Peanut component Ara h 8 sensitization and tolerance to peanut

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Background: Isolated Ara h 8 sensitization is suggested to be associated with no or mild symptoms among peanut-sensitized subjects.

Objective: We sought to investigate the occurrence of systemic reactions in children with isolated sensitization to Ara h 8.

Methods: Participants were 144 children sensitized to Ara h 8 (≥0.35 kU_A/L) but not to Ara h 1, Ara h 2, or Ara h 3 (<0.35 kU_A/L). An open oral challenge with peanut was performed in those subjects who did not consume peanut regularly, and an extended IgE reactivity profile was obtained. If the child had a documented history of systemic reactions up to grade I anaphylaxis, double-blind, placebo-controlled food challenges were performed.

Results: One hundred twenty-nine (89.5%) children were either peanut consumers or did not react to peanut challenge. Another 14 (9.7%) children experienced oral cavity symptoms at the first 2 but not subsequent challenge doses. At the time of the double-blind, placebo-controlled food challenge, 1 boy with a previous mild systemic reaction to peanut experienced lip swelling, stomach cramping, and objective tiredness. Reanalysis of IgE levels showed an increase in peanut IgE levels from 1.5 to 8.8 kU_A/L, but IgE levels to Ara h 8 remained stable and IgE levels to Ara h 1, Ara h 2, and Ara h 3 were all still less than 0.35 kU_A/L. The IgE level to Ara h 6 was 0.45 kU_A/L.

Conclusion: Isolated Ara h 8 sensitization indicates tolerance to peanuts in almost all cases. However, sensitization against thus far unidentified determinants in peanut might cause symptoms in rare cases. (J Allergy Clin Immunol 2012;130:468-72.)

Key words: *Ara h 1, Ara h 2, Ara h 3, Ara h 6, Ara h 8, Ara h 9, component-resolved diagnostics, molecular allergology, oral food challenge, peanut allergy, sensitization*

Component-resolved diagnostics have provided new insight into clinically relevant sensitization in patients with peanut allergy.[1] The major peanut allergens Ara h 1, Ara h 2, and Ara h 3 are the proteins considered primarily responsible for sensitization to peanut.[2,3] Ara h 2 is stable to heat and gastric denaturation and has thus far been considered the clinically most important peanut protein.[4-9] Recently, the relevance of sensitization to Ara h 6 (the 2S albumin homologue of Ara h 2) and the lipid transfer protein Ara h 9 has been described.[7,8,10-12]

There is extensive IgE cross-sensitization between peanut allergens and homologous allergens from various plant sources,[13-15] and Ara h 8 contributes to birch pollen–peanut cross-sensitization because of homology with the major birch pollen allergen Bet v 1. This is likely true also for cross-sensitization to other pollens, particularly alder, which is botanically related to birch.[16] As a result, patients with allergy to Fagales tree pollen, particularly birch pollen, might be given a diagnosis of peanut allergy.[4,13,17]

Recently, we have shown that among children with sensitization to the peanut allergen component Ara h 8 and not to the storage proteins Ara h 1, Ara h 2, and Ara h 3, only 17% reported symptoms to peanut; moreover, those symptoms were almost exclusively mild.[4] Because children in that study were not challenged, the aim of this study was to investigate the risk of systemic reactions at oral challenge with peanuts among children sensitized to Ara h 8 but not to Ara h 1, Ara h 2, and Ara h 3.

METHODS

Study subjects

Children were recruited both from a clinical center database (group A) and a birth cohort (group B). Ethical permission was obtained from the regional ethics review board at Karolinska Institutet, Stockholm, Sweden.

