Rare Cases in Angioedema:
Lifting the Veil on a Potentially Fatal Disease

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Educational partner, RMEI, LLC

MEDICAL EDUCATION
FOR BETTER OUTCOMES
Session 6: Rare Cases in Angioedema: Lifting the Veil on a Potentially Fatal Disease

Learning Objectives
1. Describe epidemiology, pathophysiology, and burden of illness of hereditary angioedema (HAE).
2. Recognize HAE as a possible cause of recurrent angioedema and formulate an appropriate diagnostic workup for various types of HAE (Type I, Type II, and normal C1-INH).
3. Utilize individualized HAE treatment strategies, taking into consideration risks and benefits of therapies, disease characteristics and severity, comorbid conditions, patient quality of life and patient preference.

Faculty

Marc Riedl, MD, MS
Associate Professor of Medicine
Clinical Director, US HAEA Angioedema Center
University of California, San Diego
La Jolla, California

Dr Marc Riedl is associate professor of medicine at the University of California, San Diego (UCSD), and clinical director at the US HAEA Angioedema Center at UCSD, La Jolla, California. He received his medical degree from the University of Chicago–Pritzker School of Medicine, completed a residency in internal medicine at Barnes-Jewish Hospital of Washington University, St. Louis, and a fellowship in clinical immunology and allergy at UCLA. Dr Riedl received a master of science degree in clinical research and completed advanced training in clinical pharmacology at UCLA. He is board certified in internal medicine, clinical pharmacology, and allergy and immunology.

Dr Riedl’s professional interests include the development of novel therapeutics for the treatment of allergic and immunodeficient conditions. He is integrally involved in phase I to III development of several investigational and orphan drugs, with particular interest in the treatment of hereditary angioedema and common variable immunodeficiency.

William R. Lumry, MD
Clinical Professor of Internal Medicine
University of Texas Southwestern Medical School
Dallas, Texas

Dr William Lumry is a clinical professor of internal medicine at the University of Texas Southwestern Medical School, Dallas and teaches at Parkland Memorial and Presbyterian Hospitals, also in Dallas. After receiving his medical degree from the University of Texas Medical Branch, Galveston, Dr Lumry completed his internal medicine residency at Washington University, St. Louis, Missouri. He then received clinical and research fellowships in allergy and immunology from Scripps Clinic, La Jolla, California, before returning to Dallas to establish his private practice. Dr Lumry is a fellow of the American College of Physicians, American College of Allergy, Asthma and Immunology; and American Academy of Allergy, Asthma and Immunology.

As medical director of the Allergy and Asthma Research Association (AARA) Center in Dallas, Dr Lumry participates actively in clinical research projects involving new treatments for asthma and allergic diseases and hereditary angioedema. He has lectured to local, national and international conferences and published many articles and abstracts in such peer reviewed journals as New England Journal of Medicine, The Lancet, and Annals of Allergy, Asthma, and Immunology.
Faculty Financial Disclosure Statements
The presenting faculty reported the following:

Marc Riedl, MD, MS, has affiliations with BioCryst, CSL Behring, Dyax, ISIS, Shire, Pharming, ViroPharma (Consulting Fees); and Dyax, CSL Behring, Shire, ViroPharma (Honoraria).

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Education Partner Financial Disclosure Statement
The content collaborators at RMEI, LLC, have reported the following:

Lora Rhodes, MSW, has no financial relationships to disclose.
Cynthia M. Kunzer, CMP, has no financial relationships to disclose.

Suggested Reading List


SESSION 6
3:30–4:45pm

Rare Cases in Angioedema:
Lifting the Veil on a Potentially Fatal Disease

SPEAKERS
Marc Riedl, MD, MS
William R. Lumry, MD

 Presenter Disclosure Information

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Off-Label/Investigational Discussion
► In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Drug List
• KALBITOR® (ecallantide)
• FIRAZYR® (icatibant injection)
• CINRYZE® (plasma-derived nanofiltered C1 inhibitor)
• Danazol
• Stanazolol
• Epsilon aminocaproic acid
• Tranexamic acid

Educational Objectives
• Review the differential causes of recurrent angioedema
• Describe the epidemiology, pathophysiology, and burden of illness of hereditary angioedema (HAE)
• Recognize HAE as a possible cause of recurrent angioedema and formulate an appropriate diagnostic workup for various types of HAE (Type I, Type II, and normal C1-INH)
• Utilize individualized HAE treatment strategies, taking into consideration risks and benefits of therapies, disease characteristics and severity, comorbid conditions, patient quality of life and patient preference

