Food Allergy: Why is Everyone Going Nuts?

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Objectives

1. Differences between IgE and non-IgE mediated food allergy.
2. Appropriate diagnosis of food allergy.

Patient History

19 year-old female – college junior

- Sorority party - ate 1 bite of Rice Krispy treat
  - Immediate throat itching, urticaria on face and neck
  - Significant coughing
  - Wheezing
  - Feeling of impending doom
- 911 called at this point
- Vomited
- As ambulance arrived - had respiratory arrest
- Intubated on site
- Recovered in 3 days at local hospital

FACULTY DISCLOSURE

FINANCIAL INTERESTS
I have disclosed below information about all organizations and commercial interests, other than my employer, from which I or a member of my immediate family or household receive remuneration in any amount including consulting fees, grants, honoraria, ownership, etc., which may create or be perceived as a conflict of interest.

<table>
<thead>
<tr>
<th>Name of Organization</th>
<th>Nature of Relationship</th>
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<tbody>
<tr>
<td>AllerTrain</td>
<td>Minority Stockholder</td>
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<tr>
<td>Dannon Co., Probiotics</td>
<td>Advisory Board</td>
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<tr>
<td>Mast Cell, Inc.</td>
<td>Minority Stockholder</td>
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<td>McNeil Nutritional</td>
<td>Consultant</td>
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<td>Novartis</td>
<td>Consultant</td>
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<td>Nutricia</td>
<td>Expert Panel</td>
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RESEARCH INTERESTS
I have disclosed below information about all organizations which support research projects for which I or a member of my immediate family or household serve as an investigator.

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<td>Food Allergy and Anaphylaxis Network</td>
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<tr>
<td>Food Allergy Initiative</td>
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<tr>
<td>Food Allergy Project</td>
<td>Grantee</td>
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<tr>
<td>Wallace Research Fund</td>
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Patient History - I

• Birth history
  • Normal pregnancy and delivery – 7 lbs. 13 oz.
  • Family history - mother with asthma, AR
  • Breast fed - 4 months
  • Mild atopic dermatitis - started at 6 months
• 12 months - ate pancakes (egg) - first bite, had urticaria on face, neck and upper trunk, resolved in ~1 hour

Patient History - I

Classic areas of AD

Lessons Learned

• Children with atopic dermatitis (AD) and eventual food allergy
  • 40% - 50% of children with AD in the first 3 years of life have food allergy – triggers disease (not cause)
    Sampson 2003 J Allergy Clin Immunol. 111:S540-S547
  • If have food allergy - what foods?
    • Milk, egg, peanut, wheat, soy
    • Fish, shellfish, tree nuts
    Sampson 2005 Allergy 60 Suppl 79:19-24
  • % of children with AD -
    • ~75% develop allergic rhinitis
    • ~50% develop asthma
    Sampson 2003 J Allergy Clin Immunol. 111:S540-S547

Lessons Learned

Four out of every 100 children have a food allergy.

Figure 1: Percentage of children under age 18 years with a reported food or egg allergy in the past 12 months, by age, sex, and race and ethnic group. By sex, 2007.
Oral Tolerance - Definition

- Specific suppression
  - cellular and/or humoral immune responses to an antigen by prior administration of the antigen by the oral route
- Development of oral tolerance - dietary proteins is the norm
- Evolved as an analog of self-tolerance
  - prevent hypersensitivity reactions to food proteins and bacterial antigens present in the mucosal microbiota

Oral Tolerance

A

\[ \text{Ag} \rightarrow \text{Immunity} \]

B

\[ \text{Ag} \rightarrow \text{T cell transfer} \rightarrow \text{Tolerance} \]

C

\[ \text{Ag} \rightarrow \text{Tolerance} \]

Central Role of TGF-β in Tolerance Induction

High dose

Low dose

TGF-β

Adapted from Chehade, Mayer J Allergy Clin Immunol 2005:3-12
Patient History II

Lesson Learned

- Peanut allergy prevalence -
  - ~1% of young children - 2008
  - Doubled – since 1997

- Peanut allergy - presenting at earlier age to physicians
  - Average age - after 2001 - 15 months
  - Green 2007 Pediatrics 120:1304-1310

- At risk for future systemic allergic reactions – give epi
  - previous systemic symptoms
  - peanut, tree nut, fish and shellfish allergy
  - significant asthma

