Learning Objectives

- Understand the types of adverse food reactions.
- Differentiate food allergy and food sensitivity.
- Understand the role of IgE (Immunoglobulin E) in allergic reaction.
- Explore the types of IgE and non-IgE mediated food allergy.
- Summarize the series of events in allergic reaction.

Learning Objectives

- Examine symptoms of allergic reaction including local and systemic anaphylaxis.
- Summarize the approach to food allergy diagnosis.
- Survey common food allergens.

Adverse Reactions to Food

- 30% of population report family member with food “allergy”
- Actual % estimates vary <1-7%
- Subpopulations/ethnic groups differ markedly

Most Common Allergic Foods/Groups

- Cows milk
- Crustacea
- Eggs
- Fish
- Peanuts
- Soybean
- Tree nut
- Wheat

Adverse Food Reactions

Allergy – Sensitivity - Intolerance

- General terms that can be applied to any clinically abnormal response to food or food additives.
- Many symptoms are similar.
Types of Adverse Food Reactions

- Allergy
- Non-immune anaphylaxis (anaphylactoid)
- Intolerance
- Metabolic
- Idiosyncrasy

- Pharmacological (drug interaction)
- Toxicity

Types of Food Sensitivities and Allergies

- True food allergy
- Food sensitivities
  - Anaphylactoid reactions
  - Metabolic food disorders
  - Idiosyncratic reactions
- Some in several classes
- Food aversions
  - Mimic sensitivity but no blinded response

Food Allergy: Hypersensitivity

- Immune-mediated reaction
- Can be triggered by very small amounts of food
- Occurs on second exposure or to a cross reacting antigen
- Anaphylaxis and cutaneous reactions most common

Food Allergies: History

- Observed since early Greeks and Romans
  - Hippocrates documents milk sensitivity
- Injected normal person with fish extract - no effect (1921)
  - Injected serum of sensitive person, then fish extract - allergic reaction
- Researchers discovered IgE (Immunoglobulin E, antibody subclass) in serum was cause (1966)

Food Allergy Epidemiology

- Affect ~ 6% of children < 3 years old
  - Milk & soy
  - Cow’s milk: 2.5%
    - Over 80% tolerant by 5th birthday
  - Egg allergy: 1.5%
    - Over 85% tolerant by 3rd birthday
  - Peanut allergy: 0.5%
    - Clinical tolerance reached in a minority
    - Prevalence may be increasing in children

Epidemiology

- Small subpopulation at risk <1%
- 65% of susceptible people have close relative with allergy
- Increased intestinal permeability to macromolecules predisposes
  - Viral gastroenteritis, premature birth, cystic fibrosis
  - Leaky gut syndrome (LGS)
Epidemiology

- Higher in children with other atopic disorders
  - 36% of children with moderate to severe atopic dermatitis (eczema)
  - 6% of asthmatic children
- Adverse reactions to food additives 0.5-1% of children

Pathophysiology

- GI tract forms a barrier to outside environment
- GALT inhibits responses to non-dangerous antigens while mounting responses to pathogens
  - Gut-Associated Lymphoid Tissue
- Oral tolerance = unresponsiveness
- Intact food antigens may penetrate the GI tract but not cause clinical symptoms
- Develop in genetically predisposed individuals when oral tolerance fails

Types of Hypersensitivity

- Type I: Immediate hypersensitivity
- Type II: Antibody dependent cytotoxicity
- Type III: Antigen-antibody complex mediated
- Type IV: Cell-mediated hypersensitivity

IgE Mediated

- Type I: Immediate hypersensitivity
  - Failure in oral tolerance leads to excessive food-specific IgE antibodies
  - These bind receptors on many cells (esp basophils and mast cells)
  - Food allergens penetrate mucosal barrier and bind these IgE antibodies
  - Cellular mediator release

Cutaneous
- Urticaria (hives)
- Angioedema (welts)
- Morbilliform rashes
- Flushing