Angioedema Overview and Diagnosis of Hereditary Angioedema

Marc A. Riedl, MD, MS
Clinical Director – US HAE Angioedema Center
University of California, San Diego
La Jolla, CA

Clinical Presentation of Angioedema
• Non-pitting
• Localized swelling
• Involves skin or mucosa
• Result of fluid extravasation into deeper dermis and subcutaneous tissues
• Relatively rapid onset: minutes to hours
• Frequently asymmetric distribution
• Distribution not in dependent areas
• Among top three “allergic” conditions resulting in hospitalization
Case Study: Sharon 16-year-old Female

Chief Complaint: 4-year history of recurrent swelling of the lip and face
- Swelling typically lasting 2-3 days and includes:
  - Intermittent facial swelling, especially around the lips and eyes
  - One episode of left hand swelling
  - Infrequent severe abdominal pain
  - No hives or itching reported with swelling attacks
- 3 ED visits for facial swelling and abdominal pain
  - Treated with diphenhydramine, prednisone, epinephrine for skin swelling
  - Discharged to home with persistent swelling lasting 3 days in each occasion
  - Surgical consultation, observation, analgesics for abdominal pain

Causes of Angioedema
- Allergic: Foods, drugs, insect stings/bites
- Radiographic contrast media
- ASA and other NSAIDs
- Autoimmune
- ACE inhibitor-induced
  - Bradykinin-mediated
  - C1 inhibitor deficiency
    - Hereditary – Types I, II
    - Acquired
  - Hereditary with normal C1 inhibitor

Etiology of Angioedema
- Mast cell-mediated
  - Release of mast cell mediators increase vascular permeability
    - Histamine
    - Leukotriene C4
    - Prostaglandin D2
    - Heparin
    - 90% associated with urticaria and/or pruritis
- Kinin-related
  - Generation of bradykinin and complement-derived mediators increase vascular permeability
  - Absence of urticaria or pruritis

Major Types of Angioedema

<table>
<thead>
<tr>
<th>Mast-cell mediated or allergic</th>
<th>Bradykinin mediated or non-allergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Urticaria</td>
</tr>
<tr>
<td>Minutes to hours</td>
<td>+</td>
</tr>
<tr>
<td>Hours</td>
<td>-</td>
</tr>
</tbody>
</table>

Hereditary Angioedema (HAE)
- Potentially fatal genetic disorder associated with deficiency or dysfunction of C1 inhibitor (C1-INH)
- Characterized by swelling involving the deep dermis; generally localized; mildly pruritic and/or burning or painful; lasts hours to several days
C1-INH Mutations

- C1 INH deficiency caused by mutations in C1-INH gene
  - Located on chromosome 11
- >200 mutations currently identified

Epidemiology of HAE

- Estimated prevalence is difficult to ascertain
  - Autosomal dominant inheritance
  - Varying estimates of as high as 1 in 30,000 to as low as 1 in 80,000
  - Translates to 4000–10,000 affected individuals in United States
  - No known ethnic or gender differences
- Average attack frequency in untreated patients
  - Approximately one episode per 2-week period
- Disease severity is highly variable
  - Between patients and within families
  - No simple relationship between disease severity and C1 esterase inhibitor (C1-INH) level

Delay in HAE Diagnosis

- Documented failure to recognize and diagnose HAE
  - 1976 survey by Frank et al. found a mean delay in diagnosis of 22 years
- Delay still observed in recent survey
  - Mean age at diagnosis: 16.8 years (range, 1–42 years)
  - Mean age when symptoms began: 7.8 years (range, 1–18 years)
  - Mean delay in diagnosis: 9.1 years (range, 0–32 years)
- Delay still observed in recent surveys (mean delays)
  - Denmark: 16.3 years
  - Spain: 13.1 years
  - Argentina: 15.3 years

Triggers in HAE Attacks

- Attacks often unpredictable; 40% of patients can identify the cause of an episode
  - Physical trauma
  - Surgical/Medical procedures
  - Infection
  - Emotional stress
  - Some medications (ACE inhibitors, oral contraceptives)
- Hormonal influence
  - Estrogens increase attack severity/frequency

