Predictors of childhood food allergy: significance and implications

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Summary

Background: Food allergy is common in children, and its occurrence is strongly associated with other allergies including anaphylaxis. Both genetic (e.g., CD14, STAT6, IL-10, SPINK5, and FOXP3 genes) and environmental (e.g., early exposure to highly allergic food) factors appear to contribute to food allergy.

Method: Cross-sectional study involved children in public primary schools in Al-Ain city (United Arab Emirates). 660 students from the chosen classes were provided with 35 questions to be answered by their parents with a response rate 60.2%. The objective of the study was to determine predictors for food allergy in children.

Result: Significant associations were found between childhood food allergy and a history of personal allergy (atopic dermatitis, asthma or allergic rhino-conjunctivitis) or immediate family members with food allergy or other allergic diseases. The best predictors for childhood food allergy were a personal history of asthma \( (p < 0.001) \), a personal history of atopic dermatitis \( (p < 0.001) \), a paternal history of atopic dermatitis \( (p = 0.005) \) and a paternal history of allergic rhino-conjunctivitis \( (p = 0.012) \).

Discussion: These results are consistent with the notion that “various forms of allergy, including childhood food allergy are hereditarily coupled”. Thus, predicting childhood food allergy provides an opportunity to prevent or ameliorate the symptoms. (Asian Pac J Allergy Immunol 2011;29:313-7)

Key words: Food allergy, allergy, genetics, environment, family history

Introduction

Food allergy affects 5-8% of young children.1,2 Nevertheless, this entity imposes significant health and nutritional problems and its occurrence is strongly associated with other allergies including anaphylaxis.1 The disease, like other allergies, appears to be familial.2,3

Typically, the diagnosis of childhood food allergy is considered on the basis of the symptoms. In most cases, the clinical manifestations represent an IgE-mediated hypersensitivity response, causing immediate cutaneous (itching and urticaria), respiratory (coughing, wheezing or shortness of breath), gastrointestinal (vomiting or urticaria) or systemic (hypotension, dooming or altered consciousness) symptoms. Subacute or chronic (e.g. contact dermatitis, pulmonary hemosiderosis, chronic emesis, protracted diarrhea or failure-to-thrive) manifestations of the disease, however, are generally not mediated by IgE1.

Confirming the diagnosis of food allergy requires open or blinded food challenges, which are not routinely recommended due to clinical concerns, such as anaphylaxis. Skin prick tests are widely done, but predict the disease in only 50% of the cases.2

Genetic (e.g., CD14, STAT6, SPINK5 and FOXP3 polymorphism)4-7 and environmental (e.g., diet in infancy, maternal dietary exposure, aeroallergens and geography) factors both predispose to food allergies.8,10 For example, the concordance rate for food sensitization (e.g., peanut allergy) is significantly higher in monozygotic than dizygotic twins.11 Other studies have confirmed familial aggregations of sensitization to food, especially in siblings.3,10 Furthermore, food allergy in the index child is found as an independent predictor of its existence in their siblings.3 So far, no specific gene has been conclusively linked to the disease.12

The primary objective of this study was to determine important predictors of food allergy in children. We show strong associations between
Table 1. Associations between childhood allergic disorders and food allergy by simple logistic regression.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Odds Ratio</th>
<th>95% CI for Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic Dermatitis (n = 35, 8.8%)</td>
<td>10.636</td>
<td>4.653 - 24.314</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthma (n = 54, 13.7%)</td>
<td>4.586</td>
<td>2.092 - 10.050</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Allergic Rhinoconjunctivitis (n = 25, 6.3%)</td>
<td>3.317</td>
<td>1.152 - 9.555</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

* Throughout the table, n = number of positive cases

childhood food allergy and a history of personal or familial allergy (asthma, atopic dermatitis or allergic rhinoconjunctivitis). These results may inspire the development of effective nutritional guidelines for the most susceptible infants.

