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Presenter: Aleena Banerji, MD

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Presenter’s Disclosures: Dr Banerji, MD has disclosed a relevant financial relationship with a commercial interest in the last 12 months: Shire – Consulting; CSL – Consulting; BioCryst – Consulting; Pharming – Consulting; Shire - Contracted Research; BioCryst - Contracted Research

The staff of CCME of Albert Einstein College of Medicine has no conflicts of interest with commercial interests related directly or indirectly to this educational activity.
Angioedema without Urticaria: Evaluation and Management

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TRAINING PROGRAM DIRECTOR
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JUNE 21, 2018
Disclosures

- Consultant: Shire, CSL Behring, Pharming, Biocryst

- Research Grant: Shire, Biocryst
Objectives

- Differentiate the role of histamine and bradykinin in angioedema
- Contrast histaminergic and nonhistaminergic types of angioedema
- Discuss treatment options for patients with angioedema
Angioedema

- Rapid swelling below the surface of the skin
- Self-limited and localized
- Results from extravasation of fluid into interstitial tissues
# Angioedema: Bradykinin vs. Histamine

<table>
<thead>
<tr>
<th></th>
<th>Bradykinin</th>
<th>Histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severity of swelling</strong></td>
<td>Greater</td>
<td>Lesser</td>
</tr>
<tr>
<td><strong>Duration of swelling</strong></td>
<td>Longer</td>
<td>Shorter</td>
</tr>
<tr>
<td><strong>Risk for fatal airway obstruction</strong></td>
<td>Appreciable</td>
<td>Exceedingly low</td>
</tr>
<tr>
<td><strong>Abdominal attacks</strong></td>
<td>Very common</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Response to antihistamines, corticosteroids, epinephrine</strong></td>
<td>Poor</td>
<td>Excellent</td>
</tr>
</tbody>
</table>
What is Hereditary Angioedema?

Debilitating and potentially life-threatening autosomal dominant disease

- Caused by an inherited deficiency in C1 esterase inhibitor
- Recurrent attacks of angioedema
- Swelling of extremities, face, abdomen, larynx
- If untreated, up to 40% mortality rate from asphyxiation

Incubation of HAE plasma ex vivo resulted in generation of a factor that enhanced vascular permeability.
Depletion of C1INH from normal plasma led to a similar increase in vascular permeability.
Generation of Vascular Permeability—Enhancing Activity

Increased vascular permeability

HAE plasma

37°

Increased vascular permeability

NI plasma + aC1INH

37°

Increased vascular permeability

C2 def plasma + aC1INH

37°
Generation of Vascular Permeability–Enhancing Activity

- Increased vascular permeability at 37°C
  - HAE plasma

- Increased vascular permeability at 37°C
  - NI plasma + aC1INH

- Increased vascular permeability at 37°C
  - C2 def plasma + aC1INH

- No change in permeability at 37°C
  - HMWK def plasma + aC1INH

## Laboratory Evaluation in C1Inhibitor Deficiency

<table>
<thead>
<tr>
<th></th>
<th>C1-INH Level</th>
<th>C1-INH Function</th>
<th>C4 Level</th>
<th>C3 Level</th>
<th>C1q Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAE type I</td>
<td>&lt;30%</td>
<td>&lt;30%</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>HAE type II</td>
<td>Normal</td>
<td>&lt;30%</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>HAE type III</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Acquired C1-INH I/II</td>
<td>Low</td>
<td>Low</td>
<td>&lt;30%</td>
<td>Normal/Low</td>
<td>Low</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Idiopathic angioedema</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Clinical symptoms start at a mean age of 11 (SD 7.7) years
On average, women more severe course of HAE than men
Patients with early onset of clinical symptoms were affected more severely than those with late onset
Clinical Presentation

- Repeated bouts of swelling of the face, extremities, genitals, intestines and larynx
- Edema is *not* warm, usually nonpruritic and nonpitting
- Erythema marginatum present but *no urticaria*
Function of C1-INH

Trace FXIIa or trace activity in native FXII

FXII → FXIIa

Prekallikrein

Surface HMW kininogen

Kallikrein

FXIIa → HMW kininogen

Bradykinin

Kallikrein

FXII → FXIIa

Autodigestion

C1 → C1

C4 & C2

Digestion

= Inhibited by C1-INH

FXII, factor XII; HMW, high molecular weight.