Function of C1-INH

B2 Receptor

NO

PGE_2

Angioedema

Vasodilatation

Increased Vascular Permeability

Plasminogen

Plasmin

TPA

Activation of Endothelial Cells by Bradykinin
Types of HAE

- 3 documented types of HAE

<table>
<thead>
<tr>
<th>Type</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of all HAE</td>
<td>~85%</td>
<td>~15%</td>
<td>Rare</td>
</tr>
<tr>
<td>C4 Level</td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>C1-INH antigenic level</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>C1-INH antigenic function</td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
</tr>
</tbody>
</table>


Complement Profile in Recurrent Angioedema

<table>
<thead>
<tr>
<th>Type</th>
<th>C1-INH Level</th>
<th>C1-INH Function</th>
<th>C4 Level</th>
<th>C3 Level</th>
<th>C1q Level</th>
</tr>
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<tbody>
<tr>
<td>HAE type I</td>
<td>&lt;30%</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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<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 with normal C1INH</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Acquired C1-INH III</td>
<td>Low</td>
<td>Low</td>
<td>&lt;30% Low</td>
<td>Normal</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>
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<tr>
<td>Idiopathic angioedema</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>


Algorithm for Diagnosis of HAE

- Episodes of angioedema without urticaria
- Episodes of abdominal pain and/or vomiting
- Laryngeal edema
- Family history of HAE


Sharon, 16-year-old Female: Testing and Laboratory Results

- Normal CBC, amylase, lipase, complete metabolic panel
- C4 level: 3 mg/dL (normal: 13-75 mg/dL)
- Further testing:
  - C1 INH quantitative: 4 mg/dL (normal 16-33)
  - C1 INH functional level: 25% (normal >67%)
  - C1q level: 18 mg/dL (normal 12-22)
- Diagnosis: Type 1 HAE


Importance of Early Recognition and Screening

- Specific and unique treatment for effective management
- Prevention of……
  - Mortality
    - All patients with HAE at risk for an airway attack
    - Not dependent on past history or family history
    - 30-40% incidence of asphyxiation in untreated laryngeal attacks
  - Morbidity/Disability
  - Unnecessary surgery, procedures, medications due to misdiagnoses


Hereditary Angioedema Treatment

William R. Lumry, MD
Clinical Professor of Internal Medicine/Allergy
University of Texas Southwestern Medical School
Private Practice
Dallas, TX
Hereditary Angioedema
Available Treatments

- Acute attacks
  - Supportive care: airway support, analgesics, fluids, time
  - Human plasma-derived C1-INH, ecallantide, icatibant
  - Fresh-frozen plasma
- Short-term or pre-procedural prophylaxis
  - Human plasma-derived C1-INH
  - High dose androgens (danazol, stanozolol)
  - Fresh-frozen plasma
- Long-term prophylaxis
  - Androgens
  - Anti-fibrinolytics (epsilon aminocaproic acid, tranexamic acid)
  - Human plasma-derived C1-INH


New Therapies for HAE

Factor XII → Factor XIIa → Factor XII
Prekallikrein
HMW Kininogen
BRADYKININ
B2 Receptor
ANGIOEDEMA

- C1-INH inhibitor

Angioedema Plasma C1-INH Replacement Therapy

- Multiple studies demonstrating efficacy
  - Efficacy first demonstrated >25 years ago
  - Response rate of virtually 100%
    - 629/630 attacks (193/193 laryngeal)


Home Administration of C1-INH for HAE

- Offers possibility of earlier treatment, earlier resolution of attack and overall better disease control
- Demonstrated ability of self/partner to infuse allows:
  - Increased QoL, flexibility & convenience
  - Decreased time to treatment, severity/duration of attacks
- Patient selection and training required to achieve reasonable and effective results


Ecallantide

New Therapies for HAE

Factor XII → Factor XIIa → Factor XII
Prekallikrein
HMW Kininogen
BRADYKININ
B2 Receptor
ANGIOEDEMA

Ecallantide
Ecallantide
Improvement of Acute Attack Symptoms at 4 Hours

* Treatment Outcome Score (TOS) is a measure of symptom response to treatment. A TOS value of 0 reflects an improvement of symptoms that occurred.


