Hereditary Angioedema

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October 13th, 2017

American College of Osteopathic Internist
2017 Annual Convention
Washington, DC

University Hospitals
Cleveland Medical Center

Conflict of Interest

I have no conflicts of Interest or financial disclosures.

Objectives

- Historical Perspective
- To review different types of angioedema
- Clinical and Laboratory Diagnosis
- Prophylaxis verse rescue medications
- Improve recognition and treatment of patients with Hereditary Angioedema (HAE), acquired angioedema and idiopathic angioedema.

Historical Perspective

1882 - Heinrich Irenäus Quincke initially describes 'Quincke's edema'.

1888 - HAE first described by William Osler in a 18-year old woman with episodic attacks, from five successive generations with attacks. HAE was then described as angioneurotic edema

1913 - Crowder and Crowder reported that the condition is inherited as an autosomal dominant trait (it's located on one of the 16 pairs of chromosomes called autosomes and is inherited independent of the sex)

1963 - Donaldson and Evans showed that HAE is linked to a C1-INH deficiency

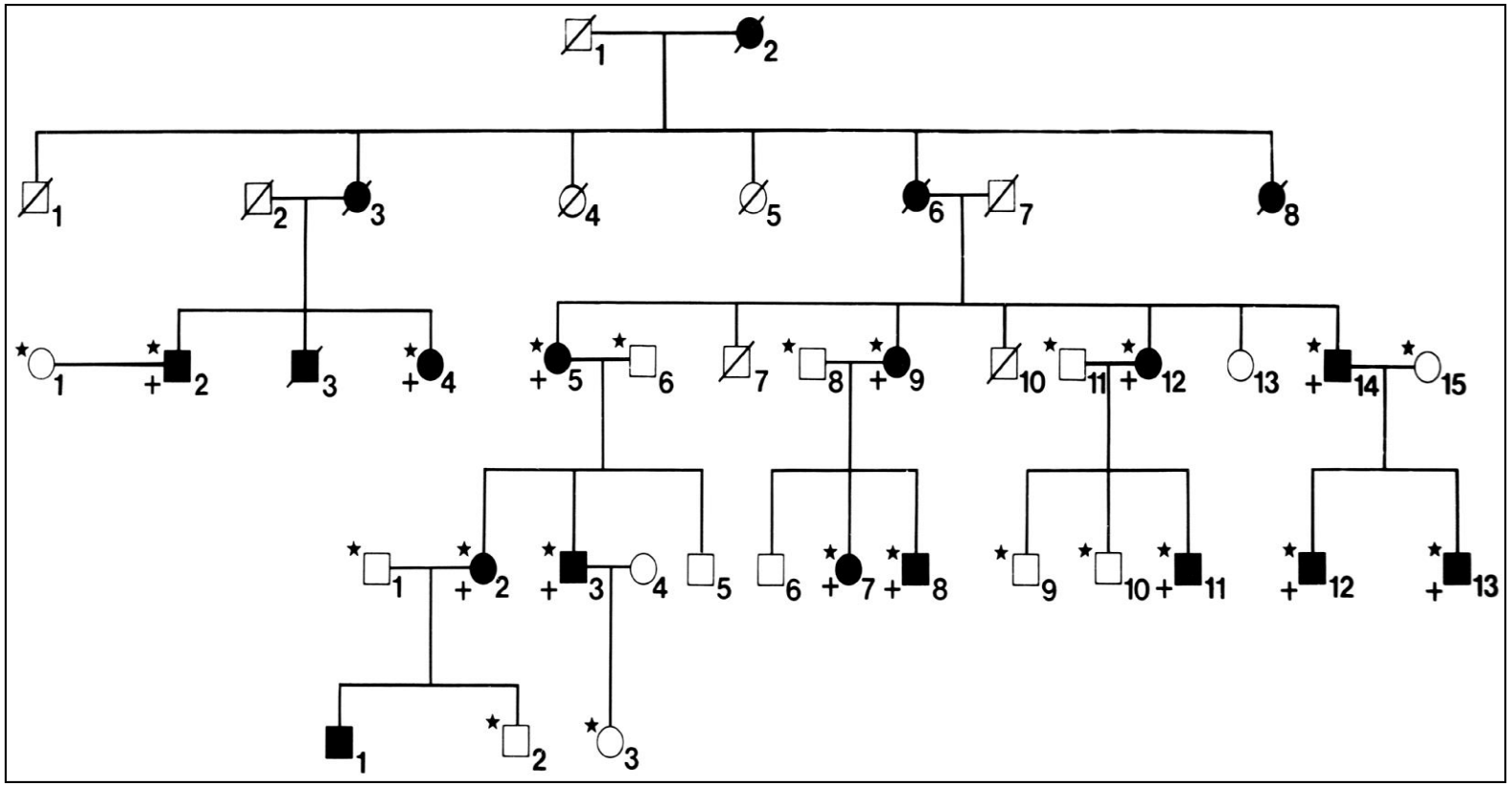
1986 - C1-INH gene localized on chromosome 11

