Anaphylaxis: The Atypical Varieties

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Disclosures:

• None
What is Anaphylaxis?

- Systemic Reaction
- Classically IgE-mediated
- Immediate hypersensitivity
- Most commonly induced by food
What Organ Systems Are Involved?

• Cutaneous (90%)
• Respiratory (40 to 60%)
• Cardiovascular (30 to 35%)
• Abdominal (25 to 30%)
Cutaneous Manifestations

- Urticaria
- Angioedema
- Flushing
- Pruritus without rash
Cutaneous Manifestations
Respiratory Manifestations

- Shortness of breath
- Wheeze
- Rhinitis
- Upper airway angioedema
Abdominal Manifestations

- Nausea/Vomiting
- Diarrhea
- Pain
Neurologic Manifestations

- Sense of impending doom
- Dizziness
- Syncope
- Seizure
Mechanism of Anaphylaxis: Mast Cell

• Primary role:
  • Inflammation
  • Homeostasis

• Mediators:
  • Histamine
  • Heparin
  • Tryptase
  • Chymase
  • Prostaglandin (PG) D2
  • Leukotriene (LT) C4/D4
Mechanism of Anaphylaxis: Basophil

- Compose 1% of circulating leukocytes
- Essentially contribute to all histamine release
- Produce more IL-4 and IL-13 in response to an allergen than any other cell type
- High cell counts in atopic individuals

Mediators:
- Histamine
- LT C4
- IL-4/IL-13
Mechanism of Anaphylaxis

Mast cell with IgE bound to surface

Allergen cross-links IgE on mast cell surface

Mediators (e.g., histamine) released from mast cells
Histamine

- Peak level within 5 minutes
- H1 receptor –
  - Vascular - Vasodilation
  - Cardiac - Tachycardia & coronary spasm
  - Pulmonary - Smooth muscle contraction
  - Glandular - Increases secretion

- H2 receptor –
  - Vascular - Relaxation of vascular smooth muscle
  - Cardiac - Increases heart rate & force of cardiac contractions
  - Glandular - Increases secretion viscosity
Tryptase

- Peak level in 15 to 120 minutes
- Vasoactive
- Pro-inflammatory
- Chemotaxis
- 300 X more in mast cell than basophil
Recruitment of Inflammatory Pathways During Anaphylaxis

• Compliment Cascade
• Kallikrein-kinin
• Coagulation Pathway
• Platelet Activation
Complement Cascade

- FcR activates C1qrs → C4 activation
- C4b → C2 activation
- C4b2a complex forms then activates C3
- C3a activates C5 to form Membrane Attack Complex (MAC)
- MAC activates C6 to C9
- Ultimately, MAC punctures cell membrane
Kallikrein-kinin System

Surface

F XII

F XIIa

Clotting Cascade (intrinsic pathway)

Fibrinolytic Pathway

Complement Activation

Plasmin

Plasminogen

Pre-Kallikrein

Kallikrein

Kininogen HMWK, LMWK

Kinin e.g. Bradykinin
Treatment for Acute Anaphylaxis

- Epinephrine
  - 1:1,000 concentration
  - Intramuscular injection
  - 30% of patient’s require 2nd dose
  - It is the only treatment

- Steroids, antihistamines, and other medications are not appropriate as sole treatment
Anaphylaxis: Types

• IgE-Dependent
  • Food, Drug, Venom
  • Exercise-induced (food dependent)

• IgE-Independent
  • Disturbance in arachidonic acid pathway (NSAID)
  • Kallikrein-Kinin contact system

• Non-Immunologic
  • Exercise-induced
  • Mastocytosis

• Idiopathic
Anaphylaxis: The Unusual Types
Exercise-induced Anaphylaxis

- Only in association with physical exertion
- Onset at any stage of exercise
- Most patients exercise regularly, but experience attacks only occasionally
- Early phase:
  - Warmth
  - Flushing
  - Generalized pruritus
  - Urticaria
- Improvement with exercise cessation
Exercise-induced Anaphylaxis: Food-dependent

• Most commonly implicated foods:
  • In the West – wheat, oats & nuts
  • In the East – wheat & shellfish
• Trigger is usually a specific food
• Solids more common than liquids
• Processing of food makes difference
• Exercising minutes to 6 hours after ingestion
Exercise-induced Anaphylaxis: Epidemiology

- Reported to occur globally
- Most presentations involve young adults
- Prevalence was 0.03% (EI) & 0.017% (Food-dependent) based on study of adolescents living in Yokohama, Japan
  - EI – No gender predilection
  - FDEI – males > females
Exercise-induced Anaphylaxis: Theoretical Pathogenesis

- Mast cell activation by unknown mechanism
- Food-dependent form
  - Patients are sensitized to culprit food, but tolerate ingestion in absence of exercise
  - Increased gastric permeability
  - Aspirin/NSAIDs effect on arachidonic acid
Exercise-induced Anaphylaxis: Evaluation

• Clinical Diagnosis
  • Meticulous History

• Diagnostic Testing
  • Baseline serum tryptase
  • STAT histamine & tryptase may support dx
  • Food-dependent – skin or IgE immunoassays to implicated food
  • Positive exercise challenge confirms dx
Idiopathic Anaphylaxis

• No specific trigger
• Must rule out other causes
• More common in adults than children
• Up to 70% are female
• Approximately 50% are atopic
Idiopathic Anaphylaxis

• Labs
  • Elevation of histamine and tryptase during acute episodes
  • Increase of activated T cells during acute episodes compared to remission
  • Increased activated B cells during both acute episodes and remission compared to general population
Idiopathic Anaphylaxis: Classification

• Frequency of episodes:
  • Frequent – at least 2 in preceding 2 months or at least in the preceding year
  • Infrequent

• Manifestations:
  • Systemic symptoms plus...
  • Urticaria
  and/or
  • Angioedema
Idiopathic Anaphylaxis: Classification

• Diagnosis of exclusion!!

• Occasionally patient’s with IA are found to have unusual triggers...
  • Medications (NSAIDs, ACE-I)
  • Food additives
  • Spices (caraway, coriander, fennel)
  • Food contamination/Undeclared
  • Alpha-gal sensitization
  • Histamine fish poisoning (Scombroid)
Idiopathic Anaphylaxis: Classification

• Other disorders:
  • Angioedema
  • Mast cell activation syndrome
  • Systemic mastocytosis (Elevated histamine not during acute episode)
    • Up to 50% with initial diagnosis of IA
Idiopathic Anaphylaxis: Management

• Acute – Same as any acute anaphylactic episode

• Long term:
  • Prednisone + H1 antihistamine (most common)
  • Montelukast
  • Ketotifen
  • If refractory, Omalizumab or Rituximab
Questions