Non-IgE Mediated Food Reactions

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Objectives

- Discuss various definitions regarding adverse reactions to food
- Remind physicians that not all reactions are allergic (IgE) or life threatening
- Discuss presentation/characteristics of some common non-IgE mediated reactions to foods
- Discuss basics of evaluation and treatment

Definitions

- "Allergy" doctor vs patient definition
- Adverse food reactions – any untoward reaction (colic, reflux, constipation)
- Food hypersensitivity – adverse reaction due to an immune mechanisms (may be stated now as non IgE mediated food allergy)
- Food intolerance – any non-IgE mediated adverse reaction to food: milk, soy intolerance
  - Food poisoning/infection
  - Non-toxic/Tonic reactions
  - Pharmacologic reactions (caffeine, tyramine)
  - Idiosyncratic reactions
  - Metabolic

Non IgE Mediated Diseases

- Protein Intolerance
  - Enterocolitis
  - Protein Enteropathy
  - Protein Enterocolitis
- Celiac Disease/Dermatitis Herpetiformis
- Heiner's Syndrome
- Disaccharidase Deficiencies/Metabolic
- Auriculotemporal Syndrome
- Gustatory Rhinitis

Other considerations

- GI Disorders: pyloric stenosis, pyloric stenosis, TE fistula, cystic fibrosis, malabsorption, peptic ulcer, GE reflux
- Metabolic disorders : Galactosemia, phenylketonuria
- Pharmacologic: jitteriness (caffeine), headache (tyramine), pruritus (histamine)/Toxic (fish)
- Psychologic disorders: phobias/aversions
- Gallbladder/liver disease; hiatal hernia

Pre Test

1. Heiner's Syndrome is associated with:
   a. circulating IgM antibodies to Milk
   b. macrocytic anemia
   c. cow's milk and pulmonary infiltrates
   d. usually occurs after age 2

2. Protein Induced Enterocolitis:
   a. has prominent diarrhea and vomiting
   b. occurs usually with protein hydrolysate formula
   c. is associated with normal growth
   d. patch testing has a definitive diagnostic role

3. A group of businessmen are having seafood at a Japanese restaurant. Each experienced flushing. Three of the four developed urticaria, one shortness of breath. Paramedics gave epinephrine to one and the others felt well enough to go home.
   The most likely cause was:
   a) MSG intolerance
   b) Scromboid fish contamination
   c) seafood allergy
   d) neurotoxic shellfish poisoning
**Non IgE Mediated/IgE Mediated Diseases?**

- Eosinophilic Esophagitis
- Eosinophilic Gastritis/Gastroenteritis

**Protein Intolerance**

- Milk and Soy most likely causes
- 3 well known forms
  - Proctitis
  - Enteropathy
  - Enterocolitis

**Proctitis/Proctocolitis**

- Onset: usually occurs 2-8 weeks of age
- Proteins: cow’s milk, egg or soy via maternal breast milk
- Not IgE mediated; histology shows eos.
- Small amounts of blood/mucous in stool
- No vomiting, diarrhea, or decrease BP
- No FTT
- Resolves in 72 hrs with elimination in mom’s diet or hypoallergenic formula
- Tolerant by age one; least problematic

**Enteropathy**

- Onset: infancy – age 2
- Proteins: cow’s milk, soy, (cereals, egg, fish)
- Not IgE mediated; more severe
- Malabsorption, FTT, diarrhea, mild emesis, hypoproteinemia
- Histology: patchy villous atrophy
- Can occur also after infectious gastroenteritis

**Enterocolitis (FPIES) – food protein induced enterocolitis syndrome**

- Onset: 1st 6 months
- Protein: usually milk and soy (equal), also reported in grains (rice) and poultry
- Not IgE mediated; crypt absesses/diffuse inflammatory cells esp. plasma cells
- FTT, diarrhea, blood in stool, decrease BP possible; shock/methemoglobinemia
- Resolves usually by 3yo

**FPIES (cont.)**

- Readministration of protein after resolution with avoidance can yield characteristic 1-4 hour delay in symptoms: vomiting, dehyration, decrease BP may mimic anaphlyaxis (shock in up to 20%)
- Reported associated rise in absolute neutrophil count over 3500
- Use protein hydrosylate or AA formula
**Celiac Disease/Dermatitis Herpetiformis**