**New Therapies for HAE**

- **Icatibant**
  - Second-generation bradykinin B2-receptor antagonist
  - Subcutaneous administration with half-life of ~1.2 hours
  - Approved for all types of attacks age 18 and older
  - Dose may be repeated at 6 hours. No more than 3 doses in 24 hours
  - Primary adverse event injection site reaction (97%)
  - Approved for self-administration

**Recommendations for Treatment of Acute Attacks of HAE (HAWK Consensus)**

- Patients with HAE should have acute therapy available for treating an acute attack:
  - C1-INH inhibitor
  - Ecallantide (Kalbitor)
  - Icatibant (Firazy)
- If possible, patients should have 2 doses of an on-demand therapy at home and be trained in self-administration
- All attacks are eligible for treatment as soon as they are recognized
- Any location (of an attack) can be treated at home
- Hospital is recommended upon risk for laryngeal involvement


Challenges in Practice With the Treatment of Acute Attacks of HAE

- Patient not understanding risks associated with acute attacks (in particular laryngeal attacks)
- Not having treatment for an acute attack available
  - Hospital
  - At home
- Not knowing when to treat
- Lacking training on self-administration

Hereditary Angioedema

Angioedema Action Plan

- Identify yourself as someone with HAE
  - HAEA identification card
  - Letter from treating physician
- Plan for treatment of attacks
  - What attacks to treat
  - Where to get treatment
  - What treatment to use
- Plan for prevention of attacks
  - Medications to avoid
  - Short term
  - Long term
- Monitor for side effects of treatments

Case Study:
Sharon
23-year-old Female

Diagnosed with Type 1 HAE age 16
- Attacks occurred 3-4 times a year in high school increasing to 12 times a year in college
  - Initial home nursing treatment with ecallantide
  - Current self treatment with icatibant
- Attack frequency and severity increasing
  - Increased stress living at home again
  - Attacks 1-2 times a month with 2 ED visits for throat swelling
  - Unpredictability of attacks interfering with life needs
- Would like to discuss preventive treatments

Avoiding Triggers is Part of Prevention

- Frequently reported triggers of attacks
  - Medication
  - Estrogens in contraceptives and hormone replacement therapy
  - ACE-inhibitors
  - Menses and Pregnancy
  - Medical and Dental Procedures
    - Surgery
    - Endoscopy
    - Intubation
    - Tooth extraction
    - Deep-gum cleaning
    - Stress and Fatigue
    - Infection

Short-Term Prophylaxis

- Indications
  - Extensive dental work
  - Surgical procedures
  - Other invasive procedures
- Modalities*
  - C1-INH concentrate
    - 500-1500 units 1-6 hours before procedure
  - High-dose androgens
    - Requires at least 1 week of treatment
- * No FDA approved drugs for short-term prophylaxis

When Should Long-Term Prophylaxis Be Considered?

- Failures of "on demand therapy"
- Patients who suffer from consequences of HAE and have decreased quality of life such as:
  - > 1 attack / mo
  - Limited access to healthcare OR rapid onset of attacks
  - Prior intubation or ICU stay
  - Prior upper airway edema
  - Significant anxiety
  - > 10 days lost from school or work / year
  - Significantly decreased QoL
  - Narcotic dependence


Long-Term Prophylaxis of HAE

- Does the patient need long-term prophylaxis?
  - Not all HAE patients
  - Need varies by individual
    - Frequency, severity, and type of attacks
    - Availability of care
    - Failure of on-demand therapy
- Modalities
  - Anabolic androgens (attenuated or impeded)
    - Increase C1-INH levels
  - Antifibrinolytics
    - Mechanism of action uncertain
  - C1-INH replacement
- Acute treatment should be available for ALL patients on prophylaxis

Efficacy of Androgens for Long-Term Prophylaxis In HAE

Contraindications to Androgens

- Pregnancy
- Lactating women
- Hepatic disease (HCV hepatitis, etc)
- Children (before Tanner stage V)
- CA (prostate/breast)
- Nephrotic syndrome

58 of 118 subjects discontinued androgens: 41 due to adverse effects, 17 due to ineffectiveness


