ANGIOEDEMA

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Learning Objectives

• Define Angioedema & its types.
• State the Etiological Causes.
• Explain the Pathophysiology.
• Discuss Signs & Symptoms.
• Clarify the Diagnostic Approach.
• Discuss the Prevention and Treatment.
Angioedema

- Rapid non-pitting edema of the dermis, subcutaneous tissue, mucosa and submucosal tissues.
Angioedema

• Self-Limited, subcutaneous edema resulting from increased vascular permeability
  o Dilation of venules and capillaries
  o Limited to the dermis
• Generally resolves over 24-48 hours
ETIOLOGY

Allergic Angioedema
Ace Inhibitor Induced Angioedema
Chronic Idiopathic Angioedema
Hereditary Angioedema
Acquired Angioedema
Allergic Angioedema

- Most Common Type
- Classic histamine response
- Causes: Food, Drugs, venom, latex.
- Urticaria present often
- Complement assays normal
Triggers of Anaphylaxis: Food

- Milk
- Eggs
- Seafood
- Peanuts
- Tree nuts
- Other
Triggers of Anaphylaxis: Insect Stings and Bites

- Bees
- Vespids, Wasps
- Fire ants
- Scorpions (not in ME)
- Skeeters, Flies rare.
1. Allergic reaction

- Histamine
- Mast cell
- FcεRI
- IgE
2. Systemic effects

- Increased mucus secretion
- BV expansion and edema
- Constricted respiratory airways
- Itching and rash
• Sudden appearance of red welts, near eyes & lips, also hands, feet, and inside of throat

• Burning, painful, swollen areas; sometimes itchy or burning

• Discolored patches or rash on the hands, feet, face, or genitals

• Hoarseness, tight or swollen throat, breathing trouble
ACE INHIBITOR ANGIOEDEMA
ACE-1 ANGIOEDEMA

Facts-

More common in African Ethnicity.

Onset can be first dose or months/years out.

Angioedema occurs in 0.1% to 0.7% of patients on ACEI’s.

Average is…unknown but likely weeks to months.
• Increased Bradykinin.

• Airway edema is the most common presentation.

• Complement assay normal.
BRADYKININ

• **A mediator that functions to:**
  - Potent endothelium vasodilator
  - Contraction of non-vascular smooth muscle
  - Increases vascular permeability
  - Involved in mechanism of pain
CHRONIC IDIOPATHIC ANGIOEDEMA

- The exact mechanisms are unclear. Some may be associated with urticaria. Based on responses to medication, some cases are mediated by mast cell activation.

- Urticaria present.

- Laryngeal edema rare.

- Causes are, by definition, not identifiable.

- Complement assays normal.
Hereditary Angioedema

- Rare (1:50,000-1:150,000)
- Autosomal Dominant
- **Cause:** chromosome 11 abnormality
- **Disorder of C1INH** (only regulator of classical complement pathway activation)
  - **Type 1 (85%)** low levels of C1INH and functional deficiency
  - **Type 2 (15%)** Normal protein concentration but functional defect.
  - **Type 3-Hmmm.**
  - **Type 4??????**
Hereditary Angioedema

