

Cross-allergenicity in the legume botanical family in children with food hypersensitivity

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Sixty-nine patients with one or more positive prick skin tests to legumes (peanut, soybean, green bean, pea, and lima bean) were evaluated for food hypersensitivity with in-hospital oral food challenges. Of the 280 prick skin tests to legumes performed, 130 were positive. Forty-three positive food challenges occurred in 41 patients. The prevalence of legume allergy was not statistically different in those patients (N = 36) with two or more positive legume prick skin test (64% positive) compared to those patients (N = 33) with only one positive legume prick skin test (55% positive; $p > 0.10$). Even in this selected patient population, only two patients had symptomatic hypersensitivity to two legumes. Among patients with a positive prick skin test to peanut (N = 60), the mean wheal size was larger in patients with a positive versus a negative oral food challenge to peanut ($p < 0.001$). Results of oral food challenges demonstrate that clinically important cross-reactivity to legumes in children is very rare. Clinical hypersensitivity to one legume does not warrant dietary elimination of all legumes. Results of prick skin tests should not be used to determine prolonged food restriction diets. (J ALLERGY CLIN IMMUNOL 1989;83:435-40.)

Peanut and soybean are two of the most common food antigens causing hypersensitivity reactions in food-allergic children.¹ They comprise only two members of the legume food family, a large family that includes a variety of green beans, garden peas, garbanzo beans, kidney beans, lentils, black-eyed peas, and carob beans. Allergists often recommend restricting a patient's diet of all members of a food family when the patient is found allergic to any one member. Thus, if a child was found to be allergic to peanuts, the child would be placed on a diet avoiding all legumes. The theory behind this practice began in 1929 when Vaughan and Black² classified foods into bio-

Abbreviation used

DBPCFC: Double-blind, placebo-controlled, oral food challenge

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logically related food groups for allergic diagnosis, replacing the alphabetical listing that had been used previously. They believed that crossed allergic reactions would occur among related foods, as had been found with plant pollens, and cited a study by Withers done on legume-"allergic" patients. In this study, 17 of the 22 patients were diagnosed as allergic to two or more legumes, and it was concluded that multiple sensitization appeared to be the rule in the legume family. How the diagnosis of food allergy was made and other details of the study were not provided.³ In the years since the acceptance and use of the botanical classification of foods, various statements and conclusions about the frequency of cross-allergenicity within a food family have been cited in the literature. In one pediatric allergy text, Galant⁴ states that food allergens share antigenic and biologic similarities within botanical families and that allergy to one member of a plant-food family frequently results in a variable degree of allergy to other members of the same family. Thus, a patient allergic to peanut may be allergic to peas and other legumes. The collaborative publication of the National Institute of Allergy and

Infectious Diseases and the American Academy of Allergy and Immunology⁵ again states that a person allergic to peanut also is more likely to be allergic to other legumes because of common cross-reacting substances.

There are several reasons for questioning the belief that multiple food allergies within a food family are common and that the practice of eliminating whole botanical families is useful. (1) Recent studies documenting food hypersensitivity with DBPCFCs demonstrated that about 80% of food-hypersensitive children are allergic to only one or two foods.⁶ This finding is opposed to previously published series based on history, skin tests, and in vitro tests that contended that multiple food allergies were common in children.^{7,8} (2) There is no previous study with DBPCFCs to diagnose food allergies that either confirms or disputes this issue. (3) The more foods eliminated from a diet, the less likely a patient will be compliant with the dietary restrictions. Therefore, it is preferable to have as few foods as possible on the "eliminated" list so that patients will have greater ease in maintaining optimal nutrition and have more success in strictly avoiding food antigens to which they are truly allergic. In view of these issues, we decided to use in-hospital oral food challenges to study allergic cross-reactivity within a botanical food family. The legume family was chosen for the study for several reasons. The legume food group is believed to be particularly responsible for multiple food allergies, legumes are commonly ingested and have numerous members in their food family, and globally, legumes provide a major source of affordable protein (lentils, soybeans, and pinto beans). Furthermore, the unnecessary restriction of soy results in a significantly more limited and inconvenient diet, since soybean is a ubiquitous ingredient in prepared foods. In addition, soy-based drinks, yogurts, and frozen confections offer palatable alternatives for the cow's milk-allergic patient.⁹

