

# Food hypersensitivity in two groups of children and young adults with atopic dermatitis evaluated a decade apart

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There is an impression that children today are experiencing allergic reactions to an increasing variety of foods. We compared two separate groups of children and young adults with atopic dermatitis evaluated a decade apart and found no difference in sensitization rates or overall clinical reactivity to a variety of foods. Allergies to egg, milk, wheat, soy, peanut, tree nuts, and seafood continue to account for  $\approx 90\%$  of food-allergic reactions over the past decade.

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Food allergy affects 33–37% (1–3) of children with moderate-to-severe atopic dermatitis (AD). Studies performed more than 15 years ago (during the early 1980s) showed that despite clinical suspicions implicating numerous foods, eight foods ['major (common) food allergens'] accounted for 85% of reactions: egg, milk, soybean, wheat, peanuts, tree nuts (e.g. walnut, cashew), fish, and shellfish (4). However, there is a perception that food hypersensitivity is growing in prevalence and in scope. An increasing number of reports are emerging that document reactions to a host of foods not among those commonly referred to as the 'major allergens'. Examples of these 'minor (uncommon) allergens' include various seeds, fruits, vegetables, grains, spices, and meats (5,6). As we have been performing oral food challenges in children with AD for over a decade, we took the opportunity to determine whether there has been any change in the pattern

of food hypersensitivity over time. We evaluated sensitization and clinical reactivity in two groups of different children and young adults with AD evaluated over a 1-year period separated by a decade.

## Subjects and methods

All children and young adults with moderate-to-severe AD evaluated with oral food challenges during two separate time-periods a decade apart (Group A: May 1988 to June 1989; and Group B: May 1998 to June 1999) were included in this retrospective study. Studies were performed in the Pediatric Clinical Research Unit at Johns Hopkins Hospital for Group A and in the General Clinical Research Unit at Mount Sinai School of Medicine for Group B, with approval of the Institutional Review Board of the respective institutions. Entry criteria and test procedures were identical despite the relocation of the study, and all evaluations were performed under the guidance of the same principal investigator (H.A.S.). Children underwent skin-prick tests (SPTs), radioallergosorbent tests (RASTs), and

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oral food challenges, as described previously (4,7). Briefly, oral food challenges were performed in a double-blind, placebo-controlled manner with administration of up to 10 g of food camouflaged in juice, infant formula or moist food (e.g. cream of rice cereal), and administered over 90 min. Doses were administered at 10–15-min intervals, increasing as follows: 5%, 10%, 20%, 20%, 20%, and 25%. Two challenges separated by  $\approx 4$  h were performed each day; one challenge food contained placebo and one contained the suspected food antigen. Randomization and preparation of the challenges were performed by dieticians in the clinical research unit. All negative blinded challenges were confirmed with open feedings. Sensitization was defined by SPT wheals  $\geq 3$  mm compared to the negative control and/or by a CAP-RAST FEIA (Pharmacia Upjohn Diagnostics, Uppsala, Sweden) of  $>0.7$  kU/l. Clinical reactivity was defined as fulfilment of at least one of the following criteria: positive blinded oral food challenge; a recent history consistent with an acute severe reaction to an isolated ingestion of the food in association with a positive SPT and/or RAST; or, for patients evaluated between 1998 and 1999, serum food-specific immunoglobulin E (IgE) levels indicating a  $>95\%$  likelihood of clinical reactivity (7). Foods considered 'major allergens' were milk, egg, wheat, soy, peanut, tree nuts, and seafood. All other foods (24 types) were considered 'minor allergens'. Dichotomous variables were analyzed by using the chi-square test, and medians were analyzed by the Mann–Whitney *U*-test (significance was set at  $p < 0.05$ ).

