactive components associated mainly with subclinical sensitization or oral allergy syndromes (2, 5).

While component-resolved diagnosis has been shown to improve specificity of peanut allergy diagnosis by differentiating between dominant and cross-reactive allergens, its long-term

prognostic value has never been examined. Although in most cases peanut allergy tends to persist, previous studies have demonstrated that around 20% of children may resolve their allergy over time and resolution correlates with initial peanut IgE levels (6, 7).

In the present study, we aimed to determine whether early component-resolved diagnosis at time of peanut allergy diagnosis in infants and toddlers would provide information in addition to standard specific IgE levels to better predict future evolution of the disease. We took the opportunity of a well-characterized cohort of peanut allergic subject from a previous study, in which 110 subjects had serum drawn at diagnosis (median age, 14 months) and stored at -80°C for future analyses (6). At the time of diagnosis, all subjects reported unequivocal clinical reaction within the past 6 months and a SPT greater than 4 mm which carries a 95% PPV in this age group (8). Subjects were followed every 2 yr for a median of

Table 1 Clinical characteristics at the time of diagnosis

	Remitters (n = 22)	Non-remitters (n = 85)	p-value*
Male	11 (50%)	50 (59%)	0.46
Age (median, range)	14 months (10–18)	15 months (6–18)	0.93
Father atopy	7 (32%)	46 (54%)	0.06
Mother atopy	10 (45%)	48 (56%)	0.37
Index reaction			
Cutaneous	20 (91%)	66 (78%)	0.16
Respiratory	3 (14%)	15 (18%)	0.65
Gastrointestinal	1 (5%)	13 (15%)	0.18
Altered consciousness	1 (5%)	5 (6%)	0.81
Anaphylaxis (2 systems)	3 (14%)	18 (21%)	0.43
Coexistent atopic diagnoses			
Atopic dermatitis	17 (77%)	67 (79%)	0.88
Asthma	1 (5%)	10 (12%)	0.32
Bronchiolitis	3 (14%)	16 (19%)	0.57
Rhinitis	5 (23%)	20 (24%)	0.94
Other food allergy	9 (41%)	31 (36%)	0.70
Peanut SPT (median, range)	9.5 mm (4–19)	11 mm (4–27)	0.20

*Calculated with Pearson's uncorrected chi-square for dichotomic variables and Student's *t*-test for continuous variables.

Abbreviations:

CCD, cross-reactive carbohydrate determinant; DBPCFC, double-blind-placebo-controlled food challenge; HR, hazard ratio; nsLTP, non-specific lipid transfer protein; OIT, oral immunotherapy; OR, odds ratio; PN-IgE, peanut-specific immunoglobulin E; PPV, positive predictive value; RR, relative risk; SPT, skin prick test.

12 yr and offered DBPCFC past age 5 yr to confirm resolution if PN-IgE were below 15 kU/l (Siemens, Muenchen, Germany).

Over the study period, three patients were lost to follow-up. Of the 107 remaining, 22 (21%; 95 CI = 13–34%) underwent

Table 2 Peanut-specific IgE profiles of remitters and non-remitters

Component	Remitters	Non-remitters	Resolution rate	Uncorrected p-value***	Corrected p-value***
Ara h 2	n = 22†	n = 85†			
<0.1	3	2	0.6	<0.0005	0.11
0.1–1.0	13	23	0.36		
1.0–5.0	6	25	0.19		
5.0–25.0	0	20	0		
>25	0	15	0		
Ara h 1	n = 19	n = 72			
<0.1	13	21	0.38	0.005	0.37
0.1–1.0	5	24	0.17		
1.0–5.0	0	11	0		
>5.0	1	16	0.06		
Ara h 3	n = 19	n = 72			
<0.1	15	37	0.29	0.03	0.78
0.1–1.0	4	25	0.14		
1.0–5.0	0	4	0		
>5.0	0	6	0		
Diversity‡	n = 19	n = 72			
0	2	2	0.50	0.001	0.68
1	11	21	0.34		
2	6	15	0.29		
3	2	35	0.05		
PN-IgE	n = 22	n = 85			
<0.35	12	11	0.52	<0.0005	0.04
0.35–0.7	3	7	0.3		
0.7–3.5	7	60	0.1		
3.5–17.5	0	7	0		
Ara h 8	n = 22	n = 85			
<0.1	21 (95%)	85	0.20	0.05	0.99
1.0–2.0	1 (5%)	0	1.0		
Ara h 9	n = 21	n = 83			
<0.1	21	79	0.21	0.31	0.99
0.1–1.0	0	3 (5%)	0		
1.0–2.0	0	1	0		
CCD	n = 19	n = 75			
<0.1	18	74	0.20	0.49	0.99
0.1–1.0	1 (5%)	1 (1%)	0.5		
Pru p 4	n = 19	n = 71			
<0.1	19	70	0.21	0.60	0.99
0.1–1.0	0	1 (29%)	0		