An outpatient clinical database of 237 children at Sachs' Children's Hospital (Stockholm, Sweden) was used for inclusion (group A). The patients in the database were sensitized (IgE ≥0.35 kU_A/L) to peanuts or tree nuts and were entered in the database consecutively between 2007 and 2010. Among these children, 98 were identified as being sensitized to Ara h 8 (≥0.35 kU_A/L) but not to Ara h 1, Ara h 2, or Ara h 3 (all <0.35 kU_A/L, Fig 1). For the purpose of inclusion in this study, this allergen recognition profile was defined as an isolated Ara h 8 sensitization, even though a few might have been Ara h 9 sensitized.[12]

Inclusion in group B was derived from the 8-year follow-up of the unselected BAMSE birth cohort study (Stockholm, Sweden).[18] One hundred

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Abbreviations used
DBPCFC: Double-blind, placebo-controlled food challenge
OAS: Oral allergy syndrome
OOFC: Open oral food challenge

ninety-five of the 2480 children were sensitized to peanut (≥0.35 kU_A/L). Sera from these children were analyzed for IgE to Ara h 1, Ara h 2, and Ara h 3 and Ara h 8, and 62 children with isolated Ara h 8 sensitization (≥0.35 kU_A/L) were identified (Fig 1).

The 160 children from groups A and B constitute the study population. Data on consumption of, reactions to, or avoidance of peanuts, as well as background data about other allergic diseases, were retrieved from medical records, telephone interviews, and questionnaires.

Inclusion criteria for oral challenge included children with current sensitization as described above and no previous exposure to peanuts, avoidance of peanuts for different reasons, or anaphylaxis of grade I or milder after previous exposure to peanuts.[19,20]

Exclusion criteria for oral challenge included children with anaphylaxis of grade II to III after previous exposure to peanuts[19,20] and children with ongoing allergic reactions to other food or inhalant allergens at admittance for challenge.

Peanut tolerance was defined as a child with reported peanut consumption on at least 1 occasion in the last 12 months without symptoms or discomfort.

Oral food challenge

An open oral food challenge (OOFC) was performed in 4 stages only: 100 mg, 1 g, 5 g, and an additional 5 g of pure roasted peanut at 20-minute intervals, which is equivalent to 13 to 15 peanuts. Roasted peanuts were chosen because this is the form to which children are exposed, even if this most likely will reduce the allergenicity of Ara h 8.[17] In cases of a well-documented history of a systemic reaction up to grade I and if a nonsystemic or systemic reaction up to grade I anaphylaxis is observed on the OOFC, a double-blind placebo-controlled food challenge (DBPCFC) was performed, as previously described.[21,22] Challenges were to be performed outside of the pollen season.

A *negative food challenge outcome* was defined as no objective symptoms during 60 minutes after the last dose of peanut at oral provocation and no parental report of late symptoms 24 hours after challenge. Oral allergy syndrome (OAS; ie, local symptoms from the oral cavity, such as itching and tingling of the lips, mouth, and throat but without skin symptoms, breathing difficulties, or tissue swelling)[23] was also regarded as a negative outcome provided that the symptoms disappeared spontaneously during the 1-hour observation period with no rescue medication.

A *positive food challenge outcome* was defined as a systemic reaction with manifestations from the skin, gastrointestinal tract, upper or lower respiratory tract, or cerebrovascular system.[19,20]

Analysis of blood samples drawn at the time of challenge

Identification of study subjects was based on IgE levels to peanut and component-resolved diagnostics analyzed with ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) at the Department of Clinical Immunology, Karolinska University Hospital.

At challenge, new blood samples were drawn for reanalysis of IgE levels to peanut extract and Ara h 1, Ara h 2, Ara h 3, and Ara h 8 but now also including Ara h 6 and Ara h 9. In addition, IgE levels to the birch pollen extract Bet v 1 were analyzed at Thermo Fisher Scientific. Ara h 6 (sequence accession no. Q647G9) was produced in *Escherichia coli* as a hexahistidine-tagged recombinant protein by using a synthetic gene construct and purified by means of immobilized metal ion affinity chromatography followed by ion exchange chromatography, as previously described.[24] Experimental ImmunoCAP Ara h 6 tests were prepared,[25] and IgE levels of 0.35 kU_A/L or greater were considered positive.