Loss of Function of C1-INH

Trace FXIIa or trace activity in native FXII

FXII → FXIIa

Surface HMW kininogen

Prekallikrein

HMW kininogen

Kallikrein

HMW kininogen

Bradykinin

FXII → FXIIa → FXIIif

Surface

Autodigestion Kallikrein

=C1

C1 → C1−

C4 & C2 Digestion

= Inhibited by C1-INH

HAE Attacks

- Caused by the extravasation of plasma into the deeper cutaneous or mucosal layers as a result of bradykinin release
- Recurrent and unpredictable with painful, localized edema or visceral swelling
- Attacks may be frequent and/or severe, but are highly variable between patients and within families

Peripheral Angioedema

- Affects 96% of patients
- Functionally disabling
  - Hands: difficulty holding, typing, use of phone
  - Feet: impedes walking, standing
- Interferes with school
- Rarely results in hospitalization
Abdominal Attacks

- Occur in 93% of patients with HAE
- Mild to severe colicky pain
- Vomiting common
- Functional intestinal obstruction
- Fluid loss leads to hemoconcentration and hypovolemic shock
- Protuberant abdomen, tenderness, and rebound possible
- Symptoms mimic surgical emergencies, resulting in misdiagnosis and unnecessary surgery

HAE Laryngeal Attacks

- Occur in ~50% of patients during their lifetime
- Require airway management to prevent asphyxiation
- Are of particular concern in children, given the heightened risk for asphyxiation associated with a smaller airway

Radiographs courtesy of William Lumry, MD.
Patients with Type I/II HAE are at constant risk of asphyxiation

3- to 9-fold higher risk in undiagnosed patients emphasizes the need for accurate diagnosis

In a retrospective review of 70 deaths due to HAE:

- 63 patients had no diagnosis at time of death despite a family history of HAE
- Lifespan of asphyxiated patients with undiagnosed HAE was on average ~31 years shorter than undiagnosed patients who died of other causes
- Mean age at time of asphyxiation was 40.6 ± 14.3 years

C1INH Concentrate

- Berinert: C1INH Concentrate
- Cinryze: C1INH Concentrate
- Ruconest: Recombinant C1INH
- HAEGARDA: C1INH Concentrate
HAE: Current Strategies and Treatments

Patients with HAE

- On-demand
  - Supportive care
  - C1-INH
  - Recombinant C1-INH
  - Ecallantide
  - Icatibant
  - FFP

- Short-term prophylaxis
  - C1-INH
  - Attenuated androgens
  - FFP

- Long-term prophylaxis
  - Attenuated androgens
  - Antifibrinolytics
  - C1-INH

Guidelines for the Treatment of HAE

- All patients should have access to an effective on-demand agent
- Evidence demonstrates efficacy and safety of treatment of HAE attacks with C1-INH concentrates, plasma kallikrein inhibitor, bradykinin B2 receptor antagonist
- FFP is often effective, but may exacerbate some attacks; caution is required
- Androgens and antifibrinolytics do not provide reliably effective treatment of attacks
- Epinephrine, corticosteroids, and antihistamines are not effective
- Management can involve symptomatic treatment based on region of the body

We surveyed 149 HAE patients to better understand the current state of HAE care, from a patient perspective, after the introduction of several novel therapies.

72% of HAE patients reported that HAE had a significant impact on QOL.

A third of HAE patients were diagnosed within one year of their first HAE attack, but another third reported a delay of more than 10 years.
70% of HAE patients reported being unsatisfied with the care they received during the ED visit.
Angioedema without Urticaria: Clinical Survey

- Tertiary level center where patients are referred mostly by specialists

- Reviewed all patients with angioedema without urticaria between January 1993 and December 2003

- Identified 929 patients and 776 patients completed the full work up
Evaluation

- Clinical history and physical examination
- CBC, SPEP, CRP, ESR, LFTs, TSH, ANA
- C4, C1 inhibitor level and function, C1Q
- Stool studies
- Urinalysis
- Sinus and dental x-rays

