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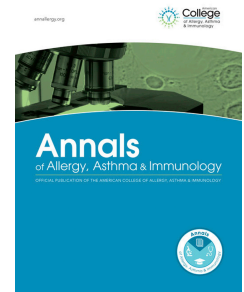
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Title: Review of 400 Consecutive Oral Food Challenges to Almond

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IgE: Immunoglobulin E
OFC: Oral food challenge
sIgE: Food-specific IgE
SPT: Skin prick test

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ABSTRACT

BACKGROUND: Diagnosis of almond allergy is complicated by a high rate of false positive test results. Accurate diagnosis of almond allergy is critical as almond is a source of nutrition and milk products for children with other food allergies.

OBJECTIVES: We reviewed the outpatient almond oral food challenges (OFCs) performed at our institution to analyze the pass rate and identify variables that predict OFC outcome.

METHODS: We reviewed all almond OFCs performed at our pediatric, university-based outpatient practice between October 2015 and July 2017. OFC details, including dosing, reactions, and treatments, as well as demographic, clinical, and laboratory data were compiled. Statistical analysis was performed using the Fisher's exact and student *t*-tests.

RESULTS: We identified 400 patients who underwent consecutive almond OFCs. Of these, 375 passed (93.8%, median sIgE 1.41 kU_A/L, mean SPT wheal 3.23 mm), 16 failed (4.0%, sIgE 2.54 kU_A/L, SPT 5.0 mm), and 9 were indeterminate (2.3%, sIgE 3.33 kU_A/L, SPT 5.0 mm). Among children who reacted, pruritus was the most common symptom. Only two children had reactions that required epinephrine. There was no difference in demographics or allergic comorbidities between those who passed and failed.

CONCLUSIONS: Among patients in our cohort, the probability of passing an almond OFC was 94%. Although higher almond sIgE level and SPT wheal size correlated with OFC failure, the pass rate remained >95% for patients with sIgE up to 10 kU_A/L and SPT wheal size up to 5 mm. Among the patients who had a reaction to almond, anaphylaxis was uncommon. Our data support that performing outpatient OFCs to almond is safe for select patients.

INTRODUCTION

Almond (*Prunus dulcis*) is one of the most consumed tree nuts in the United States. Almonds are a healthy source of protein and can be an important milk product for children with other allergies. Unfortunately, allergy to almond is the third most commonly reported tree nut allergy in the United States, and ~~there is great interest in allergy to tree nuts as the prevalence~~ appears to be increasing in recent years.¹ Tree nuts are also one of the most common causes of fatal anaphylaxis,^{1,2} although it has been reported that the rate of moderate to severe reactions to almond may not be as high as to other tree nuts, such as cashew, pistachio, pecan, and walnut.³

The diagnosis of almond allergy is complicated by a high rate of false positive results. It has previously been observed that the sIgE to almond correlates poorly with oral food challenge (OFC) outcome.⁴ A recent study from Israel on tree nut allergy found that among 83 patients recruited due to suspicion of tree nut allergy, only 1 patient was reactive to almond despite 49 (59%) patients demonstrating sensitivity to this food.⁵ Cross-reactivity between almond and birch appears to make a partial but incomplete contribution to this phenomenon.^{6,7} Given the prevalence of reported allergy to almond and the potential benefits of incorporation of almond into the diet when safe, allergists are keen to differentiate between patients with true clinical reactivity to almond and those who appear sensitized but are able to tolerate this food. Prior studies of patients with allergies to tree nuts have suggested that the majority of patients ~~diagnosed with an allergy~~ sensitized to almond may prove tolerant to almond in the diet.^{5,8,9} This appears to be an exception in contrast to other tree nuts. However, the data remain limited.

Our experience at a single institution has been that the majority of patients who undergo OFC to almond are able to pass and successfully introduce almond into the diet at home. As

such, it was decided to formally examine the OFCs to almond performed at our institution to determine the pass rate and identify any predictive variables.

