ANGIOEDEMA

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OBJECTIVES

- Differentiate types of Angioedema
- Understand acute and chronic management
- Discuss new medications that may impact treatment
WHAT TO DO WHEN FACED WITH THIS?
HISTORY

- Milton (1876)
  - First described clinical features

- Quinke (1882)
  - “acute circumscribed edema of the skin”

- Osler (1888)
  - Angioneurotic edema (Nervous System)

- Donaldson and Evans (1963)
  - Defined C1-INH deficiency
25% Incidence of Urticaria or Angioedema

Men = Women

Generally presents 3\textsuperscript{rd} and 4\textsuperscript{th} decades

Immunologic and Non-Immunologic causes
URTICARIA

Generalized, erythematous, pruritic papules in the papillary dermis
URTICARIA

Serpiginous
MECHANISMS OF URTICARIA

- Immune Mediated (cross linking IgE)
  - Penicillin/Foods
- Complement Mediated
  - Ag/Ab complexes in serum sickness
- Non-Immune Mediated
  - Alcohol, Trauma, NSAIDs, Vancomycin, Contrast
- Autoimmune Mediated
  - Circulating autoantibodies

***Mast Cell Degranulation***
Nonpitting

Abrupt Onset

Asymmetric

Well defined
EYE/FACIAL ANGIOEDEMA
EXTREMITY ANGIOEDEMA
GENITAL ANGIOEDEMA
GASTROINTESTINAL ANGIOEDEMA
TYPES

- Allergic Angioedema
- Ace Inhibitor Induced Angioedema
- Chronic Idiopathic Angioedema
- Acquired Angioedema
- Hereditary Angioedema
ALLERGIC ANGIOEDEMA

- Most Common Type
- Classic histamine response
- Trigger
  - Food
  - Drugs
  - Bee Sting
- Urticaria Present
- Complement assays normal
ALLERGIC EDEMA

- Cutaneous and laryngeal swelling
- **Urticaria**
- Wheezing
- Vomiting
- Diarrhea
- Hypotension
- Rapid progression
- Inciting event often identified
ACE-INHIBITOR INDUCED ANGIOEDEMA (AIIA)
FUNCTION OF BRADYKININ

- Potent endothelium vasodilator
- Contraction of non-vascular smooth muscle
- Increases vascular permeability
- Involved in mechanism of pain
ACE-INHIBITOR-INDUCED ANGIOEDEMA

- Incidence of 0.1-0.2%
- Increased Bradykinin
- **Airway edema is the most common presentation**
- Complement assay normal
Most similar to HAE

No Family History

Deficiency of C1-INH due to
- Type I: Lymphoproliferative Disorder (MDS/MGUS)
- Type II: Autoimmune Disorder (SLE)

4\textsuperscript{th} decade of life

All complement assays are low including C1q
CHRONIC IDIOPATHIC ANGIOEDEMA

- Wastebasket term
- Urticaria present
- Laryngeal edema rare
- Complement assays normal
HISTORY

- Symptom Duration
- Previous Events
- Rheumatologic disorders
- Other Autoimmune Disorders
- Rashes
- Pruritis
- Family History
OTHER POSSIBLE CAUSES?
Incidence
- 1 in 100,000 in the United States
- Increased in countries that do not vaccinate

Organism
- H. influenza/Staph/Strep

History
- Stridor
- Voice muffling or “Hot Potato Voice”
- Sore throat
- Odynophagia/dysphagia
- Recent URI
Febrile
Drooling/inability to handle secretions
Tachycardia
Toxic appearance of patient
Tripod position - Sitting up on hands, with the tongue out and the head forward
Stridor (Inspiratory) → Respiratory Distress
WHO IS THIS MAN?
“OF A CERTAIN TYPE OF INFLAMMATION OF THE THROAT, WHICH DESPITE THE MOST SKILLFUL TREATMENT IS ALMOST ALWAYS FATAL”
DEFINITION OF ANGINA?
ANGINA

1. **Latin** throat inflammation

2. **Greek** anchonē strangling, from anchein to strangle

First Known Use: 1578
LUDWIGS ANGINA (8)
LUDWIGS ANGINA (8)
LUDWIGS ANGINA (16)
Bilateral submandibular cellulitis
- Dental Origin 80-90% (16)
- Mortality 50% → 8%
- Generally Polymicrobial
  - Staph/Strep/Bacteroides
  - Higher incidence of Staph and black pigmented bacteroides (14)
- Predisposed
  - DM2/Alcoholism/Neutropenia
- 65% suppurative complications
TREATMENT

- **Manage Airway**
  - Wolfe et al. (17) showed tracheostomy not required in 29 patients with apparent Ludwigs
  - Intubation was required in 19/29 (65%)

- **IV antibiotics**

- **Supportive Care**
HEREDITARY ANGIOEDEMA (HAE)
15-30K ED visits per year (2)