1986 - First case of acquired angioedema (AAE) caused by anti-C1-INH antibodies described

1998 - Bradykinin appears to be main mediator of angioedema

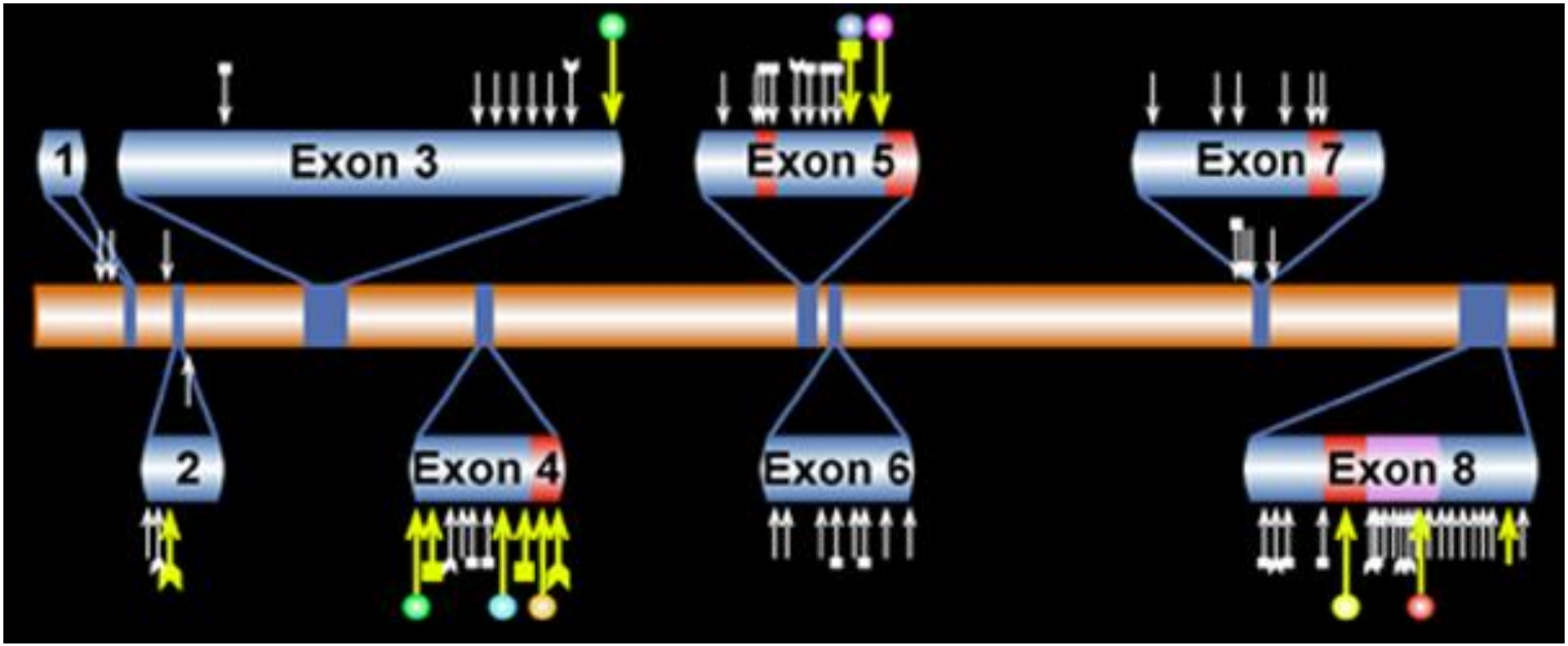
Khan, David A. "Hereditary angioedema: Historical aspects, classification, pathophysiology, clinical presentation, and laboratory diagnosis." *Allergy and asthma proceedings*. Vol. 32. No. 1. OceanSide Publications, Inc, 2011.

Autosomal Dominant Defect



CROWDER, JOSEPH R., and THOMAS R. CROWDER. "Five generations of angioneurotic edema." *Archives of Internal Medicine* 20.6 (1917): 840-852.

HAE Is Caused By C1 Inhibitor Mutations



Bissler JJ, et al. *Proc Assoc Am Physicians*. 1997;109:164-173.
Davis AE 3rd. *Annu Rev Immunol*. 1988;6:595-628.
Verpy E, et al. *Am J Hum Genet*. 1996;59:308-319.
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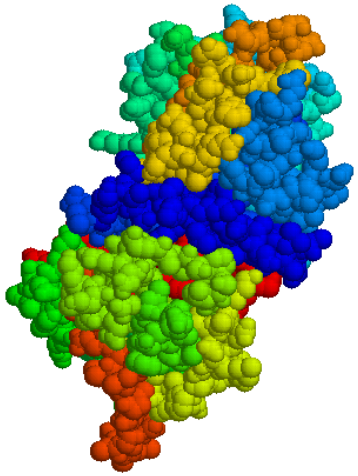