Units in kU/L

†Number of patients included for each analysis component allergen depended on the quantity of available frozen serum. Patients lost to follow-up were excluded from analyses.

‡Sum of positive tests.

***Univariate statistical analysis was performed with chi-square (uncorrected), and multivariate analysis was performed with entry method binary logistic regression (corrected).

spontaneous resolution of their peanut allergy. Initial clinical characteristics of remitters and non-remitters are shown in Table 1.

Frozen sera from initial visit were then thawed and assayed simultaneously for IgE to peanut recombinant Ara h 2 and Ara h 8 (ImmunoCAP®250 and allergen components, Phadia, Saint-Quentin-en-Yvelines, France). One-hundred and four (104) sera were further analyzed for Ara h 9 and plant

cross-reactive carbohydrate MUXF3 (CCD); 94 for Ara h 1; and 91 for Ara h 3 and recombinant Pru p 4 IgE levels, depending on the available quantity. As structure of plant profilins is highly conserved, peach Pru p 4 was used as a marker of profilin IgE reactivity (5). The measuring range of specific IgE to molecular components was between 0.10 and 100 kU/L.

Both prevalence and levels of Ara h 8-, Ara h 9-, CCD-, and Pru p4-specific IgE were low in the cohort at diagnosis (Table 2).

In contrast, specific IgE against Ara h 1, Ara h 2, and Ara h 3 was detected in 63%, 95%, and 43% of patients, respectively. This skewing in favor of dominant allergens is not surprising considering that subjects were selected based on previous clinical reactions to peanut (1, 3). Nevertheless, Ara h 2 IgE prevalence was higher in our cohort (91%) than in peanut-reactant subjects from the Swedish cohort BAMSE (73%) (2). This could be a reflection of the different age group. While BAMSE looked at children 8-yr old, children in our cohort were all younger than 18 months and thus may have been much less likely to have been sensitized to cross-reactive allergens. The sensitization profile did not vary when considering only subjects with initial PN-SPT greater or equal to 8 mm (n = 82), which carries a 95% PPV regardless of previous history of reaction (9).

Ara h 9-specific IgE prevalence and levels were universally low in our population, confirming previous findings with Central and Northern European cohorts (2, 10) but not with patients from Southern Europe (4). This geographical difference in sensitization to nsLTP could result from genetic or environmental differences between the two populations. It might again be due to cohort characteristics as our patient suffered from very early-onset disease which might be different from later-onset peanut allergy. Finally, profilin and CCD IgE prevalences were 2% each, which is in line with those reported in the BAMSE cohort for children exclusively sensitized to peanut, but lower than those reported for polysensitized children and adults (2, 10).

In univariate analysis, levels of Ara h 1-, Ara h 2-, and Ara h 3-specific IgE correlated with the persistence of peanut allergy (Table 2). Peanut IgE diversity defined by the sum of IgE detectable tests to the three dominant allergens also correlated strongly with remission (Table 2). However, when analyzed with a log regression multivariate analysis including PN-IgE levels, those association did not reach significance. This suggests that results from sensitivity profile are redundant with PN-IgE and do not provide additional independent information when evaluating the prognosis of an infant or toddler with peanut allergy.

While the diagnostic value of component-resolved diagnosis for peanut allergy has been demonstrated, to the best of our knowledge, this study is the first to examine its prognostic value with regard to long-term evolution. Although we show the initial sensitization profile does not provide independent

information in addition to initial PN-IgE levels, one should note that this was a very young population with early-onset disease and lack of cross-reactive component sensitization. It cannot be excluded that with later-onset disease, which may be associated with more sensitization to cross-reactive components, component-resolved diagnosis could have some use in predicting disease evolution.

