Original Article

Food Allergy Sensitization and Presentation in Siblings of Food Allergic Children

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What is already known about this topic? Peanut allergy in 1 sibling may be a potential risk factor for peanut allergy in the younger sibling, but little data are available about sibling-to-sibling risk of other allergies.

What does this article add to our knowledge? The risk of clinically irrelevant food sensitization is several-fold more likely than sensitization with clinical reactivity, showing low frequency of sibling-associated risk of food allergy compared with falsely positive test results.

How does this study impact current management guidelines? Food allergy screening of 1 sibling based on food allergy in another may be unwarranted, given a low prevalence of clinical reactivity and a high likelihood of detecting clinically irrelevant sensitization in siblings of food allergic children.

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BACKGROUND: Many parents of food allergic children have concerns about the development of food allergies in their other children.

OBJECTIVE: We sought to determine prevalence of food sensitization and clinical food allergy among siblings of food allergic children.

METHODS: Two thousand eight hundred and thirty-four children were enrolled in the Chicago Family Cohort Food Allergy study. One thousand one hundred and twenty children (ages 0-21 years) with a food allergy (defined by a reported reaction history and evidence of food-specific IgE or skin prick test) and at least 1 biological sibling were included in this study.

RESULTS: Among siblings of children with food allergy, 33.4% had no sensitization and no clinical symptoms to food. Fifty-three percent had a positive food serum-specific IgE or skin prick test, but no reported symptoms of food allergy. Only 13.6% of siblings were both sensitized and clinically reactive to the same food. Milk allergy was the most common allergy among siblings (5.9%), followed by egg allergy (4.4%) and peanut allergy (3.7%).

CONCLUSIONS: In a large cohort of food allergic families, only a small proportion of siblings were both sensitized and clinically reactive to a food. Sensitization without reactivity was common among siblings. Testing for food allergy in siblings without a history of clinical reactivity appears to be unjustified. Screening may lead to negative consequences related to potential misdiagnosis and unnecessary avoidance of a food. More data are needed to determine the absolute risk of food allergy development in siblings of food allergic children. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;■:■-■)

Key words: *Childhood food allergy; ImmunoCAP; Milk allergy; Peanut allergy; Risk; Sensitization; Siblings; Skin testing*

Abbreviations used
HRQL- Health-related quality of life
kU/L- Kilo International Units per Liter
NIAID- National Institute of Allergy and Infectious Diseases
OFC- Oral food challenge
RSV- Respiratory syncytial virus
sIgE- Allergen-specific IgE
SPT- Skin prick testing

Food allergy is a growing public health concern impacting 8% of US children, 40% of which report having experienced symptoms of a potentially life-threatening reaction.[1] Given the absence of current preventative treatments for food allergy[2] beyond food avoidance, the ubiquity of food in our society, and the potentially fatal nature of reactions, food allergy has been associated with negative psychosocial impact, anxiety, and impaired health-related quality of life (HRQL).[2-12] Moreover, food allergic children managed with avoidance diets may experience nutritional deficiencies and growth impairment in addition to reduced HRQL.[13,14]

A common concern for families is the degree of risk related to the family history of food allergy and if siblings of food allergic children benefit from screening for food allergies before introducing potential allergenic foods. Multiple prevention guidelines suggest that a bi-parental history of any allergic disease is a risk factor for developing food allergy, but few studies have investigated if family history can be better specified at the level of a specific family member (eg, mother, father, or sibling).[15-17] The available studies have been limited in scope to very few allergens (ie, either solely focused on peanut allergy,[18-20] or peanut, egg, and sesame allergy as a group[21]), were conducted in small numbers, and only 2 used oral food challenge (OFC) to confirm a reported food allergy. Current National Institutes of Health guidelines state that there is insufficient evidence to recommend routine screening with specific IgE (sIgE) or skin prick testing (SPT) before introducing commonly allergenic foods to any child, including siblings of food allergic children.[2] Serum sIgE and SPT have poor precision in patients not previously exposed to the food (eg, with no known history of ingestion, and thus a low pretest probability for disease). The poor specificity and poor positive predictive value of these tests in such contexts may result in falsely positive results, potentially mislabeling many patients who are tolerant as allergic to the food allergen[22-26] (ie, sensitization to food vs true allergy to food). Such asymptomatic sensitization results may be overinterpreted, given a conservative sentiment toward potential food allergy, resulting in unnecessarily recommending such children avoid those specific foods, impairing the child[13,14] and family's HRQL.[2-12]

