Idiopathic Anaphylaxis

Paul A. Greenberger, MD, FAAAAI
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Course # 1605
Objectives

• Review definition and classification of idiopathic anaphylaxis
• Consider the differential diagnosis
• Critique lab tests/procedures used in the work up of patients with idiopathic anaphylaxis
• Examine treatment recommendations
Definition of Idiopathic Anaphylaxis

• “...is anaphylaxis not explained by a proved or presumptive cause or stimulus. It becomes a diagnosis of exclusion after other causes have been considered, such as foods, medications, exercise, food and exercise, insect stings or bites, mastocytosis, and C1 esterase inhibitor deficiency/dysfunction.”

Besides The Careful History, The Work Up

- May include skin and *in vitro* tests for serum specific IgE to foods and drugs, serum IgE to galactose-alpha-1,3-galactose (alpha-gal), baseline and acute phase serum tryptase, 24-hour urinary histamine metabolites, urinary prostaglandin D$_2$, oral challenges, peripheral blood for the mutation of the gene D816V and in some cases, a bone marrow examination.
Idiopathic Anaphylaxis

Mast cell activation but a diagnosis of exclusion
Tryptase elevated acutely
Urine Histamine elevated acutely (even with tongue or uvula enlargement) IA-Angioedema
B cell activation CD19+CD23+
Responsiveness to prednisone/H1 antagonists
Normal C4 and complements
+ Prick skin tests to foods non-contributory
Conditions/Initials

- Indolent Systemic Mastocytosis (ISM)
- Monoclonal mast cell activation syndrome (MMAS)
- Mast cell activation syndrome (MCAS)
- Idiopathic anaphylaxis (IA)
Classification of Idiopathic Anaphylaxis

• IA-Generalized (urticaria, angioedema, respiratory distress, upper airway angioedema, hypotension, abdominal pain, diarrhea)

• IA-Angioedema (urticaria, upper airway angioedema-obstructive)

• IA-Questionable (Urticaria without objective evidence of upper/lower airway obstruction, hypotension when syncopal etc)
Atopy in 48% of 333 IA Patients
Ann Allergy Asthma Immunol 1996;77:285-91

- Allergic rhinitis alone: 19%
- Asthma alone: 13%
- Allergic rhinitis and asthma: 11%
- Food induced anaphylaxis: 5%
- Atopic dermatitis: 1.5%
- Pre-existing urticaria or angioedema: 23%
Is There an Effect of Atopy on Anaphylaxis?

Yes

• Foods
• Latex
• Radiocontrast material
• Asthma
• Idiopathic anaphylaxis
• Exercise induced anaphylaxis
• Aspirin Exacerbated Respiratory Disease

No

• Penicillin
• Muscle relaxants
• Hymenoptera stings
• Insulin
Idiopathic Anaphylaxis

• Considering and excluding other causes of anaphylaxis
• Being aware of new observations
• Knowing the patient and disease
<table>
<thead>
<tr>
<th></th>
<th>SM</th>
<th>MMAS</th>
<th>MCAS</th>
<th>IA*</th>
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</thead>
<tbody>
<tr>
<td>Baseline tryptase</td>
<td>&gt;20</td>
<td>Normal or mildly increased</td>
<td>Normal or mildly increased</td>
<td>Normal</td>
</tr>
<tr>
<td>c-kit D816V</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Multifocal mast cell aggregates</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Aberrant CD25</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
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<tr>
<td>UP</td>
<td>+/-</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Mediator release symptoms</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypotensive episodes</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Urine N-MH or PGD₂</td>
<td>Increased at baseline</td>
<td>Increased during symptoms</td>
<td>Increased during symptoms</td>
<td>Increased during symptoms</td>
</tr>
<tr>
<td>Response to ant mediator therapy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
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Mast Cell Activation Syndrome
JACI 2010;126;1099-1104

1. Episodic symptoms (≥ 2) of Skin, GI, Cardiovascular, Wheezing, Naso-ocular

2. Decrease/resolution with anti-mediator therapy (H1, H2, LTRA or biosynthesis inhibitor or oral cromolyn)

3. Evidence of an increase in urinary or serum marker on ≥2 occasions when symptomatic

4. r/o primary or secondary causes of mast cell activation and idiopathic entities
Mast Cell Activation Syndrome
JACI 2010;126;1099-1104

• If baseline serum tryptase is > 15 ng/mL, require an increase during symptoms above baseline
## Classification of Idiopathic Anaphylaxis

