The Natural History of Food Allergy

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Disclosures

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Objectives

1. Review the natural history of IgE-mediated food allergy in children and adults
2. Discuss the epidemiology of IgE-mediated and non-IgE-mediated food allergies in the United States
3. Evaluate the risk factors for food-induced anaphylaxis and recognize the epidemiology of anaphylaxis
FOOD ALLERGY BACKGROUND
GI Hypersensitivities

**IgE-Mediated**
- Immediate Hypersensitivity (aka Food Allergy)
- Oral Allergy Syndrome

**Mixed**
- Eosinophilic Esophagitis (EoE)
- Eosinophilic GI Disease (EGID)

**Non-IgE-Mediated**
- Food Protein-Induced Enterocolitis (FPIES)
- Milk Protein Intolerance
- Lactose Intolerance
- Celiac Disease
- “Food Sensitivities”
Background

- Roughly 8% of children have a food allergy
  - ~3% of all children have multiple food allergies
- Children with eczema are at significantly increased risk for food allergy
- More common in males (~60%)
- IgE-mediated food allergy is triggered by a specific protein in the food

- Significant burden on quality of life
- Standard of care is unsatisfying
- Strict avoidance
- Education
  - Reading labels
  - Recognizing and treating a reaction
  - Natural history
  - Managing special situations
  - How to use autoinjectable epinephrine
  - Providing Food Allergy Action Plans
- Nutritional monitoring

Epidemic Increase in Food Allergy

Food Allergy Prevalence
(Reported, NHIS data)

Jackson KD, et al. NCHS data brief, no 121. 2013
TOP 8 FOOD ALLERGENS

- Milk
- Soybeans
- Peanuts
- Shellfish
- Fish
- Tree Nuts
- Eggs
- Wheat
Global Variability

- Thailand
  - Fish, shrimp
  - Cow’s Milk
  - Egg
  - Ant egg
- South Korea, Japan
  - Buckwheat
  - Fish, shellfish
  - Bird’s nest
  - Royal jelly

- India
  - Chickpea
- Middle East
  - Sesame seed
- Turkey
  - Beef
- Europe
  - Fruit
  - Vegetables

CAUTION
Limitations

- General v. referral/selected populations
- Retrospective v. prospective
- Oral food challenges
  - Frequency – as clinically indicated v. scheduled intervals
  - Open v. DBPC
- Length or frequency of follow-up evaluation
- Selection bias
- Varying definitions of food allergy
- Overall paucity of data
IN AN IRONIC TWIST OF FATE, DEATH SUCCUMBS TO HIS PEANUT ALLERGY

PEANUT & TREE NUTS
Natural history of peanut allergy and predictors of resolution in the first 4 years of life: A population-based assessment

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Lyle C. Gurrin, PhD, a,c for the HealthNuts study Parkville, Australia, and Manchester, United Kingdom
Peanut Allergy After Diagnosis

- 20% outgrow PN allergy
- Reactions occur in 3 to 33% of patients per year
  - May be decreasing
- Repeated exposures do not appear to increase severity
- After age 6y, PN sIgE levels tend to remain relatively stable
- 95% PPV for persistent PN allergy
  - SPT 1y >13mm, 4y > 8
  - sIgE 1y >5, 4y > 2
- Risk of recurrence after passing OFC if not eating regularly
  - Encourage regular consumption
  - Recommend continuing to carry epinephrine for 1-2 years

Tree Nuts

- 30-40% of children with peanut allergy will have at least 1 tree nut allergy
  - ~70% of tree nut allergic children are also allergic to peanut
- 40% with cross-allergy to another tree nut
  - Cashew and Pistachio
  - Walnut and Pecan
  - Increased risk with AD
- ~10% of children will outgrow a tree nut allergy
  - More likely if they outgrew their peanut allergy
- Severe reactions are most common with cashew and walnut

Phenotypical characterization of peanut allergic children with differences in cross-allergy to tree nuts and other legumes

Mathias Cousin\textsuperscript{1,2}, Stéphane Verdun\textsuperscript{3}, Maxime Seynave\textsuperscript{1}, Anne-Christine Vilain\textsuperscript{1}, Amélie Lansiaux\textsuperscript{3}, Anne Decoster\textsuperscript{4} & Christine Sauvage\textsuperscript{1}

