
Resolution of childhood peanut allergy

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Background: Peanut allergy creates great fear in many families because it is one of the leading causes of fatal and near-fatal food-induced allergies.¹ Earlier reports suggested that peanut allergy was life-long, but a recent study described resolution of peanut allergy in some children.

Objective: Tolerance to peanut allergy in childhood was studied. Examination of the natural history of childhood peanut allergy was explored.

Methods: A retrospective review of all children with peanut allergy seen at the Children's Hospital of Philadelphia in a 3-year period ($n = 293$). Children with histories of peanut allergy were challenged at the mean age [3.8 years; range 1.5 to 8 year] which was 1.8 years [range: 0.5 to 6.8 years], following their last known clinical reaction. Food allergy or tolerance was confirmed by open challenges.

Results: Thirty-three patients with histories of peanut allergy and a positive skin test to peanut underwent oral challenges. Not one patient ($n = 5$) with a history of peanut anaphylaxis developed tolerance to peanuts. In comparison, 9 of 17 patients with history of urticaria upon ingestion to peanuts developed tolerance. Also, 4 of 10 patients with flaring of their atopic dermatitis upon ingestion to peanuts developed tolerance. The 14 patients with a negative challenge to peanut had a significantly smaller wheal and flare reaction than the 19 patients with positive challenges. Tolerance to peanut was documented by a positive challenge reverting to a negative challenge in one patient. Oral challenge of 13 additional patients with positive skin tests and histories of only refusing to eat peanut resulted in 5 (39%) positive challenges.

Conclusion: A selected group of peanut-allergic children, who do not have a history anaphylaxis to peanut, may develop tolerance to peanuts.

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INTRODUCTION

Peanut allergy creates great fear in many families because it is one of the leading causes of fatal and near-fatal food-induced allergies.¹ A random telephone survey of self-reported peanut allergy in the general US population is estimated at 0.6%.⁴ This is similar to the rate of clinical reactions (0.5%) in a study from the Isle of Wight which followed children from birth to age 4 years.⁵ The latter study also recorded a positive skin test rate to peanut of 1.0%, reflecting the discordance between sensitization and clinical reactivity for food allergies. This difference may be due to the fact that

skin tests have a significant false positive rate. As peanut is becoming more common in the diet, peanut allergy is being observed in earlier ages,^{6,7} creating additional problems. Furthermore, peanut allergy is also seen in very young children due to sensitization in utero and infancy via breast milk.^{6,8}

Despite the impact of peanut allergy, the natural history of peanut allergy is unclear. Peanut allergy, like tree nut and shellfish sensitivities, was thought to be life-long, but few longitudinal studies have been described.^{2,9} In contrast, the natural history of milk and egg allergy has been described in longitudinal studies. Tolerance may develop in approximately 80% to 85% of children with milk allergy by 3 years of age¹⁰ and in children with egg allergy by 5 years of age.¹¹ For peanut allergy, an early report by Bock et al² suggested that peanut allergy was life-

long; however, a recent study by Hourihane et al³ described resolution of peanut allergy in some children. Hourihane examined 15 “resolvers” and 15 “persisters” for peanut allergy matched for age and sex from among 120 challenges. The two groups were similar in many aspects including age of initial reaction, type of reaction, and both total and allergen-specific IgE. Some differences existed between the groups. Resolvers had fewer additional food allergies and smaller positive skin tests when compared to the persisters.

Hourihane and colleagues pointed out a major limitation of their study. Some of the patients in their resolver group may have not been allergic since no patients were identified with both an initial positive challenge followed by a negative challenge. We will describe our experience with resolution of peanut allergy, including resolution documented by a positive challenge reverting to negative.

METHODS

We undertook a retrospective chart review of all patients seen in the Allergy Section at The Children's Hospital of Philadelphia for peanut allergy over a 3-year period. Characteristics of the patients were compared including the results of open food challenges performed to confirm clinical sensitivity. All patients with peanut allergy were offered an open challenge to confirm their diagnosis.

