Angioedema: Pathophysiology and Current Treatment

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Hershey, Pennsylvania
## Conflicts of Interest

<table>
<thead>
<tr>
<th>Company</th>
<th>Speaker</th>
<th>Research</th>
<th>Consultant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyax</td>
<td></td>
<td>XX</td>
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<tr>
<td>CSL Behring</td>
<td>XX</td>
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<tr>
<td>Viropharma</td>
<td>XX</td>
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<tr>
<td>Pharming</td>
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<td>XX</td>
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<tr>
<td>Shire</td>
<td></td>
<td>XX</td>
<td>XX</td>
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</tbody>
</table>
Case 1: 15 year old female with swelling
• Mary just turned 15 yesterday and shortly after her party she developed swelling of her left eye and lips.
• She denies having hives at this time.
• Her swelling is uncomfortable, but not itchy or painful.
• **What else would you like to know about Mary’s present illness?**
• Mary has had recurrent swelling since age 12.
• She states that at times she also gets hives.
• She admits to recurrent abdominal pain, but feels it is secondary to milk products.
• She denies dyspnea or light-headedness.
• She is unsure of what causes her swelling.

• **What PMH, social or family history would you like to ask?**
• Medications- just BCP started last year
• PMH- Hives secondary to a bee sting at age 5
• Family history- her mother had hives, but never angioedema.
• No allergies to medications or foods.
• ROS normal
• **What would you expect on exam?**
• On exam she is noted to have non-pitting edema of the face
• Otherwise her exam is normal.
• **What is your working diagnosis?**
Working Diagnosis

• Food allergy
• Bee sting allergy
• Drug allergy secondary to BCP
• Hereditary Angioedema
• Chronic idiopathic urticaria with angioedema
• Anaphylaxis

• What laboratory tests would you like to order?
Laboratory Tests:

- CBC - normal
- UA normal
- Chemistry panel - normal
- C4 was 18 (normal above 12)
- RAST test to honey bee was positive, but milk was negative
- TSH was normal, but her anti-thyroid antibodies were elevated

**What is your diagnosis and how would you treat her?**
Diagnosis:

- Chronic Idiopathic urticaria and angioedema
- Bee sting allergy unrelated to this event
- Probable lactase deficiency
- **How would you treat her in the ED?**
Therapy

In the ED:
• prednisone 50 mg PO
• benadryl 25 mg PO

Sent home on:
• cetirizine 10 mg po each day
• Prednisone 50 mg PO for 3 days
• Epipen for throat swelling and bee sting allergy

Referred to an allergist for assessment and follow-up for her chronic idiopathic angioedema and bee-sting allergy
Case of a 26 yo female with recurrent swelling

- Bell is a 26 yo female
- She presents to the ED with severe swelling of the face.
- She states she thinks she is having difficulty swallowing and breathing.
- Her symptoms started late last night and have progressed over the past few hours
- **What other questions about her present illness do you want to ask Bell?**
• Bell has similar symptoms about every other week.
• She has never had hives.
• She also frequently has abdominal pain, but no one has been able to find out why.
• Her swelling and abdominal pain usually lasts about 3 days.
• She denies having lightheadedness.
• What questions about her PMH and social history do you want to ask?
• Medications- synthroid, Tylenol #3 for pain, claritin for swelling and frequent use of prednisone
• PMH- positive for thyroid deficiency
• PSH- chole, appy, and a exploratory abd surgery
• FH- DM-II, HTN, CVA, CAD
• No drug allergies, bee allergies or food allergies
• **What would you expect on physical exam?**
What is your working diagnosis?
• Anaphylaxis
• Idiopathic angioedema
• Acquired angioedema
• Hereditary angioedema
• Drug allergy
• Food allergy
• Narcotic induced angioedema

• What laboratory tests would you get now?
Laboratory tests:

• CBC- WBC was 18,000
• UA and CMP were normal
• Lateral neck X-ray was positive for upper airway swelling
• C4- 6 (normal 14)
• Tryptase was normal
• 2 weeks earlier a CT of the abd- see next page.
During Abd. pain

What is the diagnosis?
Diagnosis is Hereditary Angioedema (HAE)

What is the treatment?

