ANGIOEDEMA - WHAT YOU NEED TO KNOW

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No relevant disclosures
OBJECTIVES

- Review the etiologies of angioedema without urticaria
- Discuss the diagnostic approach to angioedema
- Discuss acute and chronic management strategies of angioedema
INITIAL EVALUATION
HISTORY

- Presence/absence of urticaria
- Associated systemic findings
  - Shortness of breath
  - Abdominal pain and cramping
  - Distal extremity edema
- History of food or medication allergies
- Known history of malignancy
- Family history
EXAMINATION OF THE EYES

- Eyes
- Lips
- Tongue
- Lymph nodes
- Extremities
- Abdomen
- Larynx
EXAMINATION OF THE ORAL CAVITY

- Eyes
- Lips
- Tongue
- Lymph nodes
- Extremities
- Abdomen
- Larynx
EXAMINATION OF THE ORAL CAVITY

- Eyes
- Lips
- Tongue
- Lymph nodes
- Extremities
- Abdomen
- Larynx
EXAMINATION OF THE LYMPH NODES

- Eyes
- Lips
- Tongue
- Lymph nodes
- Extremities
- Abdomen
- Larynx
EXAMINATION OF THE EXTREMITIES

- Eyes
- Lips
- Tongue
- Lymph nodes
- Extremities
- Abdomen
- Larynx
EXAMINATION OF THE ABDOMEN

- Eyes
- Lips
- Tongue
- Lymph nodes
- Extremities
- Abdomen
- Larynx
EXAMINATION OF THE LARYNX

- Eyes
- Lips
- Tongue
- Lymph nodes
- Extremities
- Abdomen
- Larynx
CLINICAL FEATURES OF ANGIOEDEMA

- Recurrent, nonpitting, nonpruritic, nonurticarial edema
- Main sites of cutaneous involvement: face, hands, arms, legs, genitalia, and buttocks
- Abdominal pain → Nausea/Vomiting → Surgical abdomen
- Laryngeal edema → Asphyxia
- May persist for 2 to 5 days
- Attacks are triggered by trauma, pressure, stress, menstruation, ovulation, or infectious diseases
PITFALL

Erythema marginatum
DIFFERENTIAL DIAGNOSIS

- Allergic contact dermatitis
- Ludwig angina
- Quincke’s disease
- Granulomatous cheilitis
- Facial cellulitis
- Dermatomyositis
- Crohn’s disease
ANGIOEDEMA WITH URTICARIA

- Acute urticaria
- Physical urticaria
- Urticarial vasculitis
- Episodic angioedema with eosinophilia
ANGIOEDEMA WITHOUT URTICARIA

- Hereditary angioedema
  - Type I
  - Type II
  - Type III

- Acquired angioedema

- Angioedema due to ACE Inhibitors
DIAGNOSIS

- Plasma C4 level
  - Normal value essentially excludes HAE
  - Low C4 levels should prompt further investigation

- Plasma C1 inhibitor assays
  - Functional
  - Quantitative

- Plasma C1q levels
  - Low in acquired angioedema
Increased vascular permeability
ANGIOEDEMA

C1 INH
HEREDITARY ANGIOEDEMA
TYPE I

- Autosomal dominant
- 20-25% spontaneous mutation
- Accounts for 80-85% of cases
- Low functional plasma levels of a normal C1 esterase inhibitor protein
HEREDITARY ANGIOEDEMA
TYPE II

- Autosomal dominant

- Accounts for 15-20% of cases

- Two variants
  - Functionally inactive protein present in normal amounts
  - Nonfunctioning inhibitor present in increased amounts
HEREDITARY ANGIOEDEMA TYPE III

- Predominantly in females
- Normal quantitative and functional C1 INH and C4 levels
- Missense mutation in Factor XII
- Excessive bradykinin formation
- Family history
ACQUIRED ANGIOEDEMA

- C1-INH deficiency due to increased C1-INH catabolism

- C1q is usually decreased

- AA Type I may be presenting feature of underlying lymphoreticular disease

- AA Type II may be due to an autoantibody directed against C1-INH
ACE INHIBITOR ASSOCIATED ANGIOEDEMA

- ACE inhibitors interfere with the degradation of bradykinin
- Most commonly involves the face and tongue; rarely the bowel and extremities
- Most frequently occurs within the first month of therapy
- Increased risk in African-Americans
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>C4</th>
<th>C1 Inhibitor Function</th>
<th>C1 Inhibitor Level</th>
<th>C1q</th>
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<td>HAE Type 1</td>
<td>Low</td>
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<td>Low</td>
<td>Normal</td>
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<tr>
<td>HAE Type II</td>
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<td>HAE Type III</td>
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<tr>
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<tr>
<td>ACE inhibitor-associated angioedema</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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</tbody>
</table>
**INITIAL MANAGEMENT**

- Intubation or tracheostomy for serious respiratory obstruction

- Blood pressure monitoring

- Subcutaneous adrenaline (0.3 mg every 10 minutes) may be helpful

- Intravenous fresh frozen plasma or C1 inhibitor concentrate

- Antihistamines and corticosteroids are ineffective
MAINTENANCE THERAPY

- Attenuated androgens
  - Danazol
  - Stanozolol
  - Oxandrolone

- Antifibrinolytic agents
  - ε-Aminocaproic acid
  - Tranexamic acid

- Coadministration of ACE inhibitors and estrogens is contraindicated
NEW THERAPIES

- Cinryze
- Berinert
- Ruconest
- Ecallantide
- Icatibant
C1 ESTERASE INHIBITORS

- **Cinryze**
  - Human derived, nano filtered C1 esterase inhibitor concentrate
  - Approved by the FDA in 2008 for **prophylaxis** of HAE attacks
  - Reported to be effective in **acute** attacks
  - Patient self-administration after proper training by a healthcare professional
C1 ESTERASE INHIBITORS

- Berinert
  - Human derived C1 esterase inhibitor concentrate
  - FDA approved in 2009 for **acute** abdominal and facial angioedema attacks in patients with HAE
  - FDA approved in 2012 for laryngeal angioedema
  - Patient self-administration after proper training by a healthcare professional
C1 ESTERASE INHIBITORS

- Ruconest
  - Recombinant C1 esterase inhibitor concentrate
  - FDA approved in 2014 for **acute** attacks of HAE
  - Contraindicated in patients with a history of allergy to rabbits
  - Patient self-administration after proper training by a healthcare professional
Ecallantide
- Recombinant peptide produced in Pichia pastoris yeast
- Selective, reversible inhibitor of plasma kallikrein
- Approved by the FDA in 2009 for the treatment of acute attacks of HAE
- Inhibits the production of bradykinin
- Black box warning – development of antidrug antibodies leading to anaphylactic-like reactions
**BRADYKININ ANTAGONIST**

- Icatibant
  - Selective bradykinin B2 receptor antagonist
  - FDA approved in 2011 for treatment of **acute** attacks of HAE
  - May potentially have a pharmacodynamic interaction with ACE inhibitors - may attenuate antihypertensive effect
SUMMARY

- Understanding the causes of angioedema without urticaria is a must
- Ask the right questions
- Be systematic in your work-up
- Chronic management of angioedema can be managed by medical dermatology
- Be confident in your knowledge and skills
Thank you.