Open food challenges were performed by starting at 0.15 mL. The administered dose was doubled every 15 to 20 minutes until 15 mL of peanut butter was reached or the patient reacted. The positive endpoints were defined as anaphylaxis (eg, multi-organ systemic reactions), lower respiratory symptoms, vomiting, systemic hives, or flaring of atopic dermatitis within 2 hours of the last dose. Hives that could be due to contact with the food, such as

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on the face or hands, were not considered positive. The challenges were done from 1 month to 5½ years after the initial evaluation.

Skin testing was performed by the prick method using commercial extracts (Bayer Laboratories, Spokane, WA; Greer Laboratories, Lenior, NC) and bifurcated needles. All skin tests were done at the initial evaluation of the patient. Reactions were recorded in millimeters of the largest diameter of the wheal and flare. A wheal of 3 mL greater than the negative control accompanied by a flare was considered positive. The positive control was 10 mg/mL of histamine dihydrochloride.

Collection of patient data was in compliance with the Institutional Review Board of The Children’s Hospital of Philadelphia.

RESULTS

Patient Characteristics

Among the 293 patients with clinical histories suggestive of peanut sensitivity and positive skin test reactions, 46 patients underwent peanut challenge. Among the 46 children, 33 had clinical histories suggestive of an immediate hypersensitivity reaction to peanut prior to the first evaluation and a positive skin test to peanut. An additional 13 patients were challenged due to a clinical history of persistently refusing to eat peanuts and a documented positive peanut skin test. Challenge results for the group of 33 patients with im-

mediate hypersensitivity reactions revealed 19 patients who persisted with positive challenge (PC) and 14 patients who had a negative challenge (NC) despite positive skin tests. Results of challenges in the 13 additional patients with histories of refusing to eat peanuts revealed 8 NC and 5 PC patients.

Many characteristics were not significantly different among the PC and NC patients with immediate hypersensitivity reactions (Table 1). Patients who evolved from a PC to NC were classified as NC patients for analysis. Both groups had equivalent backgrounds of atopic dermatitis and family atopy (Table 1). Both groups showed a high prevalence of atopy and family history of atopy, although asthma and allergic rhinitis were more common in the patients with persistent sensitivity (Table 1).

Neither NC nor PC groups had significant differences in distribution of other food allergies including milk, egg, and other legumes (Table 1). Other food allergies were documented based on either a clear history of anaphylaxis or positive food challenge. Milk allergy was the most common food allergy seen in either group. Both NC (2/14) and PC (4/19) groups had a similar number of patients with multiple food allergies. Tree nut allergy was seen in 1 NC and 3 PC patients.

Negative challenge and PC groups had a similar age of initial reaction to peanut (NC: 1.83 ± 1.34 years and PC:

1.65 ± 0.99 years) (Table 2). The longest interval from age of first clinical reaction to challenge performed was 6.8 years. There was no significant difference in the mean interval length between reaction to challenge in either NC: 1.77 ± 1.44 years or PC: 1.83 ± 1.60 years groups (Table 2). In the group of 46 challenged patients, there were no reports of accidental exposure to peanuts. This is in contrast to the remaining 247 peanut-allergic non-challenged patients when there was accidental exposure rate of 15.4% (38 patients).

Among the NC patients, 9 of 14 had only a clinical history of urticaria after peanut ingestion; 1 of 14 had lower airway symptoms; and 4 of 14 patients had a flare of their atopic dermatitis upon ingestion of peanuts. The PC group had a similar profile: 8 of 19 patients had urticaria and 6 of 19 patients had a flare of atopic dermatitis. A significantly larger percentage of the PC patients (5/19) had anaphylaxis as an initial reaction compared with none of the NC patients (Table 3).

The size of the skin test reactions differed significantly between the two groups. The PC patients had significantly larger mean wheal and flare diameters at initial evaluation (Table 4). Although there was a large overlap in the range between the PC and NC patients, a wheal greater than a 20-mm diameter and flare greater than a 35-mm diameter was not seen in any NC patients.