• 1
• 2
• 3
• 4
• 5
• 6
• 7
Diagnosis is HAE

What is the treatment?
• 1- C-1-esterase inhibitor if available
• 2- FFP- but be careful
• 3- intubation precautions
• 4- volume support
• 5- on discharge start prophylaxis with androgens or C-1-esterase inhibitor
• 6- refer for care
• 7- confirm with repeat C-4, C-1-esterase inhibitor level and functional assay.
Autosomal Dominant Defect

Crowder JR, Crowder TR. Five generations of angioneurotic edema. *Arch Inter Med* 1917; 20:840-52
Common triggers of HAE attacks

- Trauma
- Menstruation
- Medications
- Infection
- Stress
Hereditary Angioedema (HAE)

- Patients may describe prodromal symptoms:
  - Erythema marginatum
  - Vague symptoms, such as:
    - Fatigue
    - Tingling
    - Rumbling
    - Bowel movement changes
    - Nausea
    - Flu-like feelings
Rash on arm of patient during Hereditary Angioedema attack.
Clinical Presentation of Initial Attacks

% of Patients*

- Angioedema of the extremities  75
- Angioedema of the face or throat  36
- Recurrent abdominal pain  32

*Not mutually exclusive categories
C-4 levels in HAE
What Is C1-Inhibitor?

Human plasma protein...that mediates inflammation

Key regulator of *three* biochemical pathways

1. Complement
2. Contact
3. Fibrinolytic

C1-Inhibitor deficiency can cause:

- debilitating pain
- disfiguring swelling
- asphyxiation & death
The edema associated with HAE is due to?

• 1. histamine
• 2. bradykinin
• 3. Factor 12
• 4. Plasmin
• 5. Complement

• Answer 2
C1-INH involved in 3 systems → C1-INH depletion

- **Contact System**
  - Factor XII
  - Prekallikrein
  - HMW-K
  - Kallikrein
  - C1-INH
  - Bradykinin

- **Complement System**
  - C1
  - C1-INH
  - C1rs
  - Plasminogen
  - Plasmin
  - C4
  - C2

- **Fibrinolytic System**
  - Increased vascular permeability → ANGIOEDEMA
Therapy

HAE responds to?

• 1. corticosteroids
• 2. androgens
• 3. epinephrine
• 4. antihistamines
• 5. H-2 blockers

Ans: 2
Acute Attacks: C1-INH-RP Not Available

<table>
<thead>
<tr>
<th>European</th>
<th>Canadian</th>
<th>USA?</th>
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<tbody>
<tr>
<td>• FFP or solvent detergent-treated plasma may be given, but can worsen Sxs during acute phase</td>
<td>• Treat as early as poss. before full-blown attack (prodromal Sxs)</td>
<td></td>
</tr>
<tr>
<td>• Risk of pathogen transmission increases with plasma</td>
<td>• Consider ↑ danazol dose</td>
<td></td>
</tr>
<tr>
<td>• Adrenaline may treat AE and hypovolemia of type 1 hypersensitivity (ineffective?)</td>
<td>• Consider TA</td>
<td></td>
</tr>
<tr>
<td>• Fluids for hypotension</td>
<td>• Early use of adrenaline (might be ineffective?)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pain management</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IV fluids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Supportive care</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• FFP could theoretically worsen attacks, remains controversial</td>
<td></td>
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</tbody>
</table>
FFP data
## TREATMENT RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Total Courses</th>
<th>Attack-Free Courses</th>
<th>Attacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danazol</td>
<td>42</td>
<td>41</td>
<td>1</td>
</tr>
<tr>
<td>Placebo</td>
<td>46</td>
<td>3</td>
<td>43</td>
</tr>
<tr>
<td>Total</td>
<td>88</td>
<td>44</td>
<td>44</td>
</tr>
</tbody>
</table>
New Therapies for acute HAE

- C1 Inhibitor (plasma): Viropharma and CSL Behring
- C1 Inhibitor (recombinant): Pharming
- Kallikrein Inhibitor DX-88: DYAX
- Bradykinin receptor type 2 antagonist - Icatibant: Shire
Prophylactic Self Administration of C1 Inhibitor:

Levi, et al., 2005
Serum levels of C-1-I after infusion compared to lower limits of normal (Waytes, NEJM, 1996)

* = infusion
**C-4** serum levels after infusion of C-1-I compared to lower limits of normal

*(Waytes, NEJM, 1996)*

![Graph showing C-4 serum levels after infusion of C-1-I compared to lower limits of normal.](image)

- **C-1-I**: Red line
- **Placebo**: Yellow line
- **Normal**: Green line

* = infusion

Days
Table 2. Length of Time to the Response to C1 Inhibitor Concentrate or Placebo.

