Food Allergy and Atopic Dermatitis

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Outline of Talk - 1

- Frequency of food sensitization among AD patients.
- Proof of causal relationship between food and AD
  - Results of food challenge, pros vs cons
  - Symptoms upon food ingestion
  - Results of food avoidance
- Common foods sensitized by AD patients
- Identify AD patients which food allergy may be involved

Outline of Talk - 2

- Work up in AD patients in which food allergy is suspected
- What comes first AD or food allergy? Proposed pathogenesis
- Can we prevent AD by food avoidance?
- Can other means of treatment of food allergy affect AD?
Prevalence of Atopic Dermatitis in the Asia-Pacific

- Prevalence of atopic dermatitis in Asia = 3-16% (Williams et al., ISAAC-I, JACI 1999;103:125)
- Prevalence in Japan and Singapore is very high (20%) and is increasing (Yura 2001 and Tay 2002)
- Prevalence of AD in Australian infants = 28%
  - 9.4% need topical steroids for 6 weeks in the first 12 mo of life
  - Risk of IgE-mediated food allergy = 5.5 fold of control subjects

Prognosis of Atopic Dermatitis
The MAS study 2004

Illi et al J Allergy Clin Immunol 2004;113:925
Atopic dermatitis in the new centuries

Food Allergy And AD in Children - Historical Aspects

- 1918 Talbot described a series of eczema patients with positive SPT
- 1936, Engman challenged child with AD and wheat allergy.
  - 2 hrs itching and scratching.
  - Next morning typical eczematous lesion
- Wilson & Walzer—absorption of egg protein in infant – wheat at remote previously sensitized area

Food Allergy and AD Dermatologists'view

- AD is rarely associated with food allergy
- Food elimination has no role in AD Rx
- Food allergy in AD - controlled studies
  - Sampson & McCaskill 1985 – 33% (allergy clinic)
  - Burks 1986– 37% (allergy + derm)

<table>
<thead>
<tr>
<th>Foods</th>
<th>No of Prs Challenged</th>
<th>Positive Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eggs</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Milk</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Wheat</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Soy</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Total no = 17, No of positive SPT = 4, No of positive rast = 3

Rowland and Hanifin Dermatology Therapy 2006;19:97-103
Food Allergy in AD patients referred to Ped Dermatologists at Johns Hopkins

- 63 AD patients referred to a pediatric dermatologist were studied (mean age 2.8 years)
- 41 were ImmunoCAP positive (65%)
- SCORAD of CAP pos pts = CAP neg pts
- 12 had convincing allergic history to food
- 19 underwent food challenge with 11 positive
- Overall relevant food allergy in this AD populations = 23/63 (37%, CI 25-50%)

Eigenmann et al Pediatrics 1998;101:1

Food sensitization and AD in Valencia - Spain

- Service of Dermatology and Unit of Allergy
- 44 infants (27M, 17F) mean age 7.5 mos
- SPT, positive in 27/44 (61%)
  - Eggs 100%, milk 30%
- Open challenge to egg
  - Positive 44% (12/27)

Garcia et al. Allergol et Immunopathol 2007;35:15-20

Food allergy in AD referred to Derm Clinic in Australia

- 55 consecutive AD infants referred to Derm clinic (median age = 34 weeks)
- SPT and CAP FEIA to milk, egg and peanut
- 86% positive by SPT, 83% by CAP exceeding cut-off
- A large majority developed reaction on
  - Breast feeding
  - Never ingested the food before

Hill et al J Pediatr 2007;151:359
Food Allergy in Patients Atopic Dermatitis

- Conflicting data on prevalence exist
  - Hanifin - 10%
  - Sampson - 74%
- Melbourne cohort study
  - 620 children with + family history of atopy
  - group 1 - no AD (402)
  - group 2 - mild AD (150)
  - group 3 - severe AD (41)
- Attributable risk from food allergy = 63-65%

EPAAC study
AD and IgE to food

- 2048 AD patients from 94 centers from 12 countries
- Mean age 17.6 mos
- Mean age of AD 4.3 mos
- Mean SCORAD – 33
- IgE-FA to milk, egg, peanut
- 65.5% sensitized to food
- There were association between
  - AD severity
  - HR-IgE-FA level
  - Age of onset of eczema