Statistics

Results are expressed as numbers and proportions (as a percentage). The χ^2 test was used for comparison of dichotomous variables between groups. The Fisher exact test was used if one comparison group consisted of 5 observations or less. Group IgE levels are expressed as median values and ranges. Two-tailed *t* tests were used on the logarithmic scale for group comparisons of IgE levels. *P* values of less than .05 were considered significant. All statistical analyses were performed with STATA software (release 11.1; StataCorp, College Station, Tex)

RESULTS

Demographic and immunologic data of the 160 children at inclusion are shown in Table I. Sixteen children could not be challenged for the reasons shown in Fig 1. Thus 144 children remained in the study. Eighty-two (57%) children, 31 from group A and 51 from group B, were already eating peanuts and were therefore not required to undergo challenge (Fig 1). Sixty-two children were invited for challenge, of whom 44 had never tasted peanuts, and 12 had previously experienced reactions to peanut, of whom 4 reported systemic reactions without documentation and 1 had a documented history of such a reaction. Another 6 had eaten peanuts earlier in life without symptoms but had been advised to avoid peanuts because of previous allergy test results. No children were found to have anaphylaxis of grade II to III after previous exposure to peanuts. It is noteworthy that the children who ate peanuts and were therefore not challenged did not exhibit lower IgE levels to peanut or Ara h 8 than the group of challenged children; in fact, the results showed the contrary (Table I).

Fourteen (23%) children undergoing OOFCs reported oral cavity or pharyngeal itch (OAS) during the challenge, after the challenge, or both, but symptoms could be verified objectively in only 2 of these children (Table II and Fig 1). Interestingly, the OAS symptoms occurred at the first or second dose, ceased spontaneously without treatment, and did not occur at the following dose steps. There was no association between IgE levels to birch pollen in relation to OAS symptoms (Table II).

Sera from 59 (95%) of the challenged children were reanalyzed for IgE to peanut and birch pollen extracts, as well as to peanut components. All children still had negative test results (<0.35 kU_A/L) for IgE to Ara h 1, Ara h 2, and Ara h 3, despite the fact that 9.7 months had passed, on average, between identification and challenge. Two children had positive test results to Ara h 6 (≥0.35 kU_A/L): one with 0.73 kU_A/L passed the challenge, whereas the other had 0.45 kU_A/L and failed (see below, Table III). Ara h 9 IgE levels were not associated with any symptoms at challenge. Two children had positive test results for Ara h 9 IgE (4.07 and 8.25 kU_A/L), one of whom had subjective OAS at challenge.

In 2 children DBPCFCs with peanut were carried out because of earlier systemic reactions/grade I anaphylaxis to peanut. One study subject (subject 1) had symptoms of allergic rhinoconjunctivitis caused by birch pollen exposure and was accidently challenged openly with peanut while exposed to birch pollen. He reacted with exacerbated conjunctivitis and rhinitis, as well as subjective breathing difficulties. His dyspnea could not be verified based on use of a stethoscope or his Pao_2 value (96%). At rechallenge (DBPCFC) 6 months later, outside of the birch pollen season, he passed the test. His IgE levels to peanut extract and peanut components were almost unchanged (including Ara h 6 and Ara h 9, <0.35 kU_A/L) at challenge compared with those at the time of inclusion.

The second study subject (subject 2) had grade I anaphylaxis after ingesting peanut before our study. He underwent a