- All ages; occurs over months
- Symptoms of malabsorption with chronic diarrhea, steatorrhea, abdominal pain/distension, gas, weight loss, FTT
- Immune response to Gliadin (alcohol soluble portion of gluten in wheat, rye, barley)
- Biopsy: extensive flattening of villi
- Associated with HLA-DQ2 and 8

**Celiac Disease (cont.)**

- 90% IgA anti-gliadin; antiendomysium Abs
- Immune responses to gluten can also cause chronic, intensely puritic papulovesicular rash over extensor surfaces of elbows, knees, and buttock
- May have IgA in skin biopsy
- Often not seen with GI symptoms
- Rash resolves with elimination of gluten – life long
- Increase risk of malignancy

**Distinguishing Clinical Features**

Adapted from Pediatric Allergy Practice and Principles. D Leung 2003.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Proctocolitis</th>
<th>Enterocolitis</th>
<th>Enteropathy</th>
<th>Celiac Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>Absent</td>
<td>Prominent</td>
<td>Variable</td>
<td>Variable</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Minimal, bloody</td>
<td>Prominent</td>
<td>Moderate (may have edema)</td>
<td>Variable</td>
</tr>
<tr>
<td>Growth</td>
<td>Normal</td>
<td>Poor</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Foods</td>
<td>Breast, milk, soy</td>
<td>Milk, Soy</td>
<td>Milk, Soy</td>
<td>Gluten</td>
</tr>
<tr>
<td>Onset</td>
<td>Days to 6 mo.</td>
<td>Days to 1 yr (occurs with diathesis)</td>
<td>2 – 24 mo.</td>
<td>&gt; 4 mo.</td>
</tr>
</tbody>
</table>

**Heiner’s Syndrome**

- Adverse pulmonary response to cow’s milk with pulmonary infiltrates, pulmonary hemosiderosis, Fe def. anemia, recurrent pneumonia, FTT
- Uncommon; infancy
- Immune reaction with precipitating IgG antibodies; may have peripheral blood eosinophilia; mechanisms unknown
- Rare reports with egg and pork

**Disaccharidase Deficiency/Metabolic**

- Lack of enzyme needed to breakdown sugars
- Lactase
- Sucrase-isomaltase
- Glucose-galactose (lactose breakdown) – galactose is a monosaccharide – build up of galactose (galactosemia) toxic

**Auriculotemporal Syndrome**

- Any age
- Facial Flush/ blotch on cheek with tart foods
- No itching
- Reproducible/short lived
- Test with “Sweet tarts”
**Gustatory Rhinitis**

- Profuse rhinorrhea after spicy meal
- Substance P induced
- Treated with anti-cholinergic (Ipatropium Bromide) nose spray and avoidance
- ? Role of capsaicin (American pepper plant)

**Eosinophilic Rhinitis**

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**Eosinophilic Diseases**

- Esophagitis; gastritis; gastroenteritis; may affect varying regions causing various symptoms
- ? 8-10% of peds non responsive to GERD : EE
- Reflux like/dyspepsia/dysphagia, early satiety, post-prandial abd. pain, vomiting, diarrhea, FTT; may be obstruction
- Eosinophilic infiltration of various degrees – 6% with GERD ; ? 20-40 /hpf in EE
- Both IgE and non IgE mechanisms considered
- Recent studies emphasize role of IL-5 and Eotaxin 3 gene (single nucleotide polymorphism)

**Eosinophilic Disorders (cont.)**

- ? Role of skin testing (foods/aeroallergens)/?
  Different mechanisms TH 2 immune repsonse with eos. and IL 4/5/13 seen
- ? Role of atopy patch test
- Elimination diets improve 70-80 %; elemental diets effective 90-95%
- Diets can take 12 weeks for effect
- Treated with avoidance, steroids; ? Role of leukotrienes modifiers, Anti – IL 5