Gastrointestinal
- Lip, tongue, and palatal pruritis and swelling
- Laryngeal edema
- Vomiting and diarrhea

Respiratory
- Upper
  - Ocular pruritus and tearing
  - Nasal congestion
- Lower
  - Bronchospasm/wheezing

Generalized
- Anaphylactic shock
### Non-IgE Mediated

#### Type II: Antibody dependent cytotoxicity
- Specific antibody binds to a surface tissue antigen and induces complement activation (system of serum immunoproteins which interact in a cascade).
- Complement \(\rightarrow\) inflammatory mediators \(\rightarrow\) tissue damage
- Milk-induced thrombocytopenia

#### Type III: Antigen-antibody complex mediated
- Complement activation
- Has been implicated in food related complaints
- Can be found in sera of normal patients
- IgE-food antigen complexes are more commonly found in patients with food hypersensitivity
- Little support for causing disease

#### Type IV: Cell-mediated hypersensitivity
- Mediated by sensitized CD4+ T lymphocytes which process antigens and release lymphokines.
- The lymphokines promote a reaction mediated through macrophages beginning in hrs but reaching a peak in 2 to 3 days.
- Implicated in foods with delayed onset of sx
- Likely to contribute to a number of GI disorders
- Ingestion of sensitizing antigen may cause mucosal lesions

### Cell Mediated Hypersensitivity
- **Cutaneous**
  - Contact dermatitis
  - Dermatitis herpetiformis
- **Gastrointestinal**
  - Food protein-induced enterocolitis
  - Food protein-induced proctocolitis
  - Food protein-induced enteropathy syndromes
  - Celiac disease
- **Respiratory**
  - Food-induced pulmonary hemosiderosis (Heiner syndrome)
  - Intra-alveolar bleeding

### Mixed IgE and Cell Mediated
- **Cutaneous**
  - Atopic dermatitis
- **Gastrointestinal Inflammation**
  - Allergic eosinophilic esophagitis
  - Allergic eosinophilic gastroenteritis
- **Respiratory**
  - Asthma

### Allergic Response Type I Hypersensitivity
1. The food is eaten.
2. Reaches the stomach and small intestine where the proteins are not digested correctly
3. Intact proteins cross the small intestine and reach the blood and lymph system.
4. The immune system makes antibodies against the proteins
5. Allergic people make Immuglobulin E (IgE) which non allergic people don’t.
6. IgE binds to the surface of mast cells or basophils which sensitizes them.
Allergic Response: Second Exposure

1) The person eats the food a second time.
2) The protein enters the body
3) Binds to and cross-links two to IgE antibodies.
4) Causes the mast cell or basophil to degranulate.
5) Granules contain 40 different substances that cause allergic reactions.
   • Histamine, prostaglandins, leukotrienes

IgE Mediated Food Allergy Summary

• Production of IgE antibodies
• IgE bind to surface of mast cells or basophils
• Second exposure to allergen
• Allergen cross-links IgE on surface
• Release of histamine, bradykinin, leukotrienes, TNF
• Inflammation and swelling via capillary leakage and wbc
• Allergic reaction

Mast Cell Sensitization

Food Allergy: Symptoms

• Respiratory = asthma, wheezing, bronchospasms, dyspnea (shortness of breath)
• Cutaneous = urticaria (hives), eczema, rash, pruritis
• Gastrointestinal = vomiting, diarrhea, abdominal pain
• Inflammation, vasoconstriction, hypotension, chest pain, nausea

Food Allergy: Symptoms

• Other = anaphylaxis
• Mild and annoying to fatal
• Depend on amount ingested and length of time from initial exposure
• Not all symptoms in all people
Food Allergens

- Almost all natural food proteins
- Papain - only known additive - meat tenderizer additive - enzyme
- Penicillin contaminants in meat and dairy products are potential hazard

Local Anaphylaxis (atopy)

- About 10% of people have "atopy" (atopic syndrome) and are easily sensitized to allergens that cause a localized reaction when inhaled or ingested.
  - This can produce hay fever, hives, asthma, etc.