<table>
<thead>
<tr>
<th>Location of Edema</th>
<th>Response in ≤30 Minutes</th>
<th>Response in &lt;240 Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C1 inhibitor</td>
<td>placebo</td>
</tr>
<tr>
<td>Abdomen</td>
<td>25/35 (71)</td>
<td>0/34</td>
</tr>
<tr>
<td>Larynx</td>
<td>3/4 (75)</td>
<td>0/4</td>
</tr>
<tr>
<td>Face</td>
<td>7/7 (100)</td>
<td>0/8</td>
</tr>
<tr>
<td>Extremities</td>
<td>9/16 (56)</td>
<td>1/16 (6)</td>
</tr>
<tr>
<td>First 3 locations*</td>
<td>33/44 (75)</td>
<td>0/40</td>
</tr>
<tr>
<td>All locations*</td>
<td>38/55 (69)</td>
<td>1/49 (2)</td>
</tr>
</tbody>
</table>

*For single attacks involving more than one location, the location with the earliest response was used for statistical analysis.
Pharming

• Recombinant C1 Inh produced in rabbit milk
• The human gene is introduced into rabbits under regulatory control of the bovine αS1-caseine promoter and is secreted in the milk.
• Pharmacokinetic characteristics of the preparation
• Van Doorn et al. JACI 116:876-83,2005
DX-88

- Manufactured by DYAX
- Reversible inhibitor of plasma kallekrein
- 60 amino acid peptide derived from a Kunitz domain backbone with 7 unique amino acids.
- Kallekrein on rate: $2 \times 10^6 \text{M}^{-1} \text{s}^{-1}$
- off rate $2 \times 10^{-5} \text{s}^{-1}$
- Can be administered IV or SQ
Icatibant

- Icatibant is a potent, specific, reversible competitive antagonist of the bradykinin B₂ receptor ($IC_{50} \sim 1-4 \text{ nM}$), 98% bioavailability after s.c. injection.
- 20 laryngeal attacks treated, rapid symptom relief.
- Effective
- Not FDA approved
Case 3- Mr Lee

- Mr Lee is a 67 year old gentleman
- Presented to the ER with severe chest and Abd. pain that started 2 hours ago.
- Pain is constant, and pressure
- Pain is across the upper abdomen
- No fever, but positive nausea, and vomiting.

- **Other questions you want to ask on present illness?**
• Mr Lee has had Hereditary Angioedema for 15 years.
• Danazol 200 mg TID for symptom control.
• He has not had an attack for about 10 years.
• He admits to HTN, never smoked, unsure of his lipid status and denies CAD.
• **Do you want to ask other questions about his history?**
• His medications are HCTZ 25 mg a day, and danazol 200 mg tid.
• PMH- HAE and HTN
• NKDA
• PSH- denied
• FH- positive for CAD and HAE
• ROS- otherwise negative.
- AOX3, normal MS
- BP- 160/90, pulse 90, resp 14
- ENT is normal
- H- RRR with S4, no S3 or M
- L- CTA
- Abd- soft nontender
- Ext and Neuro normal
- **What is the differential diagnosis?**
Differential Diagnosis

- CAD- R/O MI
- HTN
- Probable hyperlipidemia
- Suspect adverse events to danazol

- **What laboratory data would you like?**
• Troponin was elevated
• CBC nl except WBC of 15000
• BMP- elevated LFT, otherwise normal
• Lipid panel chol 250, LDL of 205, HDL of 20.
• EKG- C/W MI
• Cath 90% LAD that was stented
• What is your working diagnosis?
• CAD
• HTN
• Hyperlipidemia
• Suspect androgen adverse events

• Treatment plan?
• Aggressively treat hyperlipidemia
• Aggressively treat his hypertension
• Replace his androgens with C-1-esterase inhibitor concentrate as prophylaxis.
• Screen with liver ultrasound.
Danazol: Efficacy in Long-Term Prophylaxis

Freedom From HAE Attacks vs Placebo

- Placebo: >1%
- Danazol: 98%

Cumulative Freedom From HAE Attacks at Varying Dosages

- 200 mg/d: 11%
- 300 mg/d: 56%
- 400 mg/d: 88%
- 600 mg/d: 95%

Long-Term Danazol Therapy Increases Atherogenic Indices in Patients with HAE

A. LDL/HDL Ratio

Risk of Liver Toxicity Associated With Long-Term Danazol Therapy

Danazol-associated hepatocellular adenoma in a 69-year-old female patient on long-term HAE prophylaxis (200 mg/d for 20 years)

Side Effects of Danazol Therapy

- Abnormal liver function tests
- Hematuria
- Myopathy
- Myalgias
- Elevated CPK
- Headache
- Abnormal menses requiring treatment
- Decreased libido
- Hair loss
- Anxiety reactions
Prophylactic Self-Administration of C1 Inhibitor

Angio-edema attack frequency

Number of attacks per month

Hereditary C1-inh deficiency vs. Acquired C1-inh deficiency

* indicates statistically significant difference
55 year old female with swelling of the tongue

- Ms Green has been doing very well until last night.
- About 12 hours ago she noted difficulty talking and parathesias of her tongue.
- Over the past couple hours her tongue has become very enlarged.
- She came to the ED because of inability to breath or swallow.
What questions would you like to ask her husband?
• Ms Green has diabetes, hypertension and hyperlipidemia
• Never had similar symptoms.
• Denies eating any foods that are unusual for her
• No new medications have been started for way over a year.