METHODS

The electronic medical record was reviewed to identify all patients who underwent OFC to almond between October 2015 and July 2017 at the Elliot and Roslyn Jaffe Food Allergy Institute at the Icahn School of Medicine at Mount Sinai, a pediatric, university-based outpatient practice. Patients were referred for open OFC by our allergists on the basis of their clinical impression. No cut-off age, sIgE value, or SPT wheal size [performed with commercial almond extract (Greer Laboratories, Lenoire, NC)] precluded challenge. Typically these patients did not have a history of recent objective allergic symptoms upon ingestion of almond, and the likelihood of a positive reaction was thought to be less than 50% based on the provider's clinical experience. The OFCs were performed per published guidelines, with most challenges using doubling doses every 15 minutes until an age-appropriate serving size was ingested.¹⁰ Although there was some variation for individual patients based on appropriate serving size for age or patient willingness to eat a particular form of almond, a typical OFC for a child involved four servings of almond butter in the following increments: 0.5 teaspoon, 1 teaspoon, 2 teaspoons, and 2.5 teaspoons.

Each chart was reviewed for demographic, clinical, and laboratory information relevant to food allergy and other allergic diseases. When reviewing this information, sensitization was defined as sIgE value >0.35 kU_A/L or SPT wheal size 3 mm greater than the negative control. The details of the almond OFC including dosing, any reported symptoms or signs of a reaction, any required treatment, and the physician determination of the OFC outcome were noted. The

OFC outcome was reported as negative (passed), positive (failed), or indeterminate (insufficient information to make a determination). OFCs were generally deemed indeterminate due to failure to ingest a sufficient quantity of almond or confounding concurrent illness/symptoms. OFCs were typically considered failed in the setting of objective symptoms of an IgE-mediated allergic reaction or persistent/bothersome subjective symptoms.

This study was approved by the Institutional Review Board, IRB #17-02222. Given the retrospective nature of the research, a waiver of consent was granted.

Statistical analysis was performed using the student t-test for continuous variables and the Fisher's exact test for bivariate data. In the figure, sIgE levels are depicted using a logarithmic scale (base 10).

RESULTS

In total, 400 patients underwent almond OFC during the period of interest. Of these, 375 OFCs were negative (94%), 16 were positive (4%), and nine were indeterminate (2%).

In comparing children with negative OFCs and positive OFCs, demographic, clinical, and laboratory data were examined. The characteristics of each group are presented in Table 1. There was no significant difference in sex (63% vs 69% male, $p=0.79$) or age (7.4 years vs 6.4 years, $p=0.41$). There was also no difference in reported diagnosis of other allergic diseases including atopic dermatitis and asthma. Comparing children with negative and positive OFCs, the rates of sensitization to birch (64% vs 79%, $p=0.39$), avoidance of peanut due to physician-diagnosed allergy (77% vs 88%, $p=0.53$), and avoidance of one or more other tree nuts due to physician-diagnosed allergy (96% vs 100%, $p=1.0$) were similar. Total IgE was also similar at 663 kU_A/L

and 891 kU_A/L respectively ($p=0.45$). Avoidance of cow's milk due to physician-diagnosed allergy was documented in 65 (17%) children who went on to pass the almond OFC.

Specific to almond, there was no significant difference in reported history of exposure (24% vs 44%, $p=0.13$). Most children had no history of reaction (10% vs 13%, $p=0.67$), and just two patients had a history suggestive of possible anaphylaxis to almond, both with negative OFCs. The majority of patients in both groups were sensitized to almond (94% vs 100%, $p=1.0$). Children with failed OFCs had a higher almond-specific IgE (sIgE), with a median sIgE of 2.54 kU_A/L in children who failed the OFC compared to 1.41 kU_A/L for children who passed the OFC. The mean sIgE for children with passed OFCs was 3.08 kU_A/L versus 12.1 kU_A/L for children with failed OFCs ($p=0.0001$). The range of sIgE values for children with passed OFCs was <0.10-68.0 kU_A/L and 0.53->100 kU_A/L for children with failed OFCs. The sIgE for each patient in both groups is plotted in Figure 1. The pass rates for various sIgE ranges are included in Table 2. Children with failed OFCs to almond also had a larger mean wheal size on skin prick test (SPT) at 5.0 mm compared to 3.23 mm in children with passed OFCs ($p=0.0081$). Of note, the range of wheal size in each group was similar, at 0-13 mm in children with passed OFCs and 0-12 mm in children with failed OFCs. The pass rates for ranges of wheal size are included in Table 3.