If evaluation was negative, antihistamine treatment for one month was initiated

Zingale CMAJ 2006
### Table 1: Classification of angioedema without urticaria according to clinical or etiopathogenetic characteristics, $n = 776$

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients</th>
<th>M:F ratio</th>
<th>Age at onset, yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>Median</td>
</tr>
<tr>
<td>Related to a specific factor*</td>
<td>124</td>
<td>16</td>
<td>0.51</td>
</tr>
<tr>
<td>Autoimmune disease/infection</td>
<td>55</td>
<td>7</td>
<td>0.62</td>
</tr>
<tr>
<td>ACE inhibitor-related</td>
<td>85</td>
<td>11</td>
<td>0.93</td>
</tr>
<tr>
<td>C1-inhibitor deficiency</td>
<td>197</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Hereditary</td>
<td>183</td>
<td></td>
<td>0.88</td>
</tr>
<tr>
<td>Acquired</td>
<td>14</td>
<td></td>
<td>1.8</td>
</tr>
<tr>
<td>Unknown (idiopathic) etiology</td>
<td>294</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Histaminergic</td>
<td>254</td>
<td></td>
<td>0.56</td>
</tr>
<tr>
<td>Nonhistaminergic</td>
<td>40</td>
<td></td>
<td>1.35</td>
</tr>
<tr>
<td>Peripheral/generalized edema</td>
<td>21</td>
<td>3</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Note: M = male, F = female, ACE = angiotensin-converting enzyme.
*A food, drug, insect bite, environmental allergen or other physical stimulus.
Angioedema: Causative Agent Identified

*Not Bradykinin Mediated*

- Recurrence of symptoms was clearly related to an exogenous stimulus with a consistent cause-effect relationship
  - Medications (N=56)
  - Food (N=45)
  - Medication and food (N=10)
  - Insect bite (N=5)
  - Environmental allergen (N=4)
  - Physical irritation/stimulus (N=4)
## Angioedema without Urticaria: Differential Diagnosis

### Table 1: Classification of angioedema without urticaria according to clinical or etiopathogenetic characteristics, n = 776

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients No.</th>
<th>Patients %</th>
<th>M:F Ratio</th>
<th>Age at onset Median</th>
<th>Age at onset Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related to a specific factor*</td>
<td>124</td>
<td>16</td>
<td>0.51</td>
<td>39</td>
<td>13-76</td>
</tr>
<tr>
<td>Autoimmune disease/infection</td>
<td>55</td>
<td>7</td>
<td>0.62</td>
<td>49</td>
<td>3-78</td>
</tr>
<tr>
<td>ACE inhibitor-related</td>
<td>85</td>
<td>11</td>
<td>0.93</td>
<td>61</td>
<td>32-84</td>
</tr>
<tr>
<td>C1-inhibitor deficiency</td>
<td>197</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary</td>
<td>183</td>
<td>23</td>
<td>0.88</td>
<td>8</td>
<td>1-34</td>
</tr>
<tr>
<td>Acquired</td>
<td>14</td>
<td>2</td>
<td>1.8</td>
<td>56.5</td>
<td>42-76</td>
</tr>
<tr>
<td>Unknown (idiopathic) etiology</td>
<td>294</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histaminergic</td>
<td>254</td>
<td>32</td>
<td>0.56</td>
<td>40</td>
<td>7-86</td>
</tr>
<tr>
<td>Nonhistaminergic</td>
<td>40</td>
<td>5</td>
<td>1.35</td>
<td>36</td>
<td>8-75</td>
</tr>
<tr>
<td>Peripheral/generalized edema</td>
<td>21</td>
<td>3</td>
<td>0.17</td>
<td></td>
<td></td>
</tr>
</tbody>
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Zingale CMAJ 2006
Recurrent Idiopathic Angioedema

Angioedema without Urticaria

- Angioedema from Identified Cause
- HAE with C1 inhibitor deficiency
- Acquired C1 inhibitor deficiency
- ACEI angioedema

How do we manage these patients?
Idiopathic Angioedema

Recurrent Angioedema
Normal Labs

Idiopathic Angioedema

High Dose Antihistamines

Response
Histaminergic Angioedema

No Response
Non-Histaminergic Angioedema
Idiopathic Histaminergic Angioedema

- Initial evaluation completely normal
- 254 (86%) patients responded to antihistamine therapy

Table 1: Classification of angioedema without urticaria according to clinical or etiopathogenetic characteristics, n = 776

<table>
<thead>
<tr>
<th>Condition</th>
<th>Patients</th>
<th>M:F ratio</th>
<th>Age at onset, yr</th>
</tr>
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<tbody>
<tr>
<td>Related to a specific factor*</td>
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* A food, drug, insect bite, environmental allergen or other physical stimulus.