<table>
<thead>
<tr>
<th>Terminology</th>
<th>Objective Evidence for Anaphylaxis?</th>
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<tbody>
<tr>
<td>Idiopathic Anaphylaxis – Generalized</td>
<td>yes</td>
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<tr>
<td>Idiopathic Anaphylaxis – Angioedema</td>
<td>yes</td>
</tr>
<tr>
<td>Corticosteroid Dependent Idiopathic Anaphylaxis</td>
<td>yes</td>
</tr>
<tr>
<td>Malignant Idiopathic Anaphylaxis</td>
<td>yes</td>
</tr>
<tr>
<td>Undifferentiated Somatoform Idiopathic Anaphylaxis</td>
<td>no</td>
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</table>
Idiopathic Anaphylaxis- Tips

Atopy often present

May co-exist with Exercise Induced Anaphylaxis, chronic idiopathic urticaria and/or food allergy (anaphylaxis)

May be followed by PANIC ATTACKS not additional episodes of anaphylaxis

*Rarely proved to be* Indolent Systemic Mastocytosis, Mast Cell Activation Syndrome, Urticaria Pigmentosa....
Anaphylaxis Implies a Risk of Death.......  

• Self injectable epinephrine (verify presence and use of demo)  
• H1 receptor antagonist  
• Oral albuterol (if tolerated)  
• Prednisone for initial therapy
Pharmacologic Approaches to Idiopathic Anaphylaxis

**Initial Therapy**
- Epinephrine auto-injector
- Cetirizine (or H1 receptor antagonist)
- Albuterol orally (if tolerated)
- Prednisone if severe or frequent

**If not controlled, not more than cases described**
- LTRA
- Oral cromolyn
- Oral ketotifen
- Azathioprine or tacrolimus (oral)
- Omalizumab (in literature)
Initial Treatment with Prednisone, H1 antagonist, Epi available

- Prednisone 60mg
- Prednisone alternate mornings
- Prednisone daily
Control of Episodes; Gradual tapering of Prednisone
Practice Parameters on Anaphylaxis
JACI 2010;126:477-80

• “Empiric use of oral steroids/H1 blockers has been demonstrated to reduce the frequency/severity of episodes (C)
Frequency of Idiopathic Anaphylaxis

• Frequent: 2 attacks in 2 months or 6 in 1 year
• Infrequent: < 6 attacks in 1 year
Ineffectiveness of Prednisone: Episodes Continue in First Month... Consider Undifferentiated Somatoform IA
Undifferentiated Somatoform-Idiopathic Anaphylaxis

When prednisone increases attacks
*When objective evidence cannot be confirmed*
*When there is no response to therapy*
*When the pt meets criteria for a somatoform disorder*

Manage with non-steroid therapy
Pt typically won’t obtain psychiatry consultation
Somatoform Condition

One or more physical complaints
Symptoms/signs lasting 6 months
and 1 or 2
1. Exam doesn’t confirm objective evidence
2. Symptoms, impairment or physical problems are grossly out of proportion to physical exam findings
Urticaria (limited) + passing out (NL BP, pulse)
Idiopathic Anaphylaxis

- Considering and excluding other causes of anaphylaxis
- Being aware of new observations
- Knowing the patient and disease
Considering and **Excluding** Other Causes of Anaphylaxis ......Northwestern Experience

- “Hidden” Foods........is allergic reaction > 3 hrs from onset.......or is it from beef, pork or lamb?
- Non-reported medication
- Bee pollen (pollens + molds) consumed
- $\text{K}_2\text{S}_2\text{O}_5$ (1mg, placebo, 5, 10, 25, 50, 100, 200=391mg or 4x a heavily sulfited restaurant meal)
- MSG (81mg total challenge)
- Aspartame
- Papain (consumed)
Anaphylaxis Questions/Considerations re the oligosaccharide galactose-α-1,3-galactose?

- Questions: Has glycosylation of the Fab or Fc fragment made an immunoglobulin (cetuximab) immunogenic or did a tick bite sensitize the patient to a SUGAR that caused anaphylaxis?
- Does the patient report delayed (3-6 hours) onset urticaria (anaphylaxis) after BEEF, PORK or LAMB?
- Can the patient tolerate chicken, turkey and fish?
- Have there been tick bites?
Skin Tests to Foods prick, ID in Patients + for anti-alpha Gal IgE

JACI 2009;123:426-433

Time to Onset of Anaphylaxis in 10 patients: “1-2” to 6 hours
The % of Anti-Alpha Gal IgE in the U. VA. Allergy-Immunology Pediatric Service

- 24% of 142 children/adolescents ages 4-18 seen for wheezing
- Pediatrics 2013;131:e1345-e1552
- Presumably sensitized by tick bites
How Would You Describe the Urticarial Lesions that Accompany

- Carcinoid Syndrome
- Pheocromocytoma
- Scromboid poisoning
- Non-Scromboid poisoning