Angioedema: Pathophysiology and Presentation

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## Conflicts of Interest

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<tr>
<th>Company</th>
<th>Speaker</th>
<th>Research</th>
<th>Consultant</th>
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Objectives

1. Know the mechanisms behind HAE
2. Understand how HAE presents
3. Improve outcomes of patients with HAE by early diagnosis and treatment
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 last about 3 days.
• She denies having lightheadedness.
• What questions about her PMH, family and social history do you want to ask?
• Medications- thyroid replacement, codeine for pain, antihistamines for swelling and frequent use of prednisone for angioedema
• 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?
Differential Diagnosis

- Anaphylaxis
- Idiopathic angioedema
- Acquired angioedema
- Hereditary Angioedema type 1 of 2
- Hereditary Angioedema type 3
- 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- ecallantide
• 3- FFP- but be careful
• 4- intubation precautions
• 5- volume support
• 6- pain control
• 7- confirm with repeat C-1 quant, C-4, C-1-esterase inhibitor level and functional assay.
• 8- on discharge start prophylaxis with androgens or C-1-esterase inhibitor OR arrange acute therapy with C1-INH, icatibant or ecallantide
The edema associated with HAE is due to?

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

• Answer- 2
Differential of Angioedema

Urticaria Present

Mast-cell mediated

Allergic

H1/H2 antagonists
Corticosteroids
Epinephrine
Confirmation of cause

Idiopathic

Determine etiology

Kinin-mediated

• Hereditary w/ Normal C1-INH
• Acquired
• ACE

Hereditary: C1-INH deficiency

Urticaria Absent

Hereditary w/ Normal C1-INH

Airway, analgesia, FFP, C1-INH, ecallantide, icatibant

Confirmation of cause
# C1INH Null Mice and Vascular Permeability


<table>
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<tr>
<th>Gene</th>
<th>+/+</th>
<th>+/+</th>
<th>+/-</th>
<th>+/+</th>
<th>+/-</th>
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<td>C1INH</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>B2BKR</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Evans blue</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>C1INH therapy</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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In Vivo Generation of Kinins in HAE

Patient 1
77 fmol/ml

Patient 2
46 fmol/ml

Patient 1
9.5 fmol/ml

Patient 2
16 fmol/ml

Normal Range 0.2-7.1 fmol/ml
How Does BK Cause Angioedema?

<table>
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<tr>
<th></th>
<th>VE-cadherin</th>
<th>Actin stress fibers</th>
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<tbody>
<tr>
<td>Nonstimulated</td>
<td><img src="image1.png" alt="Image" /></td>
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<tr>
<td>Stimulated</td>
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What are the genetics?

Crowder JR, Crowder TR. Five generations of angioneurotic edema. *Arch Inter Med* 1917; 20:840-52
Autosomal Dominant Defect

Crowder JR, Crowder TR. Five generations of angioneurotic edema. *Arch Inter Med* 1917; 20:840-52
What Is C1-Inhibitor?

Human plasma protein ...that mediates inflammation

Key regulator of *three* biochemical pathways
1. Complement
2. Contact
3. Fibrinolytic
4. Coagulation

C1-Inhibitor deficiency can cause:
- debilitating pain
- disfiguring swelling
- asphyxiation & death
HAE Is Caused By C1 Inhibitor Mutations

[Diagram showing exons and mutations]
C1-INH involved in 3 systems $\rightarrow$ C1-INH depletion

- **Factor XII**
  - HMW-K
  - Prekallikrein
  - Kallikrein
  - C1-INH
  - C1-INH

- **Factor XIIa**
  - C1-INH

- **Contact System**
  - Complement System

- **C4 C2**
  - C1
  - C1rs
  - C1-INH
  - Plasminogen
  - Bradykinin

- **Increased vascular permeability $\rightarrow$ ANGIOEDEMA**
What is an attack like?
Common triggers of HAE attacks

- Trauma
- Menstruation
- Infection
- Medications
- Stress
Erythema Marginatum

Rash on arm of patient during HAE attack.
Prodromal Symptoms That Patients Reported Before Their Last HAE Attack

- Unusual fatigue: 67%
- Rash on arms/legs: 47%
- Muscle aches: 44%
- Abdominal cramps: 42%
- Upset stomach or nausea: 40%
- Joint pain: 40%
- Rash on back, sides, or stomach: 33%
- Numbness/tingling in fingers/hands: 30%
- Numbness/tingling in same area as attack: 30%
- Other: 30%
- Headache: 23%
- Numbness/tingling in toes/feet: 21%
- Rash on face: 9%

Percentage of Patients

The Percentage of Time That Patients Report Being Able to Predict an Acute HAE Attack Based on Prodromal Symptoms

- 100% of attacks: 50%
- 75% of attacks: 26.1%
- 50% of attacks: 8.7%
- Unable to predict: 6.5%
- 25% of attacks: 8.6%

The Time Between the Onset of Patients’ Prodromal Symptoms and Their Last HAE Attack

- < 12 hours: 41.9%
- 12–24 hours: 16.3%
- 24–36 hours: 16.3%
- 36–48 hours: 9.3%
- No prodromal symptoms: 9.3%
- Do not recall: 4.7%
- > 48 hours: 2.3%

## Can Prodromal Symptoms be Used to Initiate Therapy?

<table>
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<tr>
<th>Query</th>
<th>Percent of patients</th>
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<td>Had Prodromal Symptoms prior to the last attack</td>
<td>85%</td>
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<tr>
<td>Have prodromal symptoms before 75% or greater of acute attacks</td>
<td>50%</td>
</tr>
<tr>
<td>Have prodromal symptoms before 25% or greater of acute attack</td>
<td>86%</td>
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Prematta et al. Allergy and Asthma Proceedings. 2009
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HAE

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In Summary

- 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 most idiopathic angioedema with adrenaline, antihistamines and steroids
- For HAE unique therapy is indicated and Dr Konrad Bork will be discussing treatment options.
HAE Awareness & Management

e-survey

Please stop by the “LAITAI” booth to complete the survey and receive a free CD on HAE CME activities
Brand new i-Phone APP!!
Thank You!

Questions please

tcraig@psu.edu