Methods

This cross-sectional study was conducted in December 2006 and involved children in public primary schools in Al-Ain city (United Arab Emirates). The subjects were selected by multistage random sampling. Eight schools were chosen from the Ministry of Education listing. Two classes from each grade were then selected randomly from each school. All 660 students from the chosen classes were provided with 35 questions to be answered by their parents. Children whose parents gave informed consent by returning the self-administered questionnaires were enrolled (397, or 60.2%).

A child was considered to have food allergy, asthma, atopic dermatitis or allergic rhinoconjunctivitis if symptoms were consistently reported by the parents and the diagnosis was strongly considered (documented in the medical record) by the treating physician.

To assess which characteristics were associated with food allergy, simple logistic regressions of each type of atopy were conducted, with food allergy as the dependent variable (Table 1-2). A \( p < 0.05 \) was considered significant.

The subjects came from distinct families; their school enrollment was not expected to influence the occurrence of food allergy. Thus, data modeling did not assume any hierarchical effects of families and schools on the food allergy status of participating children. Therefore, only logistic regression with fixed effects was used in modeling the data.

Table 2. Associations between family history of an atopic disorder and a child with food allergy by simple logistic regression.

<table>
<thead>
<tr>
<th>Family History of Atopic Disorders</th>
<th>Odds Ratio</th>
<th>95% CI for Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food Allergy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father (n = 24, 6.2%)</td>
<td>4.321</td>
<td>1.579 - 11.820</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mother (n = 17, 4.4%)</td>
<td>3.897</td>
<td>1.189 - 12.775</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sibling (n = 36, 9.4%)</td>
<td>4.909</td>
<td>2.058 - 11.709</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father (n = 30, 7.7%)</td>
<td>2.452</td>
<td>0.869 - 6.918</td>
<td>0.090**</td>
</tr>
<tr>
<td>Mother (n = 30, 7.7%)</td>
<td>3.330</td>
<td>1.247 - 8.896</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Sibling (n = 101, 26.2%)</td>
<td>1.881</td>
<td>0.878 - 4.027</td>
<td>0.104**</td>
</tr>
<tr>
<td>Allergic Rhinoconjunctivitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father (n = 68, 17.6%)</td>
<td>3.383</td>
<td>1.556 - 7.359</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mother (n = 74, 18.6%)</td>
<td>3.481</td>
<td>1.620 - 7.479</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sibling (n = 58, 15.1%)</td>
<td>3.016</td>
<td>1.339 - 6.745</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Atopic Dermatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father (n = 19, 4.9%)</td>
<td>10.424</td>
<td>3.884 - 28.345</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mother (n = 21, 5.4%)</td>
<td>2.946</td>
<td>0.926 - 9.373</td>
<td>0.067**</td>
</tr>
<tr>
<td>Sibling (n = 68, 17.8%)</td>
<td>1.391</td>
<td>0.574 - 3.375</td>
<td>0.465**</td>
</tr>
</tbody>
</table>

* Throughout the table, n = number of positive cases.

** Not Significant
Stepwise multi-logistic regression with forward entry was used to determine a subset of characteristics that predicts best the presence of food allergy within the target population (Table 3).

Data were analyzed using the SPSS statistical package (version 19). The study was approved by the Ethics Committee of the Faculty of Medicine at the Health Sciences of the UAE University.

Results

Three hundred ninety-seven children (205 female, 52%) were enrolled in the study. The mean age was 7.2 ± 1.1 years. Two hundred seventy-one (68.2%) were fed solely human milk, 122 (30.7%) were fed human milk supplemented with cow milk protein-based formulas, and 62 (13.6%) had solid food in the first 6 months of life.

The onset of food allergy was as early as the first month of life (7%), but mostly presented between 1 to 3 years (35%) and between 6 to 12 months (28%). The average age of presentation was 3.4 ± 1.2 years. The average number of food allergy symptoms was 3.0 ± 1.0.

At the time of the survey, 56% of children with food allergy were still having symptoms. The most common food causing allergies were egg (40%), fruits (40%) and fish (33%). Other foods included peanut, tree nuts, cow’s milk, wheat and vegetables.