Among children with failed OFCs, reactions were generally mild. Details are included in Table 4. The most commonly reported signs or symptoms signaling OFC failure were oral pruritus ($n=7$) and skin findings including urticaria, rash, or generalized pruritus ($n=7$). Symptoms generally resolved with a dose of an antihistamine. Epinephrine was administered to two children, in both cases after the development of wheezing. Neither patient required a second dose of epinephrine, and both children were discharged home from clinic in stable condition.

DISCUSSION

Almond (*Prunus dulcis*) is a member of the Rosaceae family. Study of patients with almond allergy has revealed that almonds contain a number of potentially allergenic proteins. These include PR-10 (Pru du 1), TLP (Pru du 2), prolamins (Pru du 2S, Pru du 3), profilins (Pru du 4), 60sRP (Pru du 5), and cupin (Pru du 6, Pru du γ -conglutin).⁷ Pru du 1 includes a family of proteins that exist in various isoforms, some of which are structurally homologous to Bet v 1, the major antigen recognized by patients allergic to the birch tree. Pru du 1 proteins tend to be heat labile, although sIgE to these proteins can still contribute to oral allergy symptoms and more severe allergic reactions are rare but have been reported.¹¹ Sensitization to Pru du 3 and Pru du 6 is more strongly associated with severe reactions to almond.

Compared to other tree nuts, our group and others have noted that patients with elevated sIgE and/or positive SPT to almond are often able to pass an almond OFC. Despite the lack of commercial availability of almond components to link elevations of specific almond proteins such as Pru du 1 to birch allergy, it has been widely observed that patients with evidence of birch allergy are likely to have positive SPT or sIgE to almond but tolerate this tree nut in the diet.⁶ In patients without allergy to birch, there also appears to be a high number of patients who belong to the sensitized but non-reactive phenotype of patients.¹² Whether this is due to patient characteristics or shortcomings of our current serologic and skin tests to almond remains uncertain.

In this study, our overall pass rate for patients undergoing OFC to almond was 94%. A pass rate of greater than 95% was observed in patients with a sIgE up to 10 kU_A/L and SPT up to 5 mm. The pass rate remained high in patients with higher sIgE levels and larger wheals as well.

These data are consistent with other studies showing high pass rates among patients undergoing almond OFCs.

Prior to this report, Couch et al's review of OFCs in patients with tree nut allergy was the largest study of patients who underwent OFCs to almond.⁸ In that cohort, 54 OFCs to almond were performed. The pass rate was 100%. The majority of these patients had very favorable features, with almond SPT wheal size < 3mm and sIgE <2.0 kU_A/L. Elizur et al also assessed almond tolerance among patients with a suspected tree nut allergy, many of whom were sensitized to almond.⁵ Among 49 patients with SPT ≥ 3 mm to almond, 48 (98%) proved tolerant. A lower pass rate was observed for patients with peanut/tree nut allergy undergoing OFC to almond in the study by Ludman et al.⁹ Of 14 patients undergoing OFC to almond, 10 (71%) passed. Due to the small number of patients, additional analysis was not possible.

It should be noted that while this work describes the largest cohort of patients undergoing almond OFCs to date, our results represent the experience at a single academic pediatric practice and may not be applicable to all populations. Additional limitations include the lack of strict criteria for offering almond OFC regarding acceptable SPT and sIgE test results. The decision to offer OFC as well as determination of the OFC outcome was made by any of eight providers at our practice during the study period.

In summary, we report a large cohort of patients undergoing OFC to almond. The included patients had a wide range of sIgE and SPT wheal size, and the overall pass rate was 94%. Although higher sIgE and wheal size did correlate with OFC failure, the pass rate remained >95% for patients with sIgE up to 10 kU_A/L and SPT wheal size up to 5 mm. Among the patients who had a reaction to almond, anaphylaxis was uncommon, with only 2 patients developing symptoms that required epinephrine. These data generally support that almond OFC is safe for

160 select patients and that additional work is needed to improve the current testing methods for
161 patients with suspected allergy to almond.

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Figure Legend

Figure 1. Almond sIgE Scatter Plot. Scatter plot of each patient's almond sIgE in the passed and failed OFC groups.

Table 1. Comparison of Patients with Passed vs Failed OFCs. Demographic and clinical characteristics of patients with passed vs failed OFCs.

Variable	Passed OFC	Failed OFC	p value
Number	N=375 (93.8%)	N=16 (4.0%)	n/a
Sex (% male)	N=236 (62.9%)	N=11 (69%)	0.79
Average Age (years)	7.4 (range 0.6-25)	6.4 (range 2-13)	0.41
Sensitized to Almond	N=354 (94%)	N=16 (100%)	1.0
Previously Exposed	N=91 (24%)	N=7 (44%)	0.13
Previously Reacted	N=37 (10%)	N=2 (13%)	0.67
Median Almond IgE	1.41 (n=369)	2.54 (n=15)	n/a
Mean Almond IgE	3.08 (n=369)	12.1 (n=15)	.0001
Almond IgE Range	<0.10-68	0.53->100	n/a
Mean Almond SPT	3.23 mm	5.0 mm	.0081
Almond SPT Range	0-13 mm	0-12 mm	n/a
Total IgE	663 (n=205)	891 (n=10)	0.45
Birch Sensitization	N=202/315 (64%)	N=11/14 (79%)	0.39
Avoid Other Tree Nuts	N=356/370 (96%)	N=16 (100%)	1.0
Avoid Peanut	n=290 (77%)	N=14 (88%)	0.53
% Atopic Dermatitis	N=279 (74%)	N=13 (81%)	0.77
% Asthma	N=162 (43%)	N=8 (50%)	0.61
% EoE	N=7 (2%)	N=1 (6%)	0.28
Avoid Cow's Milk	N=65 (17%)	N=3 (19%)	0.74

Table 2. Pass Rate for Various Almond sIgE Ranges. Analysis of the pass rate for each range of almond sIgE including the number of patients in that range.

Almond sIgE (kU _A /L)	Number of Patients	Pass Rate
<0.35	n=55	100%
0.35-1.99	n=237	97.0%
2.0-4.99	n=95	95.8%
5.0-10.0	n=31	96.8%
>10.0	n=22	86.4%

Table 3. Pass Rate for Various Almond SPT Ranges. Analysis of the pass rate for each range of SPT wheal size including the number of patients in that range.

SPT Wheal (mm)	Number of Patients	Pass Rate
<= 5 mm	n=294	97.2%
6-8 mm	n=81	92.6%
>=9 mm	n=11	81.8%

Table 4. Features of Failed OFCs. Demographic and clinical information for patients who underwent failed OFCs to almond.

Subject	Age (years)	History of Exposure	History of Reaction	Almond sIgE (kU _A /L)	SPT Wheal (mm)	Symptoms	Antihistamine	Epinephrine
1	12	No	No	3.36	6	Vomiting, oral pruritus, throat pain, nasal congestion	Yes	No
2	13	No	No	1.88	12	Oral pruritus	Yes	No
3	2	No	No	-	5	Cough	Yes	No
4	8	Yes	No	16.7	0	Oral pruritus, lip swelling	Yes	No
5	3	No	No	1.28	6	Urticaria	Yes	No
6	3	No	No	9	9	Unwilling to eat, cough, sneezing	Yes	No
7	4	Yes	Yes	2.87	4	Urticaria	Yes	No
8	4	Yes	No	1.0	5	Oral pruritus, one hive	Yes	No
9	9	Unknown	No	>100	7	Cough, throat discomfort	Yes	No
10	13	Yes	Yes	1.66	4	Oral pruritus	Yes	No
11	8	No	No	35.8	7	Wheezing	No	Yes
12	2	Yes	No	2.68	8	Facial erythema, urticaria	Yes	No
13	4	Yes	No	1.34	5	Urticaria	Yes	No
14	8	Yes	No	0.53	0	Pruritus, agitation	Yes	No
15	4	No	No	1.09	4	Oral pruritus, cough, wheezing	Yes	Yes
16	5	No	No	2.54	6	Oral pruritus, erythema, urticaria	Yes	No