Based on the correlation of in vitro and in vivo studies, we propose that multiple symptomatic legume-food allergies are very uncommon, despite extensive cross-reactivity observed with prick skin tests and RAST results.

MATERIAL AND METHODS

Subjects

During the past 4 years, patients being evaluated for food hypersensitivity who had positive prick skin tests to one or more of the following legumes were included in our legume hypersensitivity study: peanut, soybean, pea, green bean, and lima bean. A positive prick skin test was defined as a wheal ≥ 3 mm larger than the negative control wheal.¹⁰ Any amount of erythema without a sufficiently large wheal was recorded as negative.

Procedures

All patients were admitted to a Clinical Research Center (RR30 or RR0052) for challenge studies. Patients were asked to stop all antihistamines 7 to 10 days before admission. No patient had received oral corticosteroids during the previous month. All suspect foods were strictly eliminated from the patients' diets during the week before admission. On the day of admission, the patients had prick skin testing (1:20 wt/vol, Greer Laboratories, Lenoir, N.C.). Each patient, under observation in the Clinical Research Center, was challenged to five legume antigens (peanut, soybean, pea, green bean, and lima bean) by DBPCFC or open challenge, unless this was contraindicated by a recent "convincing" history of anaphylaxis. A patient's history was considered "convincing" only when the allergic reaction was potentially life threatening (laryngeal edema, severe wheezing, and/or hypotension), occurred immediately after the isolated ingestion of the suspect food, and required emergency evaluation and treatment. All such convincing histories occurred within 3 years of the patient's entry into the study. Legume antigens that were suspected by history to elicit symptoms irrespective of skin test results or that had not been ingested before by the patient but elicited a positive skin test, were evaluated by DBPCFC. Legume antigens to which the patient clearly was tolerant or to which the patient had a negative prick skin test (and no suggestive history) were tested by open challenge. Briefly, as previously published,¹¹ two double-blind challenges were performed each day, one containing placebo and the other containing the challenge food substance. Up to 8 to 10 gm of the dehydrated, powdered food or placebo substitute (i.e., cornstarch) was administered in opaque capsules or juice during a 1-hour period in gradually increasing doses. The specific content of each challenge was determined by the dietician using a computerized randomization program and was unknown to the patient, parents, staff, and physicians. All negative blinded challenges were confirmed by subsequent open challenges before discharge. Patients consumed a standard portion of the test food under observation.

All procedures were approved by the Institutional Review Board on Human Investigation.

Challenge interpretation

The type, severity, time of onset, and duration of symptoms were recorded during each challenge. Symptoms were categorized as follows: (1) gastrointestinal: nausea, vomiting, diarrhea and abdominal pain; (2) lower respiratory: wheeze and cough; (3) upper respiratory: nasal congestion, rhinorrhea, sneezing, tearing, and conjunctival injection; (4) cutaneous: pruritus, erythematous morbilliform rash, and urticaria; and (5) laryngeal edema: cough with "itchy throat," hoarseness, and throat clearing. The percentage of challenge substance ingested before the onset of symptoms was also noted.

Statistical analysis

Median wheal size, median IgE concentration, and median age at the time of challenge were compared in patients with positive versus negative oral food challenges to peanut

TABLE I. Legume prick skin test results in 69 patients

Antigen	PST		
	Total No.	No. Positive	% Positive
Peanut	69	60	87
Soybean	69	30	43
Pea	69	18	26
Green bean	41	9	22
Lima bean	32	13	41
Total	280	130	46

PST, Prick skin test.

or soybean with the nonparametric Wilcoxon rank-sum test for nonpaired data.