Incidence
- 1/50,000 – 1/100,000

Most often presents 2nd decade

Mean frequency of events → 45.3 days (18)
Autosomal Dominant

Chromosome 11

200 mutations described

20-25% are spontaneous mutations

Type 1 (85%)
  - Decreased circulating C1-INH

Type 2 (15%)
  - Dysfunctional C1-INH
EFFECTS OF C1-INH
Swelling

- Diffuse, Nonpitting, Nonpruritic edema

- Affected sites (4)
  - Extremities → 47%
  - GI Tract → 33%
  - Oral/Laryngeal Involvement → 6%

  - 50% will have at least 1 event in a lifetime (2)
  - Mortality rate of 30% if left untreated
EXTREMITY EDEMA
GASTROENTERESTINAL EDEMA
First occurs in 2\textsuperscript{nd} decade
• Delay of 10-20 years in diagnosis (1,2)
• Swelling occurs over several hours
• Reversible Disability within 1-5 days (4)
• Preceding Prodrome 40-80\% (5,15)
  • Erythema Marginatum (non-pruritic)
  • Substantial Fatigue
  • Local discomfort
NATURAL HISTORY
TRIGGERS (10)

- Infection
- Stress
- Menstruation
- OCP’s
- Trauma
- Dental Work
LAB TESTING

- CBC
  - Helpful only to r/o infectious causes

- Bradykinin levels
  - Elevated in limbs affected compared to normal side (10)

- Complement
  - C1-INH, C4, C2, C1q
Clinical criteria

- Recurrent subcutaneous angio-oedema that is non-pitting, non-pruritic, non-erythematous, and self-limiting, and usually lasts for more than 12 h with no major urticaria
- Unexplained, recurrent abdominal pain (often accompanied by vomiting and diarrhoea), which spontaneously resolves in 24–72 h
- Recurrent oral, pharyngeal, or laryngeal oedema
- Documented family history of hereditary angio-oedema

Laboratory criteria

- Antigenic concentrations of C1 inhibitor <50% of normal values obtained on two separate occasions after first year of age
- Functional levels of C1 inhibitor <50% (chromogenic assay) or <84% (ELISA assay; local normal ranges might vary) of normal values obtained on two separate occasions after first year of age
- Mutation in C1-inhibitor gene that modifies protein synthesis or function
TREATMENT

- Antihistamines, steroids, and epinephrine have no role

- Avoidance of triggers when known
  - Infection
  - Stress
  - Menstruation
  - OCP’s
  - Trauma
  - Dental Work
- Do not alter bradykinin levels

- Successful treatment reported with antihistamines as part of protocol

- Grant et al. 2007
  - Patients with ACEi-Induced Angioedema were extubated significantly earlier than those not treated with antihistamines
ANDROGENS

- Danazol/Stanazolol/Oxandrolone
- Mechanism
  - Not well understood
  - Increase C1-INH and C4
- Side Effects
  - Weight gain, acne, vasomotor sx, menstrual irregularities, HTN, CAD, Virilization, hepatic neoplasms, hair growth
  - Must also monitor LFTs
Tranexamic Acid/Aminocaproic Acid
Used if Androgens are contraindicated
Unknown Mechanism (no effects on C1-INH in serum)
Poor response
Side effects
- Nausea, diarrhea, vertigo, cramps, Orthostasis, fatigue
- Increased thrombosis, tumors, teratogen
WHAT ABOUT PREGNANCY?

- Androgens are contraindicated
- Antifibrinolytics with caution
- Baker et al. (3)
  - 6 pregnant women
  - 1-2 times a week
  - None had angioedema event
  - All had normal babies on delivery
- Attempt regional anesthesia for cesarean
FRESH FROZEN PLASMA

- Contains
  - C1-INH
  - Proteases and substrates to prolong attack

Therefore FFP should only be used in prophylactic setting
Present in Europe over 25 years

Increases amount of circulating C1-INH

Best in patients with:
- Repeat Attacks (>2/month)
- Laryngeal Attacks
- Anxiety or poor quality of life
- Those not responding to androgens therapy

*Cinryze* is $2437.50 per vial; at this benchmark monthly *cost* of therapy would range between $36562 to $48750 per patient
NOVEL THERAPIES
Lumry et al. 2011
- Randomized placebo controlled trial
- Bradykinin receptor 2 blocker
  - Constituitively expressed
  - Participates in bradykinin vasodilation
ICATIBANT EFFECTS

Figure 2. Median (95% CI) time to onset of symptom relief (non-laryngeal ITT population). Subjects who did not achieve symptom relief within the observation period were censored at the last observation time (icatibant, n = 0; placebo, n = 3).
ICATIBANT FOR LARYNGEAL ATTACKS

- Only 8 patients in the treatment arm
- Time to ≥50% reduction in symptoms
  - 2.5 hours for Icatibant
  - 3.2 hours for Placebo

*Approved for >18y/o in the United States
*Costs $6800 per treatment
A recombinant protein synthesized in the yeast
- Pichia pastoris
Inhibits plasma kallikrein
Shown to decrease length and severity of attacks
Small risk of anaphylaxis
- Limits home administration

