Food Allergy
Food Toxicology
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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 sensivities
  - 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
  – 35% 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

IgE Mediated
• Cutaneous
  – Urticaria (hives)
  – Angioedema (welts)
  – Morbilliform rashes
  – Flushing
• Gastrointestinal
  – Lip, tongue, and palatal pruritis and swelling
  – Laryngeal edema
  – Vomiting and diarrhea

IgE Mediated
• 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 → inflammatory mediators → tissue damage
  – Milk-induced thrombocytopenia

Non-IgE Mediated
• 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

Non-IgE Mediated

• 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

Non-IgE Mediated

• 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

• The food is eaten.
  4 Reaches the stomach and small intestine where the proteins are not digested correctly
  4 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.
7 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
• 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