Outline

- Case Presentation
- Angioedema
  - Clinical Features
  - Evaluation: history, physical exam, labs
  - Pathophysiology & Treatment
    - Mast cell mediated
    - Unknown
    - Bradykinin mediated
- Case Discussion
• CC: angioedema

• HPI:
  ❖ 58 yr old male presents to allergy and immunology office for angioedema. Two weeks ago had an episode of angioedema.
  ❖ 2PM started with upper lip swelling and took children's dose Benadryl.
  ❖ Woke up 11:30PM and lip got bigger so he took another children’s Benadryl.
  ❖ Then 1:30AM lip got more swollen so he went to the ER.
  ❖ In ER, he was given steroid and Benadryl but continued to swell, so then IM Epi was administered. He was discharged 24-36 hours later.
  ❖ Medication at discharge: prednisone 10mg daily, pepcid and claritin
  ❖ Upon further questioning: at noon that day he had some Cheetos and Gatorade but has eaten these foods in the past without any reactions.
  ❖ No illness at time of reaction, no new meds
  ❖ He had hives as a kid with increased body temp and in the grass but never had hives as an adult
  ❖ No history of swellings without hives
Case Presentation

- **PMHx:**
  - Seasonal allergies
  - Food allergy: fish (able to eat shellfish)
  - Diverticulitis
- **PSHx:**
  - None
- **FamHx:**
  - Allergic rhinitis: brother, sister
- **SocHx:**
  - No tobacco
- **Allergies: NKDA**
- **Meds:**
  - Prednisone 10mg po daily
  - Pepcid 20mg po daily
  - Claritin 10mg po daily
Case Presentation

- **Vitals:**
  - Weight: 186lbs  
  - Height: 5’8”  
  - BP: 130/79

- **PE:**
  - **General:** No acute distress, comfortable, oriented
  - **Eyes:** Conjunctiva and sclera normal without injection
  - **Ears:** TM's normal with normal landmarks; external auditory canals normal without erythema or exudate
  - **Nose:** Septum midline, no turbinate edema, no discharge
  - **Neck:** Supple; no cervical lymphadenopathy; no masses; thyroid normal
  - **Oropharynx/Throat:** Moist mucosa without lesions or exudate
  - **Chest wall:** Symmetric, non-tender, no deformities
  - **Lungs:** Bilaterally clear to auscultation without wheezes, rhonci, or rales; no cough; good air exchange
  - **Heart:** Regular rhythm, no murmurs, no gallop
  - **Extremities:** No cyanosis, clubbing, or edema; no joint erythema, swelling, or tenderness
  - **Skin:** No rash, no lesions; no purpura; no petechiae
Clinical Features

- Following anatomic sites can be affected:
  - Face, lips, mouth, throat, larynx, uvula, tongue, extremities, genitalia, bowel wall
  - Skin and mucous membranes
- Asymmetric distribution
Clinical Features

- **With mast cell mediated**
  - Urticaria, flushing, generalized pruritus, bronchospasm, throat tightness, hypotension
  - Onset in minutes to hours and spontaneous resolution in hours to a few days

- **With bradykinin mediated**
  - No urticaria, bronchospasm or other symptoms of allergic reactions
  - Longer timeline
    - Develops over 24-36 hours and resolves in 2-4 days
Evaluation: History

- Exposure history preceding symptoms
  - Unusual exposures, activities, foods
  - Medications?
    - NSAIDs, ACE-I, ARB, estrogens
  - Family history
Evaluation: Physical Exam

- **Angioedema**
  - Usually of the skin or mucous membranes of the upper respiratory or GI tract
  - Asymmetrical
  - Nonpitting
  - Skin color – normal or slightly erythematous

- Are there hives, flushing, pruritus, bronchospasm, throat tightness or hypotension?
Evaluation: Labs