21 years of oral food challenges in 578 patients with AD

<table>
<thead>
<tr>
<th>FOOD</th>
<th>Positive Challenge</th>
<th>Negative challenge</th>
<th>Total</th>
<th>%positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>All foods</td>
<td>1348</td>
<td>1559</td>
<td>2907</td>
<td>46.4</td>
</tr>
<tr>
<td>Major food allergens</td>
<td>777</td>
<td>766</td>
<td>1543</td>
<td></td>
</tr>
<tr>
<td>Egg</td>
<td>351</td>
<td>160</td>
<td>511</td>
<td>68.7</td>
</tr>
<tr>
<td>Milk</td>
<td>202</td>
<td>185</td>
<td>387</td>
<td>52.2</td>
</tr>
<tr>
<td>Peanut</td>
<td>40</td>
<td>56</td>
<td>96</td>
<td>41.7</td>
</tr>
<tr>
<td>Wheat</td>
<td>79</td>
<td>164</td>
<td>243</td>
<td>32.5</td>
</tr>
<tr>
<td>Soy</td>
<td>105</td>
<td>201</td>
<td>306</td>
<td>34.3</td>
</tr>
</tbody>
</table>

Lisa Ellman-Grunther and Hugh A. Sampson, Atopic dermatitis and Foods. Atopic dermatitis, Bieber T and Leung
Prevalence of sensitization and challenge-proven FA among Australian children – the Healthnut Study

<table>
<thead>
<tr>
<th>Food</th>
<th>Sensitization</th>
<th>Challenge-proven</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>11.8%</td>
<td>9%</td>
</tr>
<tr>
<td>Peanut</td>
<td>6.4%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Sesame</td>
<td>1.6%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Milk</td>
<td>5.6%</td>
<td></td>
</tr>
</tbody>
</table>

Osborne J Allergy Clin Allergy 2011;127:668

EPAAC study
High-risk Food IgE in AD

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Egg</th>
<th>Milk</th>
<th>Peanut</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 mos</td>
<td>49.7</td>
<td>43.6</td>
<td>21.6</td>
</tr>
<tr>
<td>3-5 mos</td>
<td>49.7</td>
<td>43.6</td>
<td>21.6</td>
</tr>
<tr>
<td>6-11 mos</td>
<td>26.7</td>
<td>18.1</td>
<td>11.6</td>
</tr>
<tr>
<td>&gt; 12 mos</td>
<td>26.7</td>
<td>18.1</td>
<td>11.6</td>
</tr>
</tbody>
</table>


Food allergy in Chinese infants

497 infants were screened, 80 were challenged. 18 were positive
Prevalence = 3.8% (CI 2.5-5.9%)

<table>
<thead>
<tr>
<th>Food</th>
<th>Prevalence</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg</td>
<td>18%</td>
<td>12-25%</td>
</tr>
<tr>
<td>Milk</td>
<td>18%</td>
<td>12-25%</td>
</tr>
<tr>
<td>Peanut</td>
<td>18%</td>
<td>12-25%</td>
</tr>
</tbody>
</table>

Egg allergy and AD

Food Allergy And AD
Clinical Studies in Children

• Elimination
  - Businco et al: dietary exclusion of milk and/or egg from 59 children with severe AD resulted in clinical improvement in 80% of cases
  - Lever et al: RCT placebo VS egg elimination significantly greater mean reduction in BSA affected by eczema (19.6 to 10.9%) in dietary gr comparison to control gr (21.9 to 18.9%). At the end dietary phase, egg hypersensitivity was confirmed by positive DBPCFC

Egg Elimination in Egg-sensitive Atopic Dermatitis

Percent skin area involved

Severity scores

The Allergic March

Development of IgE-mediated CMA in unselected infants - Israel

THE GERMAN MULTICENTER ALLERGIC STUDY (MAS)
Dual-allergen Exposure Hypothesis in Food Allergy

Murine Model Of AD Induced By Oral sensitization

• Development of an eczematous rash that occurs in a subset of mice orally sensitized to food proteins
• Approximately 1/3 of mice sensitized with milk or peanut proteins developing a dry, erythematous, scaly, pruritic rash within 9-14 weeks of initiating the sensitization protocol

Li XM et al, J Allergy Clin Immunol 2001;107:693-702.)
Dual-allergen exposure hypothesis