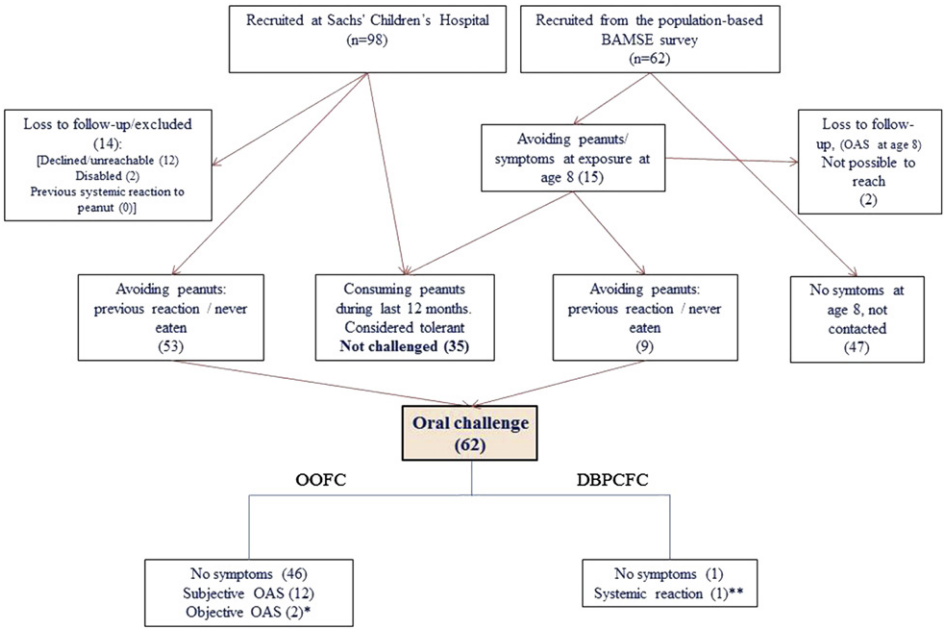


FIG 1. Flow chart of 160 children recruited from 2 different sources who were initially sensitized to Ara h 8 (≥0.35 kU_A/L) but not to Ara h 1, Ara h 2, or Ara h3 (<0.35 kU_A/L), of whom 62 underwent oral challenge. *Urticaria in perioral eczema/redness in soft palate. **See Table III.

TABLE I. Characteristics of children included, both challenged and not challenged, from 2 different sources (n = 160)

Characteristic	Sachs' Children's Hospital, challenged (n = 53)	Sachs' Children's Hospital, not challenged (n = 45)	BAMSE survey, challenged (n = 9)	BAMSE survey, not challenged (n = 53)
Male, no. (%)	29 (55)	27 (60)	4 (44)	25 (47)
Age (y), median (range)	11 (5-19)	13 (5-18)	15 (14-17)	NA (8-y follow-up)
Doctor's diagnosis				
Asthma, no. (%)	39 (74)	31 (69)	6 (67)*	16 (30)*
	$P = .61$		$P = .057$	
Hay fever, no. (%)	50 (94)	41 (91)	3 (33)*	25 (47)*
	$P = .54$		$P = .49$	
Eczema, no. (%)	32 (60)	17 (38)	3 (33)*	15 (31)*,†
	$P = .026$		$P = 1.0$	
Food allergy other than nuts,‡ no. (%)	16 (30)	8 (18)	6 (67)*	3 (6)*
	$P = .15$		$P < .001$	
Serum specific IgE (CAP [kU_A/L]), median (range) at inclusion				
Peanut	1.3 (<0.35-25)	1.6 (<0.35-6.6)	0.96 (0.27-24)	3.1 (0.46-17)
	$P = .84$		$P = .061$	
Ara h 8	9.4 (0.44->100)	14 (0.47->100)	6.45 (3.7-80)	20 (0.71->100)
	$P = .37$		$P = .13$	
Birch pollen	57 (0.67->100)	83 (1.6->100)	61 (33->100)	>100 (12->100)
	$P = .42$		$P = .51$	
Serum specific IgE (CAP [kU_A/L]), median (range) at challenge (3 missing values)				
Peanut	2.2 (<0.35-29)	NA	1.73 (0.53-39.9)	NA
Ara h 8	9.0 (<0.35->100)	NA	6.72 (5.0-55.7)	NA
Birch pollen	43.6 (2.0->100)	NA	50.5 (15.5->100)	NA
Previous reaction to peanut reported, no. (%)	8 (15)	NA	4 (44)	NA
Never had peanut, no. (%)	39 (74)	NA	5 (56)	NA

NA, Not applicable.
*Status at 8 years of age for comparison.
†Four missing values.
‡Here defined as peanuts and nuts.