RESULTS

Eighty-two of a total of 186 patients evaluated for food hypersensitivity had one or more positive prick skin tests to legumes. Thirteen of the 82 patients were excluded from our study because oral challenges with all five legumes had not been successfully obtained. A full evaluation was not carried out in these patients primarily because of low clinical suspicion that they were allergic to legume antigens other than the antigen they had received in a DBPCFC. Only one patient in the excluded group had a positive DBPCFC, and none had a history of legume-induced anaphylaxis. The median age of the remaining 69 study patients at the time of challenge was 5 years, with a range of 1 year to 21½ years. The median IgE concentration was 3300 IU/ml, with a range of 32 to 45,000 IU/ml (normal, 5 to 620 IU/ml). Sixty-seven of the 69 patients (97%) had atopic dermatitis, and 33 of the 69 patients (48%) had the constellation of allergic rhinitis, asthma, and atopic dermatitis. Family histories were positive for atopic disease in 67 of the 69 patients (97%).

Prick skin test results

The 69 study patients with legume-hypersensitivity had 280 prick skin tests performed with legume extracts, of which 130 prick skin tests were positive. All 69 patients received prick skin tests with peanut, soybean, and pea extracts. Prick skin tests were positive to peanut in 60 patients (87%), to soy in 30 patients (43%), and to pea in 18 patients (26%). Green and lima bean extracts were applied on 41 and 32 patients, respectively. Green bean accounted for nine of the positive prick skin tests, and lima bean for 13 (Table I).

TABLE II. Challenge results in 69 patients with positive legume prick skin tests

	Patients	
	No.	%
Clinically allergic (69)		
Legumes	4/69	59
>1 Legume	2/69	3
Positive reactions (43)		
By "convincing"	14/43	
anaphylactic history*		
By DBPCFCs†	29/43	
Skin	21/29	72
Respiratory	14/29	48
Gastrointestinal	19/29	66

*Each patient had sufficient respiratory distress and/or laryngeal edema (often with cyanosis) to necessitate emergency room treatment, including subcutaneous epinephrine, intravenous fluids, and antihistamines.

†See text for description of signs and symptoms.

Oral challenge results

A total of 345 challenges were performed. All patients were challenged to five legumes (peanut, soybean, pea, lima bean, and green bean) unless this was contraindicated by a convincing history of anaphylaxis, as described in the methods. Based on positive prick skin test results and history, 91 sets of DBPCFCs and 254 open challenges were performed under observation on the clinical research unit. Among the 69 patients challenged, 43 positive reactions occurred in 41 patients. Thus, 59% of the patients had a clinical hypersensitivity reaction to at least one legume antigen. Fourteen reactions considered positive were based on a recent history of a convincing episode of peanut-induced anaphylaxis. All these patients had a markedly positive peanut prick skin test. The remaining 29 of the 43 positive reactions were determined by DBPCFC. Overall, only 5/43 reactions (12%) in the study group were confined to the skin. All open challenges and placebo-controlled challenges were negative (Table II). No anaphylactic or other serious reactions occurred during any of the challenges or prick skin testing. Thirty-three patients had one positive legume prick skin test, and 18 of these patients (55%) had symptomatic legume allergy. Thirty-six patients had two or more positive legume prick skin tests, and 23 of these patients (64%) had symptomatic legume allergy.