Patient History II

Lesson Learned

- Food allergy - immune mediated
  - IgE versus non-IgE – important distinction
  - IgE - symptoms - skin, gastrointestinal, respiratory
  - Non-IgE – symptoms – generally GI only
  - Directed diagnostic testing

Burks 2008 Lancet 371:1538-1546
Mast Cell Mediators

Patient History II
Lesson Learned

- Diagnostic testing
  - IgE – sensitization vs clinical disease
  - Skin prick test - + test = > 3 mm wheal
    - Excellent negative predictive value
  - Positive predictive value
    - any positive PST without history ~50%
- In vitro test - serum, (0.35 - >100 kIU) (Phadia)
  - 95% probability of allergic reaction
    - Peanut - 14 kU/L, Milk - 15 kU/L, Egg - 7 kU/L


Patient History III

- 5 years old
  - Friend's birthday party - ate one bite of chocolate chip cooked baked by the friend's mother
    - said her throat felt funny, generalized urticaria, vomited and then wheezing
    - given Epi-Pen and Benadryl - her mother
    - symptoms resolved 1 1/2 hours
    - same spatula - used for baking peanut butter cookies for older sibling
Patient History III
Lesson Learned

- 15% of patients/year have accidental reactions
  - Management plan
    - Anticipate to be prepared - but not expect
    - Written plan for home/school
  

<20% of young children with peanut allergy outgrow the disease - generally by school age
<60% for milk, egg, wheat and soy
later now than previous reports

Fleischer 2007 Curr Allergy Asthma Rep. 7:175-181
Skripak 2007 J Allergy Clin Immunol. 120:1172-1177

Patient History V

• 19 years old – college junior
  • Sorority party - ate 1 bite of Rice Krispy treat
    • Immediate throat itching, urticaria on face and neck
    • Coughing significantly, wheezing, feeling of impending doom
    • Did not administer epi
    • 911 called at this point
    • Vomited
    • As ambulance arrived - had respiratory arrest
    • Intubated on site
    • Recovered in 3 days at local hospital
  • Rice Krispy treat – marshmallow cream and peanut butter

Burks AW. Lancet 2008;371:1538-1546

Patient History III

- Peanuts in the environment
  - Not aerosolized generally
  - Touch - maybe localized allergic reactions
  - Smell – not life-threatening symptoms

Sicherer J Allergy Clin Immunol. 112:185-182

- Must ingest - to have life-threatening or life-ending reactions
  - Can be as little as 1/1000th of peanut

**Christakis NA. This allergies hysteria is just nuts, BMJ 2008;337:a2880

Patient History V
Lesson Learned

- What do we know now - 15 years later
  • Epitope studies - stretches of 8-10 amino acids
    • IgE binding to specific linear epitopes - may predict longevity and severity - more data needed
  

- At risk group – for life-threatening episodes
  • Adolescent/young adult, asthma, known food allergy and not receiving epi

- Elevation/level of peanut IgE
  • Does not correlate with type or intensity of allergic reactions
  • Cannot say “severe” based on peanut IgE

Burks AW. Lancet 2008;371:1538-1546
Development of Treatment Options

• **Allergen non-specific**
  - Anti-IgE
  - Chinese herbal medicine

• **Allergen-specific**
  - Heat-denatured protein
  - Sublingual immunotherapy (SLIT)
  - Engineered recombinant protein
  - Oral immunotherapy (OIT)

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Skripak Current Opinion In Immunology 2008;20:690-696

Development of Treatment Options

• **Allergen non-specific**
  - Anti-IgE – previous blinded study, increased threshold at end of study
  - 25% of subjects - no difference after treatment
  - Future – utilized in combination with other IT


Skripak Current Opinion In Immunology 2008;20:690-696

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Chinese Herbal Medicine

• Herbal remedies used in Asia for centuries
• FAHF-2 used in studies, Li and colleagues
• Used in a mouse model of peanut allergy and worked to prevent symptoms of a reaction
• Increased IgE and increased IgG2a
• Favorable safety profile in early human studies