Cutaneous manifestations were most common (skin redness or hives in 57% and itching in 46%), followed by respiratory symptoms (cough in 43% and hoarseness in 39%). Anaphylaxis occurred in 36% of the patients. Other symptoms were nasal congestion/sneezing (33%), red itchy eyes (28%), palpitation (21%), diarrhea (18%), nausea/vomiting (18%), shortness of breath (14%), angioedema (14%) and wheezing (11%).

The onset of symptoms was immediate or to up to 4 hours after food ingestion. Treatment provided was either an oral antihistamine (57%) or a bronchodilator (29%). None had epinephrine auto-injectors; 30% of patients need to visit a hospital either for an emergency visit or admission.

Significant associations were present between childhood food allergy and personal atopic dermatitis (p < 0.001), asthma (p < 0.001) and allergic rhino-conjunctivitis (p < 0.05), Table 1. Age and gender had no significant effect on the presence of food allergy (p = 0.672 and 0.214, respectively).

The associations between histories of atopic interactions in the families of children with food allergy were highly significant for different close family members; father, mother and siblings (p < 0.01, <0.001 and <0.001, respectively). Significant associations were also present between childhood food allergy and immediate family members with food allergy, asthma, atopic dermatitis or allergic rhino-conjunctivitis (Table 2).

The best predictors of food allergy were a personal atopic dermatitis (p =0.000), a personal history of asthma (p =0.000), paternal atopic dermatitis (p =0.005) and paternal allergic rhino-conjunctivitis (p =0.012), Table 3.

Discussion

The data in Table 1-3 confirm prior reports showing childhood food allergy is significantly associated with a personal and family history of allergies (e.g., asthma, eczema or rhino-conjunctivitis). They are also consistent with the recent report by Joseph et al., verifying paternal asthma being the best predictor of childhood asthma. Similarly, paternal atopic dermatitis and allergic rhino-conjunctivitis are shown here to be among the best indicators of childhood food allergy (Table 3). Thus, paternal genes appear to potentially transmit food allergy and atopy to their offspring. Other studies link allergic traits to maternal genes.

To the best of our knowledge, there are no existing criteria that improve early diagnosis of childhood food allergy. The data shown in Table 1-3 could be employed to identify high risk infants, and hence implement an effective preventive or management strategy.

Epidemiologic studies confirm the genetic basis of childhood food allergy. Family-based studies

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**Table 3. Best predictors of childhood food allergy by multi-logistic regression.**

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Odds Ratio</th>
<th>95% CI for Odds Ratio</th>
<th>Chi-Square*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal asthma</td>
<td>7.873</td>
<td>3.061 – 20.252</td>
<td>18.324</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Personal atopic dermatitis</td>
<td>7.796</td>
<td>2.793 – 21.766</td>
<td>15.371</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Father with atopic dermatitis</td>
<td>5.934</td>
<td>1.733 – 20.313</td>
<td>8.042</td>
<td>0.005</td>
</tr>
<tr>
<td>Father with allergic rhinoconjunctivitis</td>
<td>3.333</td>
<td>1.307 – 8.497</td>
<td>6.354</td>
<td>0.012</td>
</tr>
</tbody>
</table>

* Wald test statistic. Results of a stepwise multi-logistic regression with forward entry (Wald test) with the child’s food allergy status as the dependent variable and all the significant characteristics shown in Table 1-2 as independent variables.
demonstrate strong familial aggregation of food allergy and sensitization to food allergens (e.g., peanut), especially among siblings.\textsuperscript{3,17} Recently, an epidemiologic survey from Finland shows 3-fold higher incidence of food allergy if both parents have allergic manifestations and 2-fold higher if only one parent has such manifestations.\textsuperscript{14}

The influence of genetics on the incidence of peanut allergy was investigated in a study of 75 twin pairs. The results showed a higher concordance rate among monozygotic twins (64.3\%) than dizygotic twins (6.8\%).\textsuperscript{11} Nevertheless, the genetic basis of food allergy is still unknown. Moreover, the limited number of available publications provide variable results (e.g., please see references 4 and 18).