• **What other questions are important to ask?**
• Her medications include ASA, inderal, lisinopril, insulin, Percocet and fish oil.
• She has no drug, food or insect allergies
• Outside of the swelling she has no other symptoms.

• What is your differential?
Differential

- Drug allergy
- Food allergy
- Idiopathic angioedema
- ACE inhibitor angioedema
- HAE
- Acquired angioedema
- Narcotic induced angioedema

What is the cause of ACE induced angioedema?
ACE Inhibitors (ACE-I) - bradykinin

- Angiotensin I
- Bradykinins
- Tachykinins

- ACE-I
- Kininase II

- Angiotensin II

- Vagal afferents
- Non-myelinated c fibers

- Substance P priming?
- TXB2 ↔ PGI2 / PGE2 Imbalance?

- ↑ Bradykinin?

- AT1
- AT2

- ACE-I
- ARB
Bradykinin “Correlations” with ACE-I Angioedema

Overproduction caused by lack of enzyme inhibition, versus accumulation from inhibition of degradation

Nussberger et al. NEJM 2002; 347:621
Theoretical problems and advantages

- **Kallikrein Inhibitor**-
  - Large foreign peptides. Some risk of allergy with repeated administration.
  - Short half life limits it to acute attacks.
  - Advantage: given SQ.
  - Relatively inexpensive to make.
  - No risk of infection.

- **Bradykinin Receptor Antagonist**:
  - Small foreign peptide.
  - Short half life limits it to acute attacks.
  - Advantage: given SQ.
  - Relatively inexpensive to make.
  - No risk of infection.
## Different types of angioedema

<table>
<thead>
<tr>
<th>TYPE</th>
<th>CAUSE/MECHANISM</th>
<th>MAIN MEDIATOR</th>
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<tbody>
<tr>
<td>Allergic and idiopathic</td>
<td>IgE to food, antibiotics or unknown cause</td>
<td>Histamine</td>
</tr>
<tr>
<td>Pseudoallergic</td>
<td>NSAIDs, arachidonic acid metabolism</td>
<td>Leukotrienes</td>
</tr>
<tr>
<td>RAE*</td>
<td>ACE-Inhibitor</td>
<td>Bradykinin</td>
</tr>
<tr>
<td>HAE</td>
<td>C1-INH deficiency</td>
<td>Bradykinin</td>
</tr>
<tr>
<td>Acquired</td>
<td>Consumption of C1-INH</td>
<td>Bradykinin</td>
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</table>

*RAE: Renin-angiotensin-aldosterone system (RAAS)-blocker-induced AngioEdema*
HAE and Acquired (AA) Summary

<table>
<thead>
<tr>
<th></th>
<th>HAE-1</th>
<th>HAE-2</th>
<th>AA-1</th>
<th>AA-2</th>
</tr>
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<tbody>
<tr>
<td>C1</td>
<td>N</td>
<td>N</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>C4</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>C2</td>
<td>+/-</td>
<td>+/-</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>C1-I</td>
<td>L</td>
<td>N</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Cl-Fu</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>%</td>
<td>85</td>
<td>15</td>
<td>lymphoma</td>
<td>SLE</td>
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- Best test to differentiate Acquired from HAE is ___?____.
### Differentiating Features of Angioedema

<table>
<thead>
<tr>
<th>Feature</th>
<th>HAE</th>
<th>ACID</th>
<th>Idiopathic</th>
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</thead>
<tbody>
<tr>
<td>Angioedema</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Urticaria</td>
<td>No</td>
<td>No</td>
<td>Usually</td>
</tr>
<tr>
<td>Age at onset</td>
<td>6-20 years</td>
<td>&gt;50 years</td>
<td>Anytime</td>
</tr>
<tr>
<td>Family History</td>
<td>Usually</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Location of swelling</td>
<td>All</td>
<td>All</td>
<td>Especially face/lip</td>
</tr>
<tr>
<td>Precipitated by trauma</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Duration of swelling, hours</td>
<td>48-72</td>
<td>48-72</td>
<td>2-48</td>
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<tr>
<td>Response to treatment with epi, antihistamines, steroids</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
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</table>

Zuraw, Ann Allergy Asthma Immunol 2008
In Summary

• There are many faces to angioedema.
• Angioedema without hives think of HAE
• C4 is the best screening test for HAE
• To distinguish HAE from AAE use a C1
• Treat allergic and idiopathic angioedema with adrenaline, antihistamines, steroids
• For HAE unique therapy is indicated.
Thank You!

Questions please

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