Generalized Systemic Anaphylaxis

- Accounts for 1/3 of all anaphylaxis seen in emergency rooms
- Symptoms
  - Skin – urticaria / angioedema
  - Respiratory – rhinitis, bronchial hyperreactivity
  - Cardiac – hypotension, arrhythmias, vascular collapse
  - GI – nausea, vomiting, abdominal cramping, diarrhea
- Dx by history and demonstration of food specific IgE

Fatal Food-Induced Anaphylaxis (32 cases)

- Most were adolescents or young adults
- History of prior reaction to implicated food
- Only 10% had epinephrine available
- Peanuts and tree nuts for majority (94%)

Exercise-Induced Anaphylaxis (EIA)

- Rare form occurring when patient exercises 2-4 hrs after ingestion of specific food
- Without exercise, food no problem
- Most common in women 15-35 y.o.
  - Sx more pronounced just prior to menstruation
  - Dx based on history and evidence of specific IgE
- Common offenders: wheat, celery, shellfish, fish, fruits, milk

Diagnosis of Food Allergy

- Self/parental often erroneous
- Food diary-when/what/how much
- Double-blind food challenge (DBFC)
  - Neither patient nor doctor know if placebo or allergen (crossover)
- Skin prick test
- RAST
Skin Prick Test
- To determine if IgE involved
- Usually preliminary test
- Apply allergen extract to skin
- Scratch to increase access to blood
- Inflammation results from release of histamine, edema and swelling
- Positive control = histamine
- Result in ~ 20 min

Radio-Allergosorbent Test (RAST)
- Also test for IgE
- Apply crude extract of allergen to solid phase (tissue culture plate)
- Add patient serum
- IgE (if present) binds allergen
- Add anti-IgE radiolabeled antibody
- Measure binding

Common Allergenic Foods: Infants/Children
- Cow's milk - most common
- Eggs
- Legumes
  - peanuts
  - soybean
- Wheat

Common Allergenic Food: Adults
- Legumes - peanuts, soybean
- Crustacea - shrimp, crab, lobster
- Molluscs - clams, oyster, scallop
- Fish
- Tree nuts
- Eggs
- Wheat

Food Allergens
- Most food allergens contain multiple proteins which are allergenic

Protein Allergens
- Milk - casein, lactoglobulins, lactoalbumins
  - No reduction by pasteurization, condensation, evaporation, and drying
- Eggs - ovalbumin, conalbumin, lipoprotein
  - Egg white more allergenic
  - No reduction by cooking
- Peanuts - arachin, lectin-reactive glycoprotein, Peanut I
  - Very heat stable, trace sensitivity
**Allergen M**
- Common protein allergen in fish
- Muscle protein - parvalbumin
- These proteins are conserved in fish species
- Very cross-reactive
- Very stable in processing

**Allergenic Proteins**
- Not many specific allergens have been identified
- Peanuts - 30% protein
- Soybeans - 42% protein
- Difficult to isolate specific moieties
- Groups - albumins, lipoproteins, globulins, glycoproteins, S-fractions

**Food Allergen Proteins**
- Cow milk
- Egg yolk
- Peanuts
- Soybeans
- Codfish
- Green peas
- Rice
- Tomatoes
  - β-lactoglobulin
  - Lipoprotein
  - Peanut I + others
  - Glycinin + others
  - Allergen M
  - Albumin
  - Glutelin/globulins
  - Glycoproteins

**Food Allergens**
- Allergens such as chocolate, strawberries and citrus often do not show positive on double blind studies

**Treatment of Food Allergy**
- Total avoidance of specific allergen
- No level is safe
- Very small doses can elicit
  - Distinguishes from other food sensitivities
- Cross reactivity is constant worry