*Approved for >16 y/o in the US
*Cost per dose is $9540 per treatment
ACTION OF ECALLANTIDE
WHAT TO DO WHEN Faced WITH THIS?
PREDICTING AIRWAY RISK IN ANGIOEDEMA: STAGING SYSTEM BASED ON PRESENTATION

- Ishoo et al. (1999)
- Otolaryngology-Head and Neck Surgery
  - 80 patient (93 episodes)
  - Retrospective review 1985-1995
  - Categorized by
    1. Anatomic site
    2. Treatment setting
Table 3. Staging by site

<table>
<thead>
<tr>
<th>Stage</th>
<th>Site</th>
<th>Episodes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Facial rash, facial edema, lip edema</td>
<td>31</td>
</tr>
<tr>
<td>II</td>
<td>Soft palate edema</td>
<td>5</td>
</tr>
<tr>
<td>III</td>
<td>Tongue edema</td>
<td>32</td>
</tr>
<tr>
<td>IV</td>
<td>Laryngeal edema</td>
<td>31</td>
</tr>
<tr>
<td>Stage</td>
<td>Outpatient (%)</td>
<td>Floor admittance (%)</td>
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<tr>
<td>-------</td>
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<td>----------------------</td>
</tr>
<tr>
<td>I</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>II</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>III</td>
<td>26</td>
<td>7</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Acute Airway Management in 9.7%

- Voice changes/hoarseness/dyspnea/stridor (p<0.05)
- Only Stage III and IV patients

ICU stay if:

- ACEi use (p = 0.05)
- Voice changes/hoarseness/dyspnea/rash (p<0.05)
MANAGEMENT OF ACEI-INDUCED ANGIOEDEMA

- Al-Khudari et al. (2011)
- Laryngoscope
  - Prospective review of 40 patients
  - What was studied?
    1. Need for airway evaluation
    2. Level of care
Assessment by PGY3

Diphenhydramine 50mg IV q 8-12 hours
Famotidine 20mg IV q 12 hours
Dexamethasone 10mg IV q 8 hours

1. Mild oral edema
2. No laryngeal edema
3. Normal clinical status

Discharged Home from ED

1. Severe Oral Edema
2. Supraglottic edema with visible glottis

Monitored on the floor or in ICU

1. Obstructed glottis
2. Drooling
3. Respiratory Fatigue

Intubation
Twice daily examination
Laryngoscopy if symptoms changed
Extubation over tube exchanger once
  1. Cuff leak test positive
  2. Mental status appropriate
Discharged w/wo steroid taper
## DEMOGRAPHICS

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<table>
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<tbody>
<tr>
<td><strong>Average Age</strong></td>
<td>62.9 years</td>
</tr>
<tr>
<td><strong>African Americans</strong></td>
<td>92.5%</td>
</tr>
<tr>
<td><strong>Lisinopril</strong></td>
<td>87.5%</td>
</tr>
<tr>
<td><strong>Days on ACEI</strong></td>
<td>233 days</td>
</tr>
<tr>
<td><strong>Time to Resolution</strong></td>
<td>29 hours</td>
</tr>
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</table>
## Presenting Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Dysphagia</td>
<td>44.7%</td>
</tr>
<tr>
<td>Voice Changes</td>
<td>42.1%</td>
</tr>
<tr>
<td>Shortness of Breath</td>
<td>23.1%</td>
</tr>
<tr>
<td>Drooling</td>
<td>7.5%</td>
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<tr>
<td>ADMISSION</td>
<td></td>
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<td>-------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Discharged from ED</td>
<td>42.5%</td>
</tr>
<tr>
<td>Admit to Floor</td>
<td>7.5%</td>
</tr>
<tr>
<td>Admit to ICU</td>
<td>50%</td>
</tr>
</tbody>
</table>
Factors for ICU Admission

- Older patients (67.2 vs 58.1 years)
- Presented with dyspnea
- Involvement of
  - FOM
  - Soft Palate
  - Aryepiglottic Folds
  - Epiglottis
- Multiple sites involved
FACTORS FOR AIRWAY EDEMA

- Multiple airway sites
  - $p=0.008$

- Soft Palate swelling
  - $p=0.047$

- Upper lip swelling
  - $p=0.008$
FACTORS FOR INTUBATION (15%)

- Prolonged symptoms from onset to resolution
  - p=0.046

- Massive Tongue Edema
  - p=0.008
MASSIVE TONGUE EDEMA
Assessment by PGY3

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Intubation
SUMMARY OF THERAPY

- Secure the Airway (based on risk factors)
- If known HAE
  - Cyrinze, Icatibant, Ecallantide acutely
- If Unknown Cause
  - Antihistamines/Steroids/Epinephrine as needed
- Thorough History/Physical exam
- Complement levels
- Prophylactic medications if indicated
REFERENCES