Li,X 2003 J.Allergy Clin.Immunol. 112:159-167

Heat-Denatured Protein

• Use of baked (or extensively heated) food for daily ingestion to promote desensitization and/or tolerance
  - Previous studies - binding to sequential and conformational epitopes, those outgrowing IgE to conformational
  - Milk-allergic children
    - challenged with baked milk product
    - 3 mo of ingestion
      – Milk SPT – wheal size less (p=0.001)
      – Increase in milk casin-specific IgG4 (p=0.005)
    - Consistent with OIT studies – “natural” form
  - Similar ongoing study with heated egg products

Sublingual Immunotherapy (SLIT)

- SLIT – hazelnut allergy in adults
  - DBPC, multi-center study
  - Adults w/ hazelnut allergy (n=22), type of patients
  - +PST and +OFC
  - Sublingual-discharge technique
  - 4 day rush build-up, 8-12 week daily SLIT (66 mg)
  - Active: 2.3 g to 11.6 g (OFC) vs. Placebo: 3.5 g to 4.14 g (OFC) (p<0.02)


- SLIT – peanut-allergic children and adults
  - Initial pilot study, 2nd-blinded study, 3rd study in Consortium of Food Allergy Res
  - 20 peanut allergic subjects (2-35 y/o)
  - SLIT to maintenance dose of 2 mg/day x 18 month
  - Safety data
    - Home doses associated w/ mild sx
    - IgE, IgG4, basophil and T-cell studies – ongoing

“Engineered” Recombinant Proteins

- Identified the peanut allergens Ara h 1-3 (Arachis hypogaea) and with the gene produced peanut proteins in the laboratory
- Identify IgE-binding epitopes on Ara h 1 – 3

- Substitute single amino acid within epitope
  - e.g. Ara h 2 – a.a. 27-36 - DRRCQSQLER
  - eliminates or markedly reduced IgE binding
  - T cell response unchanged

- Utilized the “engineered” peanut protein in a mouse model of peanut allergy – the “new” proteins worked to help prevent anaphylaxis in the peanut-allergic mice

- Initial safety studies through CoFAR starting in 2009

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Initial OIT Studies

- **Goals**
  - Clinical desensitization (tolerate more peanuts)
  - Eventual clinical tolerance (off treatment)
  - Identify immunologic markers associated with peanut OIT

- **Started with egg OIT protocol**
  - Desensitization occurred with 300 mg dose of egg white protein
  - Desensitization but not clinical tolerance after 18 months


Study Design – 300 mg Dose

<table>
<thead>
<tr>
<th>Dose Escalation</th>
<th>300 mg 4 mo</th>
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<tbody>
<tr>
<td>Initial escalation day</td>
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<tr>
<td>Maintenance</td>
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Peanut OIT Subjects

- 29 of 33 subjects completed the study - Duke and Arkansas sites
  - 4 allergic side-effects more than parents/investigators comfortable

- **Age at enrollment:** Mean 57 months (range 12-111)
  - Age at first reaction: Mean 15 months (range 8-48)
  - Peanut CAP FEIA: Mean 148 kU/L

- **Associated conditions:**
  - Atopic Dermatitis - 69%
  - Asthma - 62%
  - Allergic Rhinitis - 62%

Safety of Peanut OIT Dosing

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Initial Escalation Day</th>
<th>Buildup Phase</th>
<th>Home Dosing Phase</th>
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</thead>
<tbody>
<tr>
<td>Any</td>
<td>93% (77%, 99%)</td>
<td>46% (37%, 56%)</td>
<td>3.5% (2.3%, 5.1%)</td>
</tr>
<tr>
<td>Upper Respiratory</td>
<td>79% (59%, 92%)</td>
<td>29% (20%, 41%)</td>
<td>1.2% (0.6%, 2.5%)</td>
</tr>
<tr>
<td>Skin</td>
<td>61% (41%, 79%)</td>
<td>24% (17%, 32%)</td>
<td>1.1% (0.7%, 1.8%)</td>
</tr>
<tr>
<td>Abdominal</td>
<td>68% (48%, 84%)</td>
<td>5.5% (3.2%, 9.2%)</td>
<td>0.9% (0.6%, 1.4%)</td>
</tr>
<tr>
<td>Chest</td>
<td>58% (6%, 37%)</td>
<td>1.7% (0.6%, 5.1%)</td>
<td>0.3% (0.1%, 0.4%)</td>
</tr>
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Hofmann et al JACI 2009
Peanut Challenges