- CBC with differential
- Complete metabolic panel
- CRP, ESR
- C4 levels
- Depending on history:
  - Urinalysis
  - Serum tryptase (marker of mast cell activation, but does not rule out)
  - C3 levels, C1 inhibitor (serum level and function)
  - ImmunoCAP (specific IgE): in cases of suspected allergy
  - Abdominal CT: in cases of intestinal angioedema
Angioedema Pictures
Causes

- **Mast Cell Mediated**
  - IgE mediated allergic reactions
  - Direct mast cell mediator release
  - Alterations in arachidonic acid metabolism with mast cells

- **Etiologies of unknown**
  - Idiopathic angioedema
  - Infections
  - Drugs
  - Hypereosinophilic syndrome
  - Urticarial Vasculitis
Mast Cell Mediated

- **Allergic or Anaphylactic reactions**
  - Type 1 hypersensitivity (IgE)
  - Many triggers
    - Foods, drugs, insect stings, latex
  - Occurs within minutes to 2 hrs following exposure
  - Potentially fatal
    - Treatment consists of epinephrine

- **Direct mast cell release**
  - Opioids
  - Radiocontrast agents
  - Muscle relaxers
Mast Cell Mediated

- Arachidonic acid metabolism
  - ASA, NSAIDs
  - Inhibition of cyclooxygenase 1
    - Formation of prostaglandins from AA
    - Increased proinflammatory mediators
- Treatments
  - Epinephrine, avoidance, desensitization
Membrane Phospholipids

\[ \text{PLA}_2 \]

\[ \text{AA} \]

\[ \text{5-HPETE} \]

\[ \text{Leukocytes} \]

\[ \text{5-LO} \]

\[ \text{Platelets} \]

\[ \text{COX} \]

\[ \text{Endothelium} \]

\[ \text{Cycloendoperoxides} \]

\[ \text{Smooth Muscle} \]

\[ \text{Aspirin NSAIDS} \]

\[ \times \]

Leukotrienes

\[ (+) \text{ LTC}_4 \]

Thromboxanes

\[ (+) \text{ TXA}_2 \]

Prostacyclin

\[ (-) \text{ PGI}_2 \]

Prostaglandins

\[ (-) \text{ PGE}_2 \]

\[ (+) \text{ PGF}_2\alpha \]

Abbreviations: AA, arachidonic acid; PLA$_2$, phospholipase A$_2$; PLC, phospholipase C; COX, cyclooxygenase; NSAIDS, non-steroidal anti-inflammatory drugs; +, vasoconstriction; −, vasodilation.
Unknown Mechanisms

- Idiopathic angioedema
  - With or without urticaria
- Infections
  - Children
  - Usually viral
- Drugs
  - Many classes of medications reported
  - CCB, SSRI, PPIs, Vaccines
Hypereosinophilic Syndrome

- Overproduction of eosinophils
  - Eosinophilic infiltration
  - Overexpression of IL 5
  - 15% develop angioedema
  - Prednisone, Gleevec, Mepolizumab

- Gleich’s Syndrome

- Urticarial vasculitis
Urticarial vasculitis

Urticarial patch with central ecchymosis.
Bradykinin-Induced Angioedema

- Separate, non-allergic entity, where mast cells are not involved
- Mechanism
  - Bradykinin is a potent vasodilatory peptide which exerts its action on specific endothelial β2 receptors
  - During bradykinin-induced angioedema elevated levels of bradykinin (from increase production of decreased degradation) results in increased tissue permeability, vasodilation and edema
Tissue Permeability, Vasodilation and Edema
Bradykinin-Induced Angioedema

- **Clinical Features**
  - Angioedema will often be indistinguishable from histamine-mediated angioedema
  - The secondary features, however, will be absent in Bradykinin-induced angioedema
    - **Absence** of urticaria & bronchospasm are distinguishing features
  - Timing of angioedema may also help in differentiating
    - Onset and duration usually more prolonged, with angioedema developing over 24-36 hours and lasting 2-4 days
    - Often the trigger and onset of angioedema not apparent (i.e. ACE-I induced angioedema can develop weeks to years after first use)
Bradykinin-Induced Angioedema