Zingale CMAJ 2006
What is a high dose of antihistamines?

- The mechanism by which histamine release is initiated in this disorder is not fully understood.

- Expert opinion suggests that 4 times the typical dose is accepted as high dose.
Idiopathic Histaminergic Angioedema

- Most common form of idiopathic angioedema
- Clinical history
  - Age for onset variable
  - No family history of angioedema
  - Develops rapidly reaching maximum in 4-6 hours
  - Gastrointestinal and laryngeal mucosa are spared
  - Death has not been reported
- No precipitating factors identified
- Respond to corticosteroids and epinephrine as acute treatment
Treatment for Idiopathic Angioedema: Histaminergic

- High dose antihistamines (4x standard doses)
- Leukotriene receptor antagonists
- Corticosteroids
- Immunosuppressants
- Xolair

Epinephrine should be considered for treatment of severe symptoms in the acute setting.

Similar to refractory cases of idiopathic urticaria and angioedema.
Nonhistaminergic Idiopathic Angioedema

Sought to describe management of these patients with tranexamic acid

25 patients

Not responsive to antihistamines

Excluded all known causes of angioedema

Marco Cicardi, MD, Luigi Bergamaschini, MD, Lorenza C. Zingale, MD, Daniela Gioffré, MD, Angelo Agostoni, MD

Cicardi et al., Am J Med 1999
Table 2. Effects of Treatment with Tranexamic Acid in Patients with Idiopathic Nonhistaminergic Angioedema

<table>
<thead>
<tr>
<th>Patient</th>
<th>Attacks/Year without Treatment</th>
<th>Attacks/Year with Tranexamic Acid</th>
<th>Minimal Effective Dose of Tranexamic Acid (g/day)</th>
<th>Length of Treatment with Tranexamic Acid (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&gt;12</td>
<td>&lt;1</td>
<td>2.5</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>6–11</td>
<td>&lt;1</td>
<td>0.5</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>6–11</td>
<td>none</td>
<td>1.5</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>&gt;12</td>
<td>3</td>
<td>2.0</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>&gt;12</td>
<td>2–3</td>
<td>1.0</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>&gt;12</td>
<td>3</td>
<td>3.0</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>&gt;12</td>
<td>none</td>
<td>2.0</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>&gt;12</td>
<td>none</td>
<td>2.0</td>
<td>53</td>
</tr>
<tr>
<td>9</td>
<td>&gt;12</td>
<td>&lt;1</td>
<td>1.0</td>
<td>72</td>
</tr>
<tr>
<td>10</td>
<td>&gt;12</td>
<td>none</td>
<td>0.5</td>
<td>46</td>
</tr>
<tr>
<td>11</td>
<td>12</td>
<td>3</td>
<td>1.0</td>
<td>15</td>
</tr>
<tr>
<td>12</td>
<td>&gt;12</td>
<td>none</td>
<td>1.0</td>
<td>21</td>
</tr>
<tr>
<td>13</td>
<td>&gt;12</td>
<td>none</td>
<td>1.5</td>
<td>282</td>
</tr>
<tr>
<td>14</td>
<td>&gt;12</td>
<td>none</td>
<td>1.5</td>
<td>256</td>
</tr>
<tr>
<td>15</td>
<td>&gt;12</td>
<td>none</td>
<td>1.0</td>
<td>56</td>
</tr>
</tbody>
</table>

Cicardi et al., Am J Med 1999
Summary

- Novel therapies are available for HAE treatment
- Attacks still occur and side effects are a concern
- Patients have differential response to treatment
- QOL and BOD remains a significant issue
All evaluations must be done electronically, within 24 hours, in order for you to receive CME credit.

THE CODE FOR TODAY'S PRESENTATION IS:

03JEUX