The Chicago Family Cohort is a large cohort formed to study genetic risk factors for food allergy among families with a food allergic child. Using nested data from within this large cohort, we sought to determine the prevalence of food sensitization and clinical food allergy among siblings of food allergic children. We also aimed to understand potential factors contributing to the development of food allergy and sensitization in siblings of food allergic children.

METHODS

Sample recruitment

The 1120 children included in this study were enrolled as part of the Chicago Family Cohort Food Allergy study. The enrollment process for this cohort is described elsewhere.[27] Families were recruited through general medical and allergy specialty clinics, community support groups, and media advertisements. Participants were eligible for enrollment in the original cohort study if a parent of at least 1 biological child (ages 0-21 years) with food allergy was willing to fill out a detailed screening history for the child and family, as well as provide informed consent for the children in the family to undergo skin and serologic testing for food allergies. The present study included eligible families that had 1 index child with a confirmed food allergy and who had at least 1 sibling who participated in the study, for a total of 478 index children and 642 siblings. The Institutional Review Board of the Ann and Robert H. Lurie Children's Hospital of Chicago (formerly Children's Memorial Hospital) approved the study protocol. All participating families provided written informed consent to be a part of the Chicago Family Cohort Food Allergy study.

Data collection

Trained research staff administered a structured questionnaire as part of the cohort enrollment interview to each parent about multiple risk factors for the development of food allergy. These included the child's history of asthma (parental report of a physician diagnosis of asthma), birth order and number of siblings, reported antibiotic use in the first year of life, reported infections (common cold, skin infections, respiratory syncytial virus [RSV]), reported eczema, and pet ownership. Caregivers were also asked if the child was cared for outside of the home before age 5 and in what context (ie, child care center/preschool, home-based childcare in someone else's home, home-based childcare in their own home). Mothers were asked if the child was breastfed, bottle fed, or both and how long they exclusively breastfed. Both the older sibling(s) of an index child and the younger sibling(s) were included in the analysis.

Sensitization and food allergy status

sIgE values for 9 food allergens (egg white, sesame, peanut, soy, cow milk, shrimp, walnut, cod fish, and wheat) were measured for each subject using the Thermo Fisher ImmunoCAP system (Thermo Fisher Scientific, Portage, Mich). The reported range for sIgE was from 0.1 (lower limit of detection) to greater than 100 kU/L (upper limit of reporting), with >/=0.35 kU/L considered positive. sIgE assays were performed by the Clinical Immunology Laboratory at Ann and Robert H. Lurie Children's Hospital of Chicago, a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory for the ImmunoCAP assay.

SPTs were performed on all eligible participants using the Multitest II device (Lincoln Diagnostics, Decatur, IL) to 9 food allergen extracts (cow milk, egg white, soybean, wheat, peanut, English walnut, sesame seed, fish mix [cod, flounder, halibut, mackerel, tuna], and shellfish mix [clam, crab, oyster, scallops, shrimp]), plus negative (50% glycerinated saline) and positive (histamine, 1.0 mg/mL) controls (Greer, Lenoir, NC). The tests were placed on either the volar forearm or back (for young children) and results were measured 15 minutes after application. The test was considered positive if the mean wheal diameter was $\geq$3 mm than the saline control and the positive control wheal was at least 3 mm in diameter.

Food allergy status was determined by applying a set of clinical criteria to data gathered from the questionnaire-based interview