DBPCFC and reacted to the last dose with lip swelling, stomach cramping, and objective tiredness (Table III). IgE levels before and at challenge are displayed in Table III. At the time of the challenge, his IgE level to peanut extract was 8.8 kU_A/L, whereas the level at the time of previous testing 9 months earlier was 1.5 kU_A/L.

TABLE II. Characteristics of children with and without symptoms among those who underwent open challenges

Characteristic	No symptoms (n = 46)	OAS symptoms (n = 14)	*P* value
Serum specific IgE (kUA/L), median (range) at challenge (3 missing)			
Peanut	2.24 (<0.35-40)	1.45 (<0.35-29)	.39
Ara h 8	10.4 (<0.35-61)	5 (<0.35-62)	.28
Birch	50.5 (2.3->100)	29 (2->100)	.26
Age (y), median (range)	13 (5-19)	9 (6-18)	.17
Male sex, no. (%)	25 (54)	6 (43)	.45
Doctor's diagnosis			
Asthma, no. (%)	33 (72)	11 (79)	.61
Hay fever, no. (%)	38 (83)	13 (93)	.35
Eczema, no. (%)	25 (54)	9 (64)	.51
Other food allergy, no. (%)*	14 (30)	7 (50)	.18

*Milk, egg, fish, wheat, or soy allergy.

TABLE III. Characteristics, IgE levels (kU_A/L), and symptoms of a 9-year-old boy (study subject 2) who underwent DBPCFC because of previous suspected grade I anaphylaxis

Challenge							DBPCFC
Sex/age (y)							Boy/9
Sachs' patient/BAMSE							Sachs
Tasted peanut							Yes
	f13	**Ara h 1**	**Ara h 2**	**Ara h 3**	**Ara h 6**	**Ara h 8**	**Ara h 9**
Peanut IgE level before inclusion	<0.35	<0.35	<0.35	<0.35	ND	1.7	ND
Peanut IgE level 9 mo before challenge	1.5	<0.35	<0.35	<0.35	0.45	14	<0.35
Peanut IgE level at reanalysis 1 mo before challenge	8.8	<0.35	<0.35	<0.35	0.45	14	ND
Symptoms at previous exposure	Age 4 y; oral tingling, unilateral conjunctival swelling, stomach pain, tiredness						
Symptoms at challenge	Lip swelling, stomach cramping, tiredness						

ND, Not determined.

DISCUSSION

Studies with the new technique of analyzing IgE levels to peanut allergen components separately have suggested that IgE sensitization to Ara h 2 is a marker of genuine peanut allergy,[3,4,7] whereas IgE sensitization to Ara h 8 is a marker of a mild reaction, if any.[4,6,17,26] We tested this suggestion through oral peanut challenge of patients with an isolated Ara h 8 sensitization. Of the 144 children in this study with IgE levels of 0.35 kU_A/L or greater to Ara h 8 but with IgE levels to Ara h 1, Ara h 2, or Ara h 3 of less than 0.35 kU_A/L, 143 (99.3%) either already consumed peanuts or passed an OOFC with peanuts without any systemic symptoms at the highest dose. Furthermore, we found no association between OAS at the time of the challenge and the level of IgE to birch pollen, which has been shown by others.[27,28] Thus it is tempting to assume that patients with isolated IgE to Ara h 8 can safely consume peanuts. However, within the timeframe of our study, we challenged 3 boys (2 in the present study [subjects 1 and 2] and 1 outside the study, see below) with isolated Ara h 8 sensitization at a first viewing, all of whom experienced systemic reactions.