**Type IV Reactions: adapted from W Pichler, Ann Intern Med 2003;139:683-9**

<table>
<thead>
<tr>
<th>Type</th>
<th>Immune Response</th>
<th>Pathology</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVa</td>
<td>Th1 (IFN gamma)</td>
<td>Monocyte activation</td>
<td>Eozema</td>
</tr>
<tr>
<td>IVb</td>
<td>Th2 (IL-4 and IL-5)</td>
<td>Eozinophil infiltration</td>
<td>Maculopapular,bull, nod</td>
</tr>
<tr>
<td>IVc</td>
<td>CTL, Perforin, granzyme</td>
<td>CD8 or CD8 killing</td>
<td>Maculopapular, bull, nod, Pustular</td>
</tr>
<tr>
<td>IVd</td>
<td>T cells (IL-8)</td>
<td>Neutrophil recruit/activ.</td>
<td>Pustular</td>
</tr>
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</table>

**Scromboid Fish / Food Poisoning**

- Aging raw fish/canned (esp darker meats: tuna, mackerel) Proteus / Klebsiella
  - Can see with fermenting cheese
- Histidine decarboxylated to histamine
- Anaphylaxis like: Flushing , itching, vomiting
- History of others with similar reactions
- Monoamine oxidase inhibitors or isoniazid – anaphylactoid reactions to contaminated fish /cheese because of decreased ability to metabolize vasoactive substances
### Food Poisoning / Toxic Effects

- Poisoning from toxic substances in mushrooms, herbal teas, puffer fish/algae neurotoxin in reef fishes that ingest algae
- Green potatoes (solanine)/raw navy beans (lectins) --- severe gastroenteritis/gas
- Canned foods with Clostridium other
- Vitamin toxicity (A irritability/vomitting/Vit. D – anorexia/N - V-D)

### Cyclic Vomitting

- Idiopathic disorder; some link to abdominal migraines/dysautonomia/ hypopit/adrenal axis disorders/
  cessation of chronic cannabis use/ foods
- primarily children around age 5
- Male = female; ? Adults as well
- Recurrent bouts of stereotypical vomiting (timing of onset/acute: symptoms/duration (less than a week) 3 or more times a year with periods of normal health in between
- Diagnosis of exclusion
- Avoid triggers (physical exhaustion/motion/fasting/certain foods; supportive care

### Food Additives/Dyes

- Little data
- Few natural dyes red (carmine) and yellow (annato from tree seed (Bixa Orellana)
- Sulfites (preservative and control fermentation) - dried fruits/wine/some fruit juice; reported problems with ingestion ? Mechanism ? role in urticaria/anaphylaxis with ingestion
- Reactions (headaches, burning sensation neck/chest to monosodium glutamate hard to confirm
- Pharmacologic: tyramine; caffeine theobromine/phenylethylamine /may cross breast milk

### Diagnosis/Evaluation

- History:
  - Identify suspect food; previous exposure
  - Quantity
  - Time of onset
  - Nature and duration of symptoms
  - Reproducibility
  - Pictures/videos
  - Hidden sources (natural flavors/contamination)

### Diagnosis / Evaluation (cont.)

- Physical Exam
- Rule out other causes
- Testing/Laboratory evaluation based on results

### Testing/Laboratory Evaluation

- Prick skin tests (no ID), ? Fresh foods
- Specific IgE (no role for IgA and IgG4)
- ? Tryptase levels
- Atopy patch test
- Oral Challenges (open or blinded); single or multiple
- Elimination diets
- GI evaluation : upper GI, biopsy, swallowing studies, ph probe etc
Unproven Testing/Therapies

- Multiple body minerals/chemical studies
- Hair analysis
- Stool analysis for yeast
- Applied Kinnesiology/ electromagnetic fields
- Provocation/neutralization
- Multiple supplements

Treatment

- Dependent on disease type
- Periodic re-assessment
- Avoid unnecessary testing
- Re-assure parents

Diseases With No Proven Allergic/Immunologic Association with Foods

- Autism
- ADHD
- Bedwetting
- Other behavior disorders

Summary

- History is most important element in making diagnosis
- Recognize common signs and symptoms
- Choose appropriate testing
- Periodic Evaluation

Tranquility: View from my parents cottage on Lake Ontario

Questions?????

Post Test

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THANK YOU FOR YOUR ATTENTION!
References

- **Up To Date.** Dietary protein-induced proctitis/colitis, enteropathy, and enterocolitis of infancy. C Lifschitz. May 1, 2009
- **ACAAI/AAAAI Maintenance of Certification, Board Review Course. Food Allergy.** S Sicherer. 2007