Trends in Peanut Allergy and Sensitization

ADULT FOOD ALLERGY
• Food allergy reported by 21% of adults (20-45y) in a sample in Sweden and Iceland at baseline and 9y follow-up
  • Fruits, vegetables and nuts were most common
  • Reported food allergy was unchanged over time, but sensitization to foods decreased while aeroallergen sensitization increased
Adult-Onset Food Allergy

- Believed to be relatively rare
- More common with fish and shellfish
- Self-report of adult food allergy is uncommonly confirmed with OFC
- Many cases represent OAS

Northwestern chart review
- 15% of new food allergy diagnoses were adult-onset
- Peaked in the early 30s
- Anaphylaxis in 50%

Food triggers
- Shellfish 54%
- Tree nuts 43%
- Fish 15%
- Soy 13%
- Peanut 9%

A Cautionary Tale

- 50y female presents to an allergist
  - Hay fever
  - Vague GI complaints
- SPT
  - Multiple + aeroallergens
  - PN 2+
- sIgE PN 0.69 kU_A/L
- Instructed to avoid PN

- Strictly avoids PN for 3 year, after previously eating and tolerating with no specific concern for reaction
- Undergoes observed PN OFC
  - Develops wheezing with 1g of PN butter

MILK & EGG

Greetings from Wisconsin
"America's Dairyland"
Milk & Egg Natural History

- Generally good prognosis
  - ~70-80% outgrow
  - Persisting longer than previously observed
- Those tolerating baked goods containing milk or egg have a better prognosis
- sIgE and SPT size at diagnosis can help predict who is more likely to outgrow
  - Variability among other factors
- CoFAR calculator
  - http://www.cofargroup.org
Cow’s Milk

- Poorer prognosis
- Moderate to severe AD
- Reaction within first 30d of life
- Lower reaction threshold (<10mL)

- 79% outgrow by 16y
- CoFAR observational cohort
  - 52.6% resolved milk allergy at a median age of 63m

Early-life gut microbiome composition and milk allergy resolution

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New York, NY, Baltimore and Rockville, Md, Chapel Hill, NC, Little Rock, Ark, and Denver, Colo

- CoFAR milk allergy cohort
- No association between early life exposures shaping infant gut microbiome and milk allergy resolution
  - Delivery method, breastfeeding, solid food intake, and antibiotics
  - Microbiome at 3-6m enriched with *Firmicutes* and *Clostridia* associated with resolution
Egg

- Poorer prognosis
  - Systemic reaction to egg
  - AD flare from egg
  - Baked egg reactive
- CoFAR observational cohort
  - 49.3% resolved egg allergy at a median age of 72m
- HealthNuts
  - 47% resolved by 24m
  - Low vitamin D (<50nmol/L) associated with persistent egg allergy

OTHER FOODS
• High-risk, Australian birth cohort (MACS)
  • Born between 1990 and 1994
• Poly-food sensitized children were more likely to have probable food allergy and sensitization at 12 and 18y
• No gender change at adolescence
Wheat

- Wheat sIgE has a poor predictive value
- Unaffected by AD status, multiple food allergy, and other factors

- Hopkins- 62% tolerant by 10y
- Poland- 76% tolerant by 18y
- Japan- 66.3% tolerant by 6y

Soy

- 69% outgrow by 10y
- Unaffected by AD status, multiple food allergy, and other factors

Other Foods

• Reactions to uncommon food allergens are rare despite larger SPT and sIgE
• 18% failed these foods v. 45% for common allergens (PN, milk, egg, wheat)
ANAPHYLAXIS
Anaphylaxis

- Food is the most common trigger
  - Estimates vary from 0.4% to 40% of allergic food reactions resulting in anaphylaxis
- Incidence has increased, but fatalities have not
  - New York State, 1990-2006- >4-fold increase in hospitalization for anaphylaxis
  - UK, 1990-2012- doubling of hospitalization for food-induced anaphylaxis
- African American and Hispanic children have significantly higher rates of food-induced anaphylaxis, and more ED visits
- Risk factors for severe anaphylaxis
  - Older age and comorbid conditions (CV disease, etc)
  - Sub-optimal asthma control
  - Better prognosis with a history of AD, and AI consultation within 12m

Anaphylaxis Compared to Other Emergencies

FPIES
Food Protein Induced Enterocolitis Syndrome
What is FPIES?