By mistake, study subject 1 was challenged during the birch pollen season despite ongoing pollinosis, after which his symptoms worsened. At a DBPCFC outside the pollen season, he did not show symptoms. Thus oral challenges should not be performed in patients with ongoing allergic reactions, which is in accordance with a recent article showing that anaphylaxis to foods was more common during the pollen season among patients with pollen allergy.[29]

Some relevant allergen components might not yet have been recognized. An unidentified component appears likely to have been involved in study subject 2. Five years before this study, he had grade I anaphylaxis at exposure to peanut, and in the present study he had anaphylaxis again. His IgE level to peanut extract increased from 1.5 to 8.8 kU_A/L during a 9-month period before challenge with peanuts, and the increase could not be explained by a corresponding increase in IgE levels to Ara h 1, Ara h 2, Ara h 3, Ara h 6, Ara h 8, or Ara h 9.

Before the start of the study, another patient had anaphylaxis at peanut challenge.[30] He did not follow the study protocol because he was participating in a pilot investigation for this study. After the final dose of 10 g of peanut at challenge, he experienced grade II anaphylaxis. At retesting, his IgE level to Ara h 6 was 24 kU_A/L, whereas the test result was negative to Ara h 2. No increase in IgE levels to other peanut allergen components was observed. However, his IgE level to peanut extract increased from 6.3 to 12 kU_A/L during a 9-month period preceding peanut challenge. We assumed that the increase in the IgE level to Ara h 6 was responsible for his systemic reaction.[30]

Our results suggest that patients with an isolated Ara h 8 sensitization are highly unlikely to experience a systemic reaction to peanut. Nevertheless, the fact that 3 patients described above experienced systemic reactions at peanut challenge raises the question of whether an isolated IgE sensitization to Ara h 8 in rare cases and circumstances can cause systemic reactions at exposure or whether these subjects were not truly monosensitized to Ara h 8 but additionally sensitized to other peanut determinants.

To our knowledge, few studies have addressed the effect of IgE sensitization to Ara h 8 in relation to systemic reactions after oral challenge. The article by Mittag et al[17] showed that among a group of patients older than ours with isolated Ara h 8 sensitization, none had an objective systemic reaction at challenge. In contrast, it has been reported that patients sensitized to the Bet v 1 homologous soy allergen Gly m 4 might experience anaphylaxis on drinking a large amount of soy milk.[31-34] Nothing corresponding to the rather severe reactions reported after exposure to soy milk (which might take place when IgE to Gly m 4 from soy is present) has ever been described, to our knowledge, at peanut exposure in relation to high IgE levels to Ara h 8 in the absence of primary sensitization to peanut.

The children included in this study were recruited from 2 different sources, allergic patients and a population sample, and the study population was therefore not homogeneous. The fact that the outcomes did not differ between the 2 groups demonstrated that our results are widely applicable, and it was not considered meaningful to perform separate or comparative analyses of the 2 inclusion groups.

In summary, a previous history of a systemic reaction at exposure should always be taken into consideration when assessing the risk of experiencing a systemic reaction at challenge, irrespective of IgE test results, because all peanut proteins related to IgE-mediated reactions might not yet have been identified and characterized. The only patient in this study who displayed a systemic challenge reaction had a history of

anaphylaxis at a previous exposure to peanut, and his IgE levels to peanut extract had increased without a corresponding increase in Ara h 8 IgE levels before challenge. Thus when IgE levels to peanut increase over time, it is likely of clinical importance. In peanut-sensitized children symptoms at exposure can vary from none to death.[6,35] Our study suggests that in more than 99% of cases, exclusive IgE sensitization to Ara h 8 is completely harmless. Therefore we propose that component-resolved diagnostics might facilitate the differentiation between different phenotypes of peanut-sensitized patients. Because we also included children from a population-based birth cohort, the results are likely transferable to that population.

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Clinical implications: Isolated Ara h 8 sensitization seems to indicate peanut tolerance. Peanuts can be carefully introduced at home in children with such sensitization. However, as yet unidentified determinants can rarely induce sensitization and symptoms.

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