In conclusion, using a longitudinal cohort of peanut allergic children, we have shown Ara h 1, Ara h 2, and Ara h 3 to be the dominant peanut allergens in a population of North American infants and toddlers with early-onset peanut allergy, with sensitization to Ara h 9 and cross-reactive components being exceptional. Although reactivity to these dominant component-resolved allergens at the time of diagnosis was found to be associated with future allergy persistence at 13 yr, the information was redundant with PN-IgE levels and did not provide additional independent predictive value.

Funding

Phadia France provided reagents for component-resolved analysis.

Conflicts of interest

None to declare.

Philippe Bégin^{1,2}; Joana Vitte^{3,4,5,6}; Louis Paradis^{1,2}; Jean Paradis²; Pierre Bongrand^{3,4,5,6}; Pascal Chanez^{3,4,5,6,7} & Anne Des Roches¹

¹Department of Pediatrics, Allergy and Clinical Immunology Division, Centre Hospitalier Universitaire Sainte-Justine, Montreal, Canada; ²Department of Medicine, Allergy and Clinical Immunology Unit, Centre Hospitalier de l'Université de Montréal, Montreal, Canada; ³Laboratoire d'Immunologie, Assistance Publique Hôpitaux de Marseille, Marseille, France; ⁴Aix-Marseille Univ, INSERM UMR 1067 CNRS UMR 7333, Marseille, France; ⁵INSERM UMR 1067, Marseille, France; ⁶CNRS UMR 7333, Marseille, France; ⁷Département des Maladies Respiratoires, Assistance Publique Hôpitaux de Marseille, Marseille, France

E-mail: a.des.roches@umontreal.ca

References

- Koppelman SJ, Wensing M, Ertmann M, Knulst AC, Knol EF. Relevance of Ara h 1, Ara h 2 and Ara h 3 in peanut-allergic patients, as determined by immunoglobulin E Western blotting, basophil-histamine release and intracutaneous testing: Ara h 2 is the most important peanut allergen. *Clin Exp Allergy* 2004; **34**: 583–90.
- Asaranoj A, Moverare R, Ostblom E, Poorafshar M, Lilja G, Hedlin G, et al. IgE to peanut allergen components: relation to peanut symptoms and pollen sensitization in 8-year-olds. *Allergy* 2010; **65**: 1189–95.
- Nicolaou N, Poorafshar M, Murray C, Simpson A, Winell H, Kerry G, et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010; **125**: 191–7. e1–13.
- Krause S, Reese G, Randow S, Zennaro D, Quarantino D, Palazzo P, et al. Lipid transfer protein (Ara h 9) as a new peanut allergen relevant for a Mediterranean allergic population. *J Allergy Clin Immunol* 2009; **124**: 771–8. e5.
- Villalta D, Asero R. Sensitization to the pollen pan-allergen profilin. Is the detection of immunoglobulin E to multiple homologous proteins from different sources clinically useful? *J Invest Allergol Clin Immunol* 2010; **20**: 591–5.
- Bégin P, Paradis L, Paradis J, Picard M, Des Roches A. Natural resolution of peanut allergy: a 12-year longitudinal follow-up study. *J Allergy Clin Immunol Pract* 2013; **1**: 528–30. e4. <http://dx.doi.org/10.1016/j.jaip.2013.05.008>.

Correspondence

7. Ho MH, Wong WH, Heine RG, Hosking CS, Hill DJ, Allen KJ. Early clinical predictors of remission of peanut allergy in children. *J Allergy Clin Immunol* 2008; **121**: 731–6.
8. Sicherer SH, Wood RA. Advances in diagnosing peanut allergy. *J Allergy Clin Immunol Pract* 2013; **1**: 1–13.
9. Peters RL, Allen KJ, Dharmage SC, Tang ML, Koplin JJ, Ponsonby AL, et al. Skin prick test responses and allergen-specific IgE levels as predictors of peanut, egg, and sesame allergy in infants. *J Allergy Clin Immunol* 2013; **132**: 874–80.
10. Moverare R, Ahlstedt S, Bengtsson U, Borres MP, van Hage M, Poorafshar M, et al. Evaluation of IgE Antibodies to Recombinant Peanut Allergens in Patients with Reported Reactions to Peanut. *Int Arch Allergy Immunol* 2011; **156**: 282–90.