- **Differential Diagnosis**
  - Can be separated based on hereditary and acquired causes
    - **Hereditary Angioedema**
      - Types I, II, III (HAE with normal C1 inhibitor level)
    - **Acquired Angioedema**
      - Acquired C1 Inhibitor Deficiency (i.e. Acquired Angioedema)
      - ACE-I Induced
      - Idiopathic angioedema
Bradykinin-Induced Angioedema

- **Hereditary Angioedema**
  - Characterized by low levels (type I) or nonfunctional (type II) C1 Inhibitor leading to inappropriate regulation of the Bradykinin pathway
  - Family history of angioedema will often be identified as a result of autosomal dominant inheritance pattern
    - Types I and II – *SERPING1* mutation
  - Clinical Features
    - Recurrent angioedema episodes without urticaria or pruritis
    - Most often affects the upper respiratory and gastrointestinal tract
    - Cannot distinguish between the different types based on clinical presentation
Bradykinin-Induced Angioedema

- Hereditary Angioedema Type I
  - Makes up approximately 85% of all HAE cases
  - Characterized by low C1 INH levels
  - Diagnosis
    - C1 Inhibitor protein *Antigenic* and *Functional* levels will be decreased, low C4 levels
    - C1 INH Antigenic level range from undetectable to less than 30-50% of normal
Hereditary Angioedema Type II
- Makes up approximately 15% of all cases
- Characterized by dysfunctional C1 INH
- Diagnosis
  - Normal or increased C1 Inhibitor protein *Antigenic* level, Low C4 level
  - Low C1 Inhibitor *Functional* level
Bradykinin-Induced Angioedema

- Hereditary Angioedema with normal C1 Inhibitor (Type III)
  - Makes up very small percentage of all cases
  - Characterized by normal C1 INH levels and function
  - Family history of angioedema - possible gain-of-function mutation in Factor XII can be detected in a subset of patients
- Diagnosis
  - Normal C1 Inhibitor protein *Antigenic* and *Functional* levels, normal C4 levels
Bradykinin-Induced Angioedema

- Hereditary Angioedema Treatment
  - C1 INH concentrate- mainstay of treatment
    - Prophylaxis- *Cinryze* (Human C1 INH) can be intravenously used for both short term and long term prophylaxis
      - Upcoming dental or surgical procedures may warrant short-term prophylaxis
      - Long-term prophylaxis indicated for those with frequent and severe attacks
    - Acute treatment- *Berinert* (Human C1 INH) IV, *Ecallantide* & *Icatibant* (Bradykinin antagonists) SQ
  - Attenuated Androgens- used for both short term and long term prophylaxis
  - Antifibrinolytics and FFP- rarely used
Bradykinin-Induced Angioedema

• Acquired C1 Inhibitor Deficiency (Acquired Angioedema)
  ○ Mechanism
    ✷ Incompletely understood- depletion of C1 INH usually by B cell clonal proliferation
  ○ Clinical Features
    ✷ Present in the fourth decade of life, which is the major distinguishing factor from HAE (>90% present before 20 yo)
    ✷ Symptoms otherwise indistinguishable from HAE
  ○ Associated conditions- the majority of patients diagnosed with AAE are found to have an underlying disorder
    ✷ 30-40% are found to have some type of malignancy (lymphocytic or other)
    ✷ 30-40% are found to have monoglonal gammopathy of undetermined significance (MGUS)
    ✷ 5-10% are found to have an autoimmune condition
Acquired C1 Inhibitory Deficiency (AAE)