Reported Side Effects of Androgen Prophylaxis in HAE Patients

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>HAE Patients Taking Androgens</th>
<th>HAE Patients Using Treatments Other Than Androgens</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
<td>157 (70.7%)</td>
<td>19 (27.1%)</td>
<td>43.6%</td>
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<tr>
<td>Changes in skin</td>
<td>154 (69.0%)</td>
<td>67 (29.8%)</td>
<td>39.2%</td>
</tr>
<tr>
<td>Nausea</td>
<td>101 (46.3%)</td>
<td>21 (10.2%)</td>
<td>36.1%</td>
</tr>
<tr>
<td>Severe pain or cramps</td>
<td>101 (45.5%)</td>
<td>21 (10.2%)</td>
<td>35.3%</td>
</tr>
<tr>
<td>Increased hair growth</td>
<td>93 (41.9%)</td>
<td>12 (14.1%)</td>
<td>27.8%</td>
</tr>
<tr>
<td>Acne</td>
<td>89 (40.1%)</td>
<td>8 (9.4%)</td>
<td>30.7%</td>
</tr>
<tr>
<td>Severe pain or cramps</td>
<td>72 (32.4%)</td>
<td>7 (8.2%)</td>
<td>24.2%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>64 (28.9%)</td>
<td>17 (15.8%)</td>
<td>13.1%</td>
</tr>
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<td>64 (28.9%)</td>
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<td>Changes in skin</td>
<td>53 (23.8%)</td>
<td>7 (8.2%)</td>
<td>15.6%</td>
</tr>
<tr>
<td>Acne</td>
<td>46 (20.9%)</td>
<td>4 (4.7%)</td>
<td>16.2%</td>
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<tr>
<td>Severe pain or cramps</td>
<td>26 (11.8%)</td>
<td>3 (3.5%)</td>
<td>8.3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24 (10.9%)</td>
<td>1 (1.2%)</td>
<td>9.7%</td>
</tr>
<tr>
<td>Sleeplessness/insomnia</td>
<td>24 (10.9%)</td>
<td>1 (1.2%)</td>
<td>9.7%</td>
</tr>
<tr>
<td>Nervous system</td>
<td>21 (9.4%)</td>
<td>1 (1.2%)</td>
<td>8.2%</td>
</tr>
<tr>
<td>Other</td>
<td>17 (7.7%)</td>
<td>10 (11.8%)</td>
<td>-4.1%</td>
</tr>
<tr>
<td>None</td>
<td>14 (6.3%)</td>
<td>37 (43.5%)</td>
<td>-37.2%</td>
</tr>
</tbody>
</table>


Side Effects of Anabolic Androgens

Can include virilization, hepatotoxicity, headache, hypertension, weight gain, menstrual abnormalities, acne, psychological effects, and altered libido

C1-INH-nf Prophylaxis Associated With Lower HAE Attack Rates

- Average normalized attack rate
  - 12.73 vs 6.26, placebo vs C1-INH-nf
- Average difference in attack rates
  - 6.47 (P<0.001)

Hereditary Angioedema: Diagnosis

If a patient presents with...

✓ ...a history of recurring angioedema, especially if hives are absent
✓ ...recurring episodes or unexplained abdominal pain
✓ ...history of upper airway edema
✓ ...a positive family history of angioedema
✓ ...onset of symptoms in childhood/adolescence
✓ ...symptoms that fail to respond to antihistamines, glucocorticoids, or epinephrine

A diagnosis of hereditary angioedema should be suspected


Hereditary Angioedema: Conclusions

• Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder that causes significant morbidity and mortality
• Patients are deficient in functional C1 inhibitor (C1INH) and swell when bradykinin production is excessive
• Extremities, abdomen, face, and airway may swell massively spontaneously or as a result of trauma, stress, or hormonal fluctuation
• On-demand treatments of swelling attacks decrease bradykinin production or action and effectively stop the attack
• When swelling attacks are severe or frequent, prophylactic therapy should be considered
• And finally....


HAE International HAE Consensus Conference

• All HAE patients should have on-demand therapy
  – Patients should be trained for self-administration
  – Attacks at all locations are eligible for treatment
  – Attacks should be treated as soon as they are recognized
  – Hospitalize for progressing laryngeal involvement
• Long-term prophylaxis
  – Consider when optimized on-demand treatment fails
  – Androgens are contraindicated in patients who are:
    • ≤ 16 years of age
    • Pregnant/breastfeeding
    • Do not tolerate or accept androgens


Sharon, 23-year-old Female: Recommendations for Management

• At-home administration:
  – Plasma-derived nanofiltered C1 inhibitor for prophylaxis (1,000 U IV 2x/week)
  – Icatibant on-demand for attack management
• Detailed management plan provided to patient
• Reinforcement of education on the avoidance of triggers


Hereditary Angioedema: Conclusions

• Patients with unexplained episodes of abdominal pain, particularly if they have a personal or family history of angioedema, should be tested for HAE