“Refusal to Eat” Peanut Subgroup
In the “refusal to eat” group of 13 patients with positive skin tests, challenges revealed clinical sensitivity in 5 patients. The symptoms noted in positive challenges ranged from urticaria to anaphylaxis. All patients with PC and 7 of 8 NC patients had histories of other food allergy. Similar to patients with immediate hypersensitivity reactions, the NC patients had smaller wheal (7.1 ± 4.1 mm) and flare (21.6 ± 6.5 mm) on skin testing compared with PC patients (wheal: 15.6 ± 13.6 mm, flare: 42 ± 16 mm). In this PC group only the flare (P = .01) but

Table 1. Characteristics of Patients with Immediate Hypersensitivity Reactions that Had Challenge Procedures

	Negative Challenge (n = 14)	Positive Challenge (n = 19)	P
Atopy			
Atopic dermatitis	10 (71%)	13 (68%)	.86
Asthma	6 (43%)	13 (68%)	.15
Allergic rhinitis	3 (21%)	9 (47%)	.13
Family history of atopy	9 (64%)	13 (69%)	.58
Other food allergy			
Milk	4 (29%)	4 (21%)	.89
Egg	2 (14%)	3 (16%)	.91
Tree nuts	1 (7%)	3 (16%)	.47
Other legumes	2 (14%)	3 (16%)	.91
Other foods	1 (7%)	3 (16%)	.47
None	6 (43%)	7 (37%)	.74

Table 2. Time of Initial Clinical Peanut Reaction

	Negative Challenge n = 14	Positive Challenge n = 19	P*
Age of reaction			
Mean $\pm$ SD	1.83 $\pm$ 1.34 years	1.65 $\pm$ 0.99 years	.59
Range	6 months to 5 years	4 months to 5 years	
Age at challenge			
Mean $\pm$ SD	3.69 $\pm$ 2.0 years	4 $\pm$ 1.74 years	.72
Range	1.5 to 8 years	1.5 to 6.5 years	
Time from initial reaction to challenge			
Mean $\pm$ SD	1.77 $\pm$ 1.44 years	1.83 $\pm$ 1.60 years	.68
Range	0.5–6.8 years	0.5–4 years	

* P value based on Student's *t* test on means.

Table 3. Presentation of Clinical Symptoms of all Patients Undergoing Peanut Challenges

Clinical Reaction	Negative Challenge (n = 14)	Positive Challenge (n = 19)
Immediate hypersensitivity Symptoms		
Urticaria	9 (64%)	8 (42%)
Atopic dermatitis	4 (29%)	6 (32%)
Lower airway symptoms only	1 (7%)	0 (0%)
Anaphylaxis	0 (0%)	5* (26%)
Refused to eat peanut presentation	8	5

* P < .05 positive versus negative challenge groups.

Table 4. Skin Test Reactivity in Challenge Patients with Immediate Hypersensitivity Reactions

	Negative Challenge (n = 14)	Positive Challenge (n = 19)
Skin test size		
Wheal		
Mean $\pm$ SD	5.8* $\pm$ 5.4 mm	13 $\pm$ 7.1 mm
Range	3–20 mm	3–28 mm
Flare		
Mean $\pm$ SD	14.4* $\pm$ 9.1 mm	33 $\pm$ 12 mm
Range	4–35 mm	15–50 mm
Age at initial skin test		
Mean $\pm$ SD	2.08 $\pm$ 1.81 years	1.85 $\pm$ 1.66 years
Range	0.85–6.12 years	0.47–6.43 years

* P < .005 positive versus negative challenge groups.

not the wheal (*P* = .12), was significantly larger.

Development of Tolerance in Peanut Allergy

True tolerance to peanut was documented with a positive challenge reverting to negative. The patient had a positive challenge at 5 years of age followed by a NC 1 year later. His initial clinical reaction was a flare of atopic dermatitis at 6 months of age.

His first challenge resulted in the development of hives on his chest after ingestion of a cumulative dose of 9 mL of peanut butter. On the subsequent challenge, he was able to eat 30 mL of peanut butter without any reactions. He has had no noted reactions to peanut butter ingestion since his negative challenge during a 3-year follow-up. His skin test size was a wheal of 8 mm and a flare of 18 mm at initial evalua-

tion. He has a personal history of asthma and a parent with allergic rhinitis.