- Infants <12m (mean 5.5m)
  - Adults with fish and shellfish
- Onset of symptoms 1-4 hours after ingestion, resolution in 6 hours
  - Vomiting (100%)
  - Lethargy (85%)
  - Pallor (67%)
  - Diarrhea (24%), later onset and prolonged
  - Hypothermia (temp <36°C, 24%)
  - Hypotension (15%)

- Common triggers
  - Cow’s Milk
  - Soy
  - Grains
    - Rice
    - Oat
  - Poultry
  - Fish and Shellfish
  - Legumes
  - Banana
  - Vegetables
    - Avocado
    - Sweet potato

Epidemiology

- The incidence in a large Israeli birth cohort was 0.34%
- Male predominance (60%)
- Negative family history
- Not highly atopic

Natural History

- Majority outgrow milk/soy FPIES by the age of 30 months-3y
  - Food-specific rates vary widely by study
- No secondary cases of IgE mediated food allergy HAD been reported
  - Sinai has ~25% with FPIES and IgE-mediated FA
  - *So…SPT prior to reintroduction after a period of avoidance

FIG 5. Kaplan-Meier plot for the cumulative probability of recovery from CMP-induced FPIES. More than 90% of patients recovered from FPIES after 900 days.

<table>
<thead>
<tr>
<th>Food</th>
<th>Resolution</th>
<th>Study</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk</td>
<td>64% by 10m</td>
<td>Hwang 2007</td>
<td>Korea</td>
</tr>
<tr>
<td></td>
<td>100% by 20m</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>94% by 30m</td>
<td>Katz 2011</td>
<td>Israel</td>
</tr>
<tr>
<td>*IgE negative</td>
<td>25% by 3y</td>
<td>Caubet 2014</td>
<td>NYC (Sinai)</td>
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<tr>
<td></td>
<td>90% by 3y</td>
<td>Lee 2017</td>
<td>Australia</td>
</tr>
<tr>
<td>Soy</td>
<td>80% by 5y</td>
<td>Vazquez-Ortiz 2017</td>
<td>Spain</td>
</tr>
<tr>
<td></td>
<td>83% by 3y</td>
<td>Mehr 2009</td>
<td>Australia</td>
</tr>
<tr>
<td></td>
<td>27% by 3y</td>
<td>Anna NW 2003</td>
<td>NYC (Sinai)</td>
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<td>20% by 3y</td>
<td>Caubet 2014</td>
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<tr>
<td>Rice</td>
<td>83% by 3y</td>
<td>Mehr 2009</td>
<td>Australia</td>
</tr>
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<td></td>
<td>40% by 3y</td>
<td>Anna NW 2003</td>
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<td>30% by 3y</td>
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<td>100% by 5y</td>
<td>Vazquez-Ortiz 2017</td>
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<td>Oat</td>
<td>30% by 3y</td>
<td>Caubet 2014</td>
<td>NYC (Sinai)</td>
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<td>Fish</td>
<td>75% by 5y</td>
<td>Vazquez-Ortiz 2017</td>
<td>Spain</td>
</tr>
<tr>
<td>Egg</td>
<td>30% by 5y</td>
<td>Vazquez-Ortiz 2017</td>
<td>Spain</td>
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WHAT IS NATURAL HISTORY?
Remaining Questions and Future Directions

• What is different about the different allergens?

• Are we seeing changes in the natural history or only observing different cohorts?

• What characterizes the development of tolerance?

• Can we modify the natural history?
  • Early introduction
  • Prevent atopic dermatitis?
  • Emerging treatments?
  • Role for biologics?
  • Vitamin D?
Important Points

- Milk, egg, wheat and soy allergies have a good prognosis
  - 70-80% will outgrow during childhood
- Peanut allergy is consistently observed to resolve in 20% without intervention
- Tree nuts, seeds, fish and shellfish are uncommonly outgrown
  - 0-10%
- Data is lacking for other foods, and in adults
- Larger SPT and higher sIgE = less likely to outgrow
- Annual follow-up with sIgE (+/- SPT) is recommended
  - Space if unlikely to develop tolerance
  - Should have a higher threshold for doing an OFC if no history of reaction and if it is an uncommon food
THANK YOU!

A special thank you to my mentors, Drew Bird, Allan Bock, and Donald Leung
Questions & Discussion
The Natural History of Food Allergy

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