Only two of the 41 patients with challenge-proven legume sensitivity (5%) had clinically relevant food hypersensitivity to more than one legume. Both of

TABLE III. Correlation of positive prick skin test and oral challenge results

Antigen	Skin test positive	Challenge positive	% True positive PST	% False positive PST
Peanut	60	31	52	48
Soybean	30	10	33	67
Pea	18	2	11	89
Green bean	9	0	0	100
Lima bean	13	0	0	100
Total	130	43	33	67

PST, Prick skin test.

these individuals had a history of anaphylaxis after peanut ingestion and a positive DBPCFC to soybean. In both cases, their positive DBPCFC with soybean was relatively mild. Symptoms occurred in the first patient within 15 minutes of ingesting 100% (8 gm) of the challenge substance and were characterized by intense pruritus, cutaneous erythema, and papules on the extremities. The patient had no respiratory, laryngeal, or gastrointestinal symptoms. Symptoms occurred in the second patient 30 minutes after the challenge and consisted of generalized erythema and pruritus. The patient was nauseated but consumed 100% (8 gm) of the challenge substance. Both patients lost their clinical soybean sensitivity within 1 to 3 years after initial challenge while they were being maintained on a peanut- and soybean-restriction diet. These two patients consumed the other legume antigens without difficulty.

Peanut hypersensitivity accounted for 31 of the positive reactions (72%), whereas soybean and pea accounted for 10 (23%) and two (5%) of the positive challenges, respectively. There were no positive challenge reactions with either green bean or lima bean. Two thirds, or 87/130 positive prick skin tests, were clinically false positive; i.e., they did not correlate with clinically symptomatic food hypersensitivity, as determined by oral challenge (Table III).

In the 60 patients with a positive prick skin test to peanut, the wheal diameter was statistically greater (median, 25 mm versus 5 mm; $p < 0.001$) in the 31 children with a positive oral peanut challenge or convincing history of peanut-induced anaphylaxis than in the 29 patients with a negative oral peanut challenge. In the 30 children with a positive prick skin test to soy, there was no statistically significant difference in mean wheal diameter (median, 7.5 mm versus 4.5 mm; $p > 0.10$) when then 10 patients with a positive versus the 20 patients with a negative oral soy challenge were compared. There was no statistically significant difference in median total serum IgE concentrations (peanut positive, 3300 IU/ml versus negative,

5600 IU/ml; $p > 0.10$; soy positive, 5600 IU/ml versus negative, 3700 IU/ml; $p > 0.10$) or median age at the time of challenge (peanut positive, 5½ years versus negative, 4½ years; $p > 0.10$; soy positive, 3.8 years versus negative, 8 years; $p > 0.10$) when those patients with a positive versus a negative challenge were compared with either antigen. Statistical analysis was not performed with the other legume antigens because the number of positive food challenges was insufficient to calculate meaningful results.

DISCUSSION

The results of our study clearly demonstrate that clinically relevant cross-reactivity to legumes (i.e., manifestation of an allergic reaction after ingestion) is very rare, even in a highly selected atopic population. The incidence of food allergy in the population studied is much higher than in a general allergy practice, 60% versus an estimated 1% to 2%. Therefore, symptomatic cross-reactivity or multiple legume allergy would be expected to be even less frequent in a general allergist's office practice.

In a recent study with in vitro studies to demonstrate cross-reactivity among legumes, Barnett et al.¹² concluded that multiple food allergy within the legume family is likely to be common. They contend that their results have important implications for selection of effective hypoallergenic diets and for the diagnosis of patients with food hypersensitivity. Barnett et al.¹² support their conclusions by citing Kemp et al.¹³ Aas,¹⁴ and Hoffman and Haddad,¹⁵ all of whom concluded that RAST and prick skin testing is reliable in diagnosing food allergy. These studies did not use DBPCFC for the diagnosis of food allergy but simply demonstrated that most patients with a history of a severe reaction to food had a positive skin test or RAST against that antigen. Bock et al.,¹⁶ May,¹⁷ Sampson,¹⁸ and Atkins et al.,¹⁹ all found that history was unreliable in the diagnosis of food allergy and that most positive prick skin test and RAST results are clinically insignificant. These investigators con-

clude emphatically that DBPCFCs are needed to make an accurate diagnosis of food allergy. The reason results of positive prick skin tests and in vitro measurements of IgE lack specificity in diagnosing food allergy has never been clearly elucidated, but in view of this fact, it is not surprising that our findings contrast sharply with those of Barnett et al.¹² We conclude that because of clinically insignificant allergenic cross-reactivity, prick skin tests and RAST should not be used without challenge results when food restriction diets are being determined.