Pathophysiology

- Plasmin
- C1-INH
- Kallikrein
- Bradykinin
- Vasodilation
- Angioedema
HAE
HAE
### Table 2. Agents for HAE Treatment or Prophylaxis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Initial U.S. Approval</th>
<th>MOA</th>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berinert</td>
<td>2009</td>
<td>C1-INH</td>
<td>Treatment</td>
<td>20 U/kg body weight by IV injection</td>
</tr>
<tr>
<td>Cinryze</td>
<td>2008</td>
<td>C1-INH</td>
<td>Prophylaxis in adolescent and adult patients</td>
<td>1,000 U IV every 3-4 days</td>
</tr>
<tr>
<td>Kalbitor (ecallantide)</td>
<td>2009</td>
<td>Plasma kallikrein inhibitor</td>
<td>Treatment in patients aged ≥16 y</td>
<td>30 mg (3 mL) SQ in three 10-mg doses; administered only by health care provider because of risk of allergy/anaphylaxis</td>
</tr>
<tr>
<td>Firazyr (icatibant)</td>
<td>2011</td>
<td>Selective bradykinin B&lt;sub&gt;2&lt;/sub&gt;-receptor antagonist</td>
<td>Treatment in patients aged ≥18 y</td>
<td>30 mg SQ into abdomen; administered by health care provider or patient</td>
</tr>
<tr>
<td>Danocrine (danazol)</td>
<td>1976</td>
<td>Increases circulating levels of C1-INH, thereby raising C4 levels</td>
<td>Prophylaxis in adults</td>
<td>200 mg/day max to reduce adverse effects</td>
</tr>
<tr>
<td>Lysteda (tranexamic acid)</td>
<td>1986</td>
<td>Reduces complement activation and C1-INH consumption</td>
<td>Prophylaxis in adults; not FDA approved for this indication</td>
<td>20-50 mg/kg/day in 2-3 divided doses (max 3-6 g/day)</td>
</tr>
</tbody>
</table>

*C1-INH: C1 esterase inhibitor; C4: complement factor C4; HAE: hereditary angioedema; max: maximum; MOA: mechanism of action; SQ: subcutaneous.*

*Sources: References 6, 10-15.*
ACQUIRED ANGIOEDEMA

- Most similar in mechanism to HAE
- No Family History
- **Causes; Deficiency of C1-INH due to**
  - Type I: Lymphoproliferative Disorder (MDS/MGUS)
  - Type II: Autoimmune Disorder (SLE) 4th decade of life most common
- All complement assays are low including C1q
• Some drugs such as NSAIDS, Opiates and the use of IV contrast agents can worsen pre-existing angioedema of any type.

• These should be avoided or at least planned for with premedication given as appropriate.

• Intubation should be done early if airway compromise worsens rapidly.
• We should..
  o Look at their skin.
  o Take a great history.
  o Ask about being exposed to any irritating substances.
• A physical exam might reveal other findings.
• Consider..
  o Serology- C1Esterase Inhibitor level and function, C4, CBC with diff and Tryptase.
  o Allergy testing.
# TYPES OF AA

<table>
<thead>
<tr>
<th>Angioedema</th>
<th>C1-INH</th>
<th>Functional C1-INH</th>
<th>C4</th>
<th>C3</th>
<th>C1q</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAE I</td>
<td>&lt; 30%</td>
<td>&lt; 30%</td>
<td>Low</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>HAE II</td>
<td>NI/high</td>
<td>&lt; 30%</td>
<td>Low</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>HAE III*</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
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<tr>
<td>Inherited with normal C1-INH</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
<tr>
<td>ACID</td>
<td>Low</td>
<td>Low</td>
<td>&lt;50%</td>
<td>NI or low</td>
<td>&lt;50%</td>
</tr>
<tr>
<td>ACEI-induced</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
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<tr>
<td>Idiopathic</td>
<td>NI</td>
<td>NI</td>
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<td>NI</td>
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<tr>
<td>Allergic</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
<td>NI</td>
</tr>
</tbody>
</table>
PREVENTION

- Avoid known allergens
- Avoid Trauma, physical and emotional stress. (yeah, right?)
- Avoid ACE-1. ARB usually tolerated in AI Angloedema.
- Avoid NSAIDS, opiates, ethanol and some histaminic foods.
TREATMENT

• If the person has trouble breathing, seek immediate medical help.

• Medications include

  - Antihistamines for non HAE and Non ACE-1
  - Systemic Corticosteroids
  - Epinephrine
  - B2 agonists as needed
  - Others…H2 blockers, Mast cell stabilization
SUMMARY

- **Angioedema** can be immunologic, nonimmunologic, or idiopathic.

- Often caused by allergy and can be present with urticaria.

- It occurs in .1% to .7% of patients on ACE-1 inhibitors.

- Characterized by episodes of swelling of the face, lips, tongue, limbs and genitals.

- A careful history often illuminates the cause.

- Avoidance of triggers and treatment as needed is the key.
Thank You