- 28/29 ingested 3900 mg – 300 mg dose
  - 1 had allergic symptoms (one hive, sneeze) and the challenge was stopped at 2100 mg due to parental concern

- Peanut OIT is effective in causing desensitization
  - Most subjects can tolerate 3900 mg (~13 peanuts)
  - All subjects had symptoms at less than 50 mg on initial desensitization day

Titrated Skin Prick Testing - Peanut

Mean Wheal Size Vs. Time
Bars are One Standard Error from the Mean

Serum levels of peanut-specific IgE

ANOVA model (baseline vs. follow up time points)
*p < 0.05, n=28 subjects

Serum levels of peanut-specific IgG and IgG4

ANOVA model (baseline vs. follow up time points)
*p < 0.05, n=28 subjects
Peanut-specific Foxp3+ T cells
T regulatory cells

Study Design – End of Study

Study Design – 4000 mg Dose

Peanut OIT-2nd Cohort

- Subjects (ages 26 – 65 months) completed maintenance OIT
- underwent an initial oral food challenge (OFC)
- if peanut IgE< 2 kU/L underwent a second OFC
- then a follow-up third OFC 4 weeks after stopping OIT to evaluate clinical tolerance

- 10 subjects ingested 3900 mg peanut protein at the initial OFC
- 33 - 41 months on OIT
- 8 subjects with peanut IgE< 2 kU/L passed a second OFC
- follow-up third OFC 4 weeks after OIT
- subjects now have peanut in their diets and are clinically tolerant

- Peanut IgE levels decreased significantly over time for both groups (p<0.001)
Peanut OIT – Blinded Study

- 22 subjects (7 placebo; 15 peanut) have completed 3 phases of study and OFC.
  - All subjects reached the maximum dose of 6 mg during the initial day escalation and 4 g during build-up.
  - During OFC, placebo OIT subjects tolerated 460 mg or ~1 peanut (range 15-1900 mg); peanut OIT subjects tolerated the maximum of 5000 mg or ~13 peanuts (p=0.008).
  - Mean specific IgE (12 month period from baseline to OFC): peanut 258 to 282 vs. placebo 47 to 35 kU/L.
  - Titrated prick skin testing: peanut OIT subjects mean 12.3 to 6.2 vs. placebo mean 16.4 to 15.1 mm, (p<0.006).

Jones et al. Double-Blind, Placebo-Controlled (DBPC) Trial of Oral Immunotherapy (OIT) in Peanut Allergic Children, 2009 AAAAI meeting

Immunotherapy for Food Allergy Future

- Investigational studies to understand possible clinical benefit and mechanism
  - Randomized, blinded controlled trials – some in process now.
- Determine mechanism of action of IT – basophils/mast cells, humoral and cellular immunity.
- Determine if food IT induces clinical tolerance or simply desensitization.
- Goal: development of active treatment for food allergy.

Patient History VI

- 34 years old - married and pregnant
- Wants to know what to do to prevent what she went through growing up
  - Pregnancy
  - During nursing
  - When to start solid foods
- Recent AAP recommendations – for at risk family
  - Breast feeding >4 months (no allergy benefit thereafter)
  - No solids until >4 months

Greer, Sicherer, Burks 2008 Pediatrics 121:183-191
Sicherer, Burks 2008 J Allergy Clin Immunol. 122:29-33

Current State of Food Allergy Research

- Food allergy is an increasing health problem in “westernized” countries
  - These children go on to have other allergic diseases
- Few foods account for ~90% of food allergic reactions
  - milk, egg, peanuts, nuts, fish & shellfish
- New therapies are on the horizon
  - Anti-IgE - combined with other new therapies for treatment
  - SLIT/IT
  - Modified allergenic proteins
  - Non-traditional forms of immunomodulation - TCM
Thanks

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Team
- Physicians: Joe Roberts, Brian Vickery, Stacie Jones (AR), Hugh Sampson (Mt. Sinai), Wayne Shreffler (Mt. Sinai)
- Study coordinators: Pam Steele, Jan Kamilaris, Alison Edie
- Fellows: Amy Scurluck, Arianna Buchanan, Todd Green, Scott Nash, Pooja Varshney, Ananth Thyagarajan, and Drew Bird
- Laboratory: Xiaoping Zhong, MD/PhD, Laurent Pons, PhD, Mike Kulis, PhD, Herman Staats, PhD
- DCRU/Rankin staff