- Allergen absorption and allergen priming – increased in Filaggrin-mutated mice
- Low-dose skin exposure to arachis oil in infants led to increase peanut allergy at 5 years of age
- High household exposure of peanut – ↑ in peanut allergy patient
- High maternal peanut consumption in pregnancy – high infant specific IgE to peanut and PA
- Single oral high-dose peanut flour led to oral tolerance and IgE sensitization
- PA in the UK:Israel = 10:1 whereas consumption of peanut UK:Israel = 0:7

Diagnosis of FA in AD

- History – association of foods and AD flare
- Moderate to severe disease
- Requirement for median to high potency topical corticosteroids for symptom control
- Known history of food hypersensitivity
- Special tests
  - Skin prick test
  - Specific IgE
  - Atopy patch test

Specific IgE and Food Challenge

- Sampson J Allergy Clin Immunol 2001;107:891
Cut-off of 2.5 KIU/L in cow milk allergy patient < 1 year of age


Cut-off of Specific IgE to Egg at 0.35 KIU/L in 2 year old infants


Diagnosis: APT

Evaluation of predictive capacity of sIgE, SPT, and APT for early and/or late-phase clinical reactions to allergen challenges (n=133)

Diagnosis: APT

Evaluation of predictive capacity of specific IgE in serum, SPT, and APT for late-phase reactions (n=21)

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific IgE in serum</td>
<td>71%</td>
<td>20%</td>
<td>69%</td>
</tr>
<tr>
<td>Skin prick</td>
<td>55%</td>
<td>70%</td>
<td>41%</td>
</tr>
<tr>
<td>APT patch test</td>
<td>70%</td>
<td>95%</td>
<td>81%</td>
</tr>
</tbody>
</table>


APT, SPT and SpIgE in 437 children

Table 1: Performance of single test and combination of the SPT, and the APT

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPT</td>
<td>80</td>
<td>65</td>
<td>35</td>
<td>82</td>
</tr>
<tr>
<td>APT</td>
<td>65</td>
<td>70</td>
<td>45</td>
<td>62</td>
</tr>
<tr>
<td>Skin prick</td>
<td>52</td>
<td>85</td>
<td>56</td>
<td>36</td>
</tr>
<tr>
<td>APT patch test</td>
<td>68</td>
<td>78</td>
<td>56</td>
<td>32</td>
</tr>
</tbody>
</table>

Mehl A. et al, J Allergy Clin Immunol 2006;118:923-9

APT, SPT and Sp IgE in 437 children

Mehl A. et al, J Allergy Clin Immunol 2006;118:923-9
Atopic Patch Tests

- Variability in the test as the reagents have not been standardized
- Compared to the SPT, the APT is more specific, but less sensitive
- Combining APT with SPT or Sp IgE, only 0.5-14% of food challenges could be avoided.

Management: Allergen avoidance diets

- Allergen avoidance diets are recommended when positive food challenges
- Proper food avoidance, patients typically experience significant improvement in their symptom
- If no significant clinical improve within 2-3 week, food challenges with less common food allergens may be provoking the symptom

GINI: 3-year follow-up study showed protective effect in the per protocol analysis of AD in high-risk infants

- an extensive casein hydrolysate (odds ratio, 0.53; 95% CI, 0.32-0.88) or
- partial whey hydrolysate (odds ratio, 0.60; 95% CI, 0.37-0.97)
Preventive effect of hydrolyzed infant formulas persists until age 6 years: Long-term results from GINI ITT analyses: study formula in comparison with cow’s milk feeding

Andrea von Berg et al., J Allergy Clin Immunol 2008;121:1442-7

Prevention of AD in Children with Food Allergy


Natural History of Food Allergy in Children with AD

• 3 factors: the greatest importance in determining the probability of patients losing their clinical reactivity
  • The food to which patient was allergic (soy, wheat, milk, egg more likely to develop tolerance)
  • The level of specific IgE to particular food
  • The degree to which patient adhered to elimination diet (ingest small amount of allergen were less likely to develop tolerance)
Natural Course of Cow’s Milk Allergy in Children with AD

Egg Oral Immunotherapy

Conclusion

- Food is a significant factor for exacerbations in a significant number of AD patients
- Egg seems to be the most important food item in this group of patients followed by cow milk and peanut
- Diagnosis of FA in AD is a must, particularly in young infants with severe disease
- Atopy patch test seems to have minor role in the diagnosis
- Avoidance is a major treatment modality although oral tolerance induction may be an option