A second example of tolerance to peanut was the conversion from a positive skin test to peanut to negative. The female patient's clinical reaction was hives after eating only peanut butter at 1 year of age with a documented positive skin test with a wheal of 5 mm and a flare of 18 mm. After 2½ years, she had a negative skin test. The resolution of peanut allergy was confirmed in an open challenge. She has a history of asthma but no family history of atopy.

A third patient also showed conversion from a positive to negative skin test after an interval of 5½ years. The initial clinical reaction was facial swelling and wheezing after eating peanut butter at 8 months of age with a documented positive skin test (wheal of 3 mm and flare of 16 mm) upon evaluation at 2.5 years of age. The patient had a second exposure to peanut at 2 years with urticaria. The skin test at 8 years of age was negative. (This patient was not included in the analysis since he has not been challenged.) The patient has a history of asthma and his brother has food allergy.

DISCUSSION

Peanut allergy is a major problem in childhood, which has been thought to be life-long. New data from Hourihane's retrospective review³ along with our study indicate that some early onset patients with peanut allergy can become tolerant within the first decade of life. As in our study, the "reverters" in the Hourihane study had smaller skin test reactions; however, they found no difference in the initial type of reactions between the two groups. This contrasts with our finding that patients with anaphylaxis were less likely to have resolution of their peanut allergy.

In both studies, some of the NC patients presenting with a only clinical history may not have had true peanut allergy since false positive skin tests are very common in food allergy.^{5,12} However, all 33 patients with immediate hypersensitivity reactions discussed above had a very clear history of peanut reaction. Their history showed im-

mediate hypersensitivity reactions from seconds to 2 hours after ingestion of peanut only without other food exposure.

Double-blind placebo-controlled food challenges are considered the gold standard to document food allergy. The concern with open challenges is that patients or physicians may interpret the results giving false positive results. In our open challenge procedures, we picked specific endpoints that were not subjective and could not be generated by contact with the food. The positive endpoints of systemic urticaria (not including the mouth and hand), flaring of atopic dermatitis, vomiting/diarrhea, lower respiratory systems or anaphylaxis should eliminate most false positives. It is possible for some false negative reactions (ie., "abdominal pain") to exist due to the strict criteria for a positive challenge. This is unlikely, as no patients with negative challenges have reported new symptoms after 1 to 6 years of follow-up.

We selected 46 patients out of 289 patients with a history of peanut allergy whose family agreed to a challenge. Many families with more severe reactions did not agree to peanut challenges, skewing the challenged patients to a milder phenotype.

Characteristics of patients with peanut allergy are similar to previous studies.^{4,5,13} Similar to Rance et al, the most common reaction involved the skin as flares of atopic dermatitis or urticaria. Family and personal histories of atopy were common in this group. History of egg allergy was a risk factor for peanut allergy in the study of patients on the Isle of Wight.⁵ Similar to our study, egg allergy was a common food allergy in both groups of patients (NC and PC). In our population, milk allergy was the next most common food allergy in both NC and PC patients. Egg and milk allergies are two of the most common food allergies seen in many large scale surveys consistent with our observations in this select population.²

Similar to many studies including Hourihane, we found larger wheal and

flare on percutaneous testing in our patients with persistent symptoms.³ The measurements of wheal-and-flare were taken at the largest diameter, which can lead to larger wheal-and-flare values compared with taking the mean of orthogonal measurements.

Another important point demonstrated in this study is that refusal to eat food can be a sign of food allergy. For 13 patients who refused to eat peanuts and who had positive skin tests, 38% were documented to have clinical sensitivity by a positive challenge. It is possible that the patients had been avoiding this food since they knew it would make them sick. This is not an uncommon occurrence in patients with food allergy, but its basis remains unknown and not well tested.

Together, these studies demonstrate that selected peanut-sensitive patients can become tolerant. We identified a patient who confirmed this potential by direct challenges. A potential indicator of the possibility to revert or become tolerant may be the size of the initial wheal-and-flare. Additional studies are needed to confirm these and identify other parameters that predict which patients will become tolerant and which will not. Both increased patient acceptance of challenge procedures and longer term studies are needed to determine more accurately the total proportion of patients who may outgrow their immediate hypersensitivity reactions to peanut proteins.

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