A 3'TR polymorphism in the \textit{STAT6} gene (potentially involved in allergic diseases) was associated with susceptibility and severity of food allergies in UK Caucasion patients.\textsuperscript{3} Another retrospective investigation of four candidate genes (including \textit{STAT6}, or \textit{G2964A}) showed that the severity of food allergy is determined by combination of single-nucleotide polymorphisms (SNPs) and environmental factors.\textsuperscript{19}

In one study, a pathway for high serum IgE level and atopic manifestations was linked to SPINK5 (serine protease inhibitor Kazal type 5), a protein with a critical role in epidermal barrier function and immunity.\textsuperscript{20} A study of atopic dermatitis in Japanese children showed patients with the \textit{SPINK5} 1258AA or 1258AG genotype displayed a significantly higher prevalence of food allergy.\textsuperscript{6}

The forkhead/winged-helix transcription factor box protein (\textit{FOXP3}) is considered a reliable marker for regulatory T-cells (essential for tolerance and immune regulation). In a recent study, 54 children with IgE-dependant food allergy showed significantly lower expressions of \textit{FOXP3} and \textit{IL-10} genes than healthy children. Furthermore children acquiring tolerance to the food showed significantly higher expression of \textit{FOXP3} gene than children with active food allergy.\textsuperscript{7}

Geographic variations in the incidence of atopy could be explained by the founder effect, with random numbers of “allergic” alleles segregated within the population. For example, atopy is common in the Gulf region, perhaps reflecting the practice of endogamy, which limits “allergic” allele exchanges between tribes.

The environment and geography continue to be a significant risk factor for childhood food allergy.\textsuperscript{10} For example, the frequency of nut allergy is different between studied countries due to dietary habits and cooking procedures.\textsuperscript{21} In many cultures, peanut allergy presents earlier in life, possibly reflecting increased consumption of peanut by pregnant and nursing mothers.\textsuperscript{21,22} Shek et al. report peanut and tree nut allergies are relatively infrequent in Asian children (Singapore and Philippines) compared to Western societies.\textsuperscript{23} Shellfish allergy, on the other hand, predominates in Asian children. Furthermore, respondents born in the West are at a higher risk of peanut and tree nut allergies than those born in Asia. Thus, changes in infant feeding (nutritional guidelines) could significantly affect the natural history of childhood food allergy.\textsuperscript{22,24} Furthermore, appropriate food education is critical, especially for highly susceptible infants.\textsuperscript{25}

Predicting childhood food allergy could facilitate the implementation of nutritional strategies that ameliorate the development of the clinical disease. The American Academy of Pediatrics produced an inconclusive statement regarding high-risk infants (defined as those with at least one first-degree relative, parent or sibling, with allergic disease).\textsuperscript{18} Various reports suggested avoiding exposure to highly allergenic foods (e.g., fish, eggs, peanut protein, etc.) during pregnancy, lactation and early infancy.\textsuperscript{19} The importance of these dietary restrictions however remains uncertain.

The response to this questionnaire-based study was 60.2\%. This rate is relatively good, but selective participation could not be ruled out, as patients with the disease may be more motivated to participate than their healthy counterparts. Moreover, recall bias could not be ruled out.

In summary, the data presented support the notion that heritability estimates predict food-specific IgE. Although precise genetic factors (as discussed above) contributing to the symptoms remain largely undetermined, at least they serve to identify the infants at a higher risk for food allergy.\textsuperscript{7,12} One implication for identifying “food allergy susceptibility” is to take early precautions to control the phenotypic manifestations of the disease. Currently, there are no evidence-based guidelines to avoid or ameliorate childhood food allergy. However, the strong predictors shown in Table 1 and 3 should alert physicians to the potential for food allergy in high-risk infants. Identifying such predictors or risk factors should also help avoidance or amelioration of the disease by adopting specific nutritional guidelines.
Acknowledgement

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References