- Should be suspected in a patient with angioedema starting in the fourth decade without a family history of angioedema
- Diagnosis
  - Low C4 level
  - Low or normal C1 Inhibitor protein Antigenic level
  - Low C1 Inhibitor Functional level
  - Low C1q levels
- Initial C4 and C1 INH Antigenic and Functional levels can be drawn
  - If no family history and low C4 and C1 INH levels, C1q should be drawn to rule out AAE
Bradykinin-Induced Angioedema

- Acquired C₁ Inhibitor Deficiency (AAE)
  - Once AAE is confirmed by laboratory testing, more extensive workup for malignancy and autoimmune conditions should be undertaken and may include hematology evaluation
Bradykinin-Induced Angioedema

- **ACE-Inhibitor Induced Angioedema**
  - **Mechanism**
    - Angiotensin Converting Enzyme is a peptidase that cleaves Bradykinin and Substance P into inactive peptides
    - ACE inhibition will lead to reduction of catabolism of Bradykinin which predisposes to angioedema episodes in some patients
  - **Clinical Features**
    - Angioedema attacks show a strong predilection for the face, lips and tongue
    - Bowel and extremity edema are not common
    - First episode most frequently occurs in the first month, however many experience attacks 6 months to years after initiation
Bradykinin-Induced Angioedema

- ACE-Inhibitor Induced Angioedema
  - Treatment
    - Primary treatment is discontinuation of medication
    - Airway management
    - Antihistamines, corticosteroids, and epinephrine are commonly used but have proven ineffective
    - Bradykinin antagonists (Icatibant, Ecallantide)
Case Discussion

- **Plan after initial visit:**
  - Stop prednisone, Claritin, and pepcid
  - If another event: IM epi and to ER
  - Can take Benadryl 50mg po prn
  - Labwork
# Lab Results

<table>
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<tr>
<th>Test Name</th>
<th>In Range</th>
<th>Out of Range</th>
<th>Reference Range</th>
<th>Lab</th>
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<tbody>
<tr>
<td>ANGIOEDEMA HEREDITARY ACQUIRED</td>
<td></td>
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<td></td>
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<tr>
<td>C4, SERUM</td>
<td>LESS THAN 2 L</td>
<td>16-47</td>
<td>MG/DL</td>
<td>P</td>
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<tr>
<td>C1 ESTERASE INHIBITOR, PROT</td>
<td>7 L</td>
<td>21-39</td>
<td>mg/dL</td>
<td>G</td>
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<tr>
<td>C1 INHIBITOR, FUNCTIONAL</td>
<td>46 L</td>
<td>&gt;=68</td>
<td>%</td>
<td>G</td>
</tr>
</tbody>
</table>

Reference Range (%):
- >= 68 Normal
- 41-67 Equivocal
- <= 40 Abnormal

For more information on this test, go to:

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<th>Out of Range</th>
<th>Reference Range</th>
<th>Lab</th>
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</thead>
<tbody>
<tr>
<td>C1Q, SERUM</td>
<td>&lt;3.6 L</td>
<td>5.0-8.6</td>
<td>MG/DL</td>
<td>F</td>
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</table>

Low levels of C1q indicate either increased consumption (catabolism) or decreased synthesis.
# Bradykinin-Induced Angioedema

<table>
<thead>
<tr>
<th></th>
<th>HAE</th>
<th>ACID</th>
<th>Idiopathic</th>
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<tr>
<td><strong>C1-INH function</strong></td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
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<tr>
<td><strong>C1-INH antigen</strong></td>
<td>Low  (85%)</td>
<td>Low</td>
<td>Normal</td>
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<tr>
<td><strong>C4</strong></td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>C1q</strong></td>
<td>Normal</td>
<td>Low</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Case Discussion

- **Dx:** acquired angioedema
- Repeat labs to confirm diagnosis
  - Labs sent out to National Jewish Hospital in Denver, Colorado
- Prescribe Firazyr injection prn event
- Refer to hematology/oncology to rule out any underlying lymphoproliferative / autoimmune disorder
Questions?