## Results

### Subjects and sensitization rates

Forty-three patients were evaluated in Group A and 32 in Group B. There were no significant differences between Group A and Group B in age (median 7 years, range 2–26 years vs. 6.5 years, range 3–22 years), gender (65% male vs. 63% male), or proportion with asthma (47% vs. 62%). Results of tests for sensitization and clinical reactivity to major food allergens are shown in Table 1. There were no significant differences between the groups in sensitization rates to major allergens. There were too few tests to tree nuts and seafood or single minor food allergens to evaluate changes in sensitization.

### Challenge results and clinical reactivity

Patients in Group A underwent an average of 3.2 challenges per patient and those in Group B underwent an average of 2.4 challenges per

patient. A significantly greater proportion of challenges were performed to evaluate allergy to minor food allergens in Group B (42%) than in Group A (30%,  $p < 0.05$ ), as shown in Table 2. Despite the fact that a greater number of challenges to minor foods were performed in Group B, there was no significant difference in the low rate of clinical reactivity to these foods. Of the challenges performed to evaluate minor food allergens, there was at least one positive challenge to the following foods: barley, corn, beef, pork, tomato, and mustard. There were no positive challenges to oat, rice, chicken, potato, pea, string bean, apple, banana, grape, orange, sweet potato, lamb, turkey, carrot, cinnamon, garlic, sesame, or quinoa.

Major food allergens accounted for a similarly high proportion of clinical reactions to foods (positive challenges, high predictive RASTs) in each time-period: 86% in Group A and 92% in Group B ( $p = 0.36$ ), as shown in Table 2. When considering the rate of positive clinical reactions per major food allergen evaluated, Group B had a higher proportion of positive evaluations (64% vs. 39%,  $p = 0.001$ ). Specific foods that accounted for this increase were milk and peanut. This trend was also seen for wheat and fish, but the smaller number of challenges performed for these foods precluded meaningful analysis.

## Discussion

Despite increasing reports of food hypersensitivity to a wide range of foods, and despite an increasing number of evaluations for allergy to 'minor' food allergens, we were unable to document an increasing role for minor foods in children with AD over a span of 10 years. Previous reports have documented that relatively few foods ['major (common) food allergens'] account for food hypersensitivity reactions. In 1985, Sampson & McCaskill reported that 85% of food allergy in children with AD was accounted for by six foods: egg, milk, wheat, soy, peanut, and fish (4). Thirteen years later, Burks and colleagues (8) similarly reported that 89% of food allergy in children with AD was accounted for by seven foods: egg, milk, wheat, soy, peanut, fish, and cashew. In 1990, Bock & Atkins (9) reported the results of 480 children, not selected for AD, who underwent 1,014 oral food challenges; only 11 of 245 (5%) positive challenges were to 'minor (uncommon)' food allergens. The results of the present study document similar findings when identical entry criteria and study protocols were followed by the same investigators a decade later. Although the study was conducted at two

Table 1. Sensitization and clinical reactions to 'major (common)' food allergens

|                      | Group A (1988–89, n = 43) |                      | Group B (1998–99, n = 32) |                       | Number of subjects not challenged because reactivity was determined by RAST§ |
|----------------------|---------------------------|----------------------|---------------------------|-----------------------|------------------------------------------------------------------------------|
|                      | Sensitization†            | Clinically reactive‡ | Sensitization             | Clinically reactive‡§ |                                                                              |
| Cow's milk           | 23/35 (66%)               | 9/22 (41%)           | 22/28 (79%)               | 17/20 (85%)*          | 5                                                                            |
| Egg                  | 35/41 (85%)               | 22/30 (73%)          | 23/29 (79%)               | 14/19 (74%)           | 7                                                                            |
| Wheat                | 17/27 (63%)               | 0/14 (0%)            | 12/18 (67%)               | 2/4 (50%)             | 0                                                                            |
| Soy                  | 20/32 (63%)               | 4/20 (20%)           | 15/19 (79%)               | 2/12 (17%)            | 0                                                                            |
| Peanut               | 31/36 (86%)               | 3/8 (38%)            | 23/27 (85%)               | 11/15 (73%)           | 5                                                                            |
| Fish                 | 10/26 (39%)               | 0/1 (0%)             | 9/17 (53%)                | 1/4 (25%)             | 0                                                                            |
| Tree nuts, shellfish |                           | 0/3 (0%)             |                           | 0                     |                                                                              |

†Sensitization defined by a positive skin test or radioallergosorbent testing (RAST).