Interestingly, the prevalence of legume allergy was not statistically different in those patients with legume skin test cross-reactivity (i.e., those patients with two or more positive legume prick skin tests) compared to those patients with a single positive legume prick skin test. In the 33 patients with only one positive legume prick skin test, their positive prick skin test was a more specific indicator of clinically relevant legume food allergy, as 55% of these positive prick skin tests were true positive. The 36 children who demonstrated legume skin test cross-reactivity had a total of 97 positive legume prick skin tests, of which only 26% were clinically relevant. These results are in agreement with previous published data²⁰ that concluded that prick skin tests are very sensitive and have excellent negative predictive value (i.e., if the skin test is negative, then the patient does not have IgE-mediated food allergy to that antigen) but have poor specificity and positive predictive value.

In-hospital oral challenges are time intensive and expensive, but currently, this method is the "gold standard" for diagnosing food hypersensitivity. Investigators must continually ask if differences exist between the positive and negative challenge groups in hope of defining reliable criteria or tests that could replace oral food challenges. In our study, those children with symptomatic peanut hypersensitivity had a statistically larger peanut prick skin test wheal compared to nonsymptomatic patients with a positive peanut prick skin test. Unfortunately, on an individual basis, the mean diameter of a peanut prick skin test wheal cannot be used to determine clinical sensitivity because of significant overlap in wheal size between the positive and negative challenge groups.

Allergists often are hesitant to perform prick skin testing on patients with a history of anaphylaxis to the implicated food or antigen.²¹ In our study, the 14 children with a convincing history of severe peanut-induced anaphylaxis were all prick skin tested with peanut antigen, and all the children received oral challenges with the remaining legumes. All 14 patients had markedly positive peanut prick skin tests, and yet none experienced any serious untoward reaction after

skin testing or oral challenge with the other legumes. However, it must be reemphasized that DBPCFCs should not be performed to a food antigen that provoked a recent, clear-cut, life-threatening anaphylactic reaction. In our *pediatric* patient population, a history of peanut anaphylaxis is not a contraindication to prick skin testing with peanut antigen or oral challenges with other legume antigens. It must be emphasized that our skin testing was done exclusively by the prick technique (whereas most anaphylactic reactions to skin testing have been the result of intradermal skin testing) and that no adults were included in our study.

In conclusion, clinical hypersensitivity to one legume does not warrant dietary elimination of the entire legume food family unless hypersensitivity to each antigen is individually confirmed by blinded oral challenges. We have found multiple symptomatic legume sensitivities to occur in only 5% of our select population of legume-reactive children. These children both lost their clinical sensitivity to the second legume and safely received their skin tests and other legume oral challenges. Appropriate diagnosis of food allergy will greatly decrease the number of patients who are to receive unnecessary restriction diets. Our study contradicts claims that clinically relevant intrabotanical cross-reactivity is common in the botanical family most frequently incriminated as being responsible for multiple allergies. In evaluation of >200 children with DBPCFCs, clinically relevant cross-reactivity is equally infrequent in other botanical and intraspecies families. (At the present time, we have insufficient data in our pediatric population to comment on the clinically relevant cross-reactivity of tree nuts, fish, and shellfish. Extensive cross-reactivity still should be considered a factor in these foods until new data are forthcoming.) Therefore, we believe that the practice of individually challenging each suspect antigen should be generalized to all food groups (with the exceptions noted). Following these suggestions will vastly improve patient compliance, life-style, and ease in following a nutritionally complete diet while the patient is receiving a less limited restriction diet.

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