‡Clinical reactivity by oral food challenge or §sufficiently elevated food-specific immunoglobulin E (IgE), as indicated in the text.

\*p &lt; 0.05.

different sites, there was no alteration in general approach and procedures, and the demographic characteristics of the subjects (age, gender, atopic disease) were not significantly different at the two time-periods compared.

However, there was one significant difference in the evaluation process applied to the group evaluated in 1998–99. Compared to evaluations a decade ago, a significant number of oral food challenges to egg, milk, peanut, and fish can now be eliminated because quantitation of food-specific IgE antibodies for these foods has identified children at a high risk for clinical reactivity (7). This approach has resulted in an increase in the proportion of challenges performed to 'minor' food allergens. Despite the increase in evaluations performed to 'minor' food allergens, the present study indicates that milk, egg, wheat, soy, peanut, and fish still account for 92% of food hypersensitivity in children with AD.

Sensitization rates to the 'major' food allergens did not change dramatically over the decade, although there may have been too few participants to document small changes. However, we documented a higher proportion of clinical reactivity to peanut and milk in the latter part of the decade. This increase may reflect the general increase in atopic diseases (asthma, AD and allergic rhinitis) over the past two decades. It is also possible that our referral base has changed somewhat in that a greater number of children are being referred for evaluation of milk and

peanut allergy, with a greater proportion expected to have clinical reactions. The proportion with reactivity to milk and peanut may also be inflated slightly as patients in 1998 were not challenged to food for which their specific IgE value was in the 95% predictive range; this group could have included a small number of patients who may not have reacted to challenge. The rate of clinical reactivity to egg did not change over the decade, which is not surprising as egg already carries a particularly high rate of clinical reactivity in all studies of food allergy in AD (3,4,7,8).

In conclusion, we were unable to document an increasing role for 'minor' food allergens in children with AD, even though there was an increase in the number of oral food challenges performed to these foods. Therefore, these minor allergens do not appear to play a significant role in this population of children and young adults with moderate-to-severe AD. This is an important point for consideration in the initial clinical evaluation of AD, as expanded testing (skin tests, RASTs) for 'minor' food allergens is generally unwarranted unless there is a particular suspicion of other foods by history. Considering that these patients were referred to a tertiary care center specifically for evaluation of food allergy in AD, the issue of reactivity to 'minor' foods is probably even more rare in unselected patients with AD. It must be emphasized that this study did not select patients specifically because of a history of acute

Table 2. Distribution of challenges and reaction rates among 'major (common)' and 'minor (uncommon)' foods

|                                                                      | Group A (1988–89)<br>(n = 43) | Group B (1998–99)<br>(n = 32) |
|----------------------------------------------------------------------|-------------------------------|-------------------------------|
| Proportion of challenges undertaken to 'minor' allergens             | 40/138 (30%)                  | 33/78 (42%)*                  |
| Proportion of clinical reactions to 'major' allergens                | 38/98 (39%)                   | 47/74 (64%)*                  |
| Proportion of clinical reactions to 'minor' allergens                | 6/40 (15%)                    | 4/33 (12%)                    |
| Overall proportion of clinical reactivity owing to 'major' allergens | 38/44 (86%)                   | 47/51 (92%)                   |

\*p &lt; 0.05.

reactions to foods. It has been observed that fatal, food-induced anaphylaxis is also most often caused by the classical 'major' food allergens (10). However, this study did not address any possible shift in the type of foods responsible for acute reactions over the past decade in otherwise unselected patients. Further studies in the general population and in individuals with food allergy, but without AD, are needed to explore the full impact of allergy to the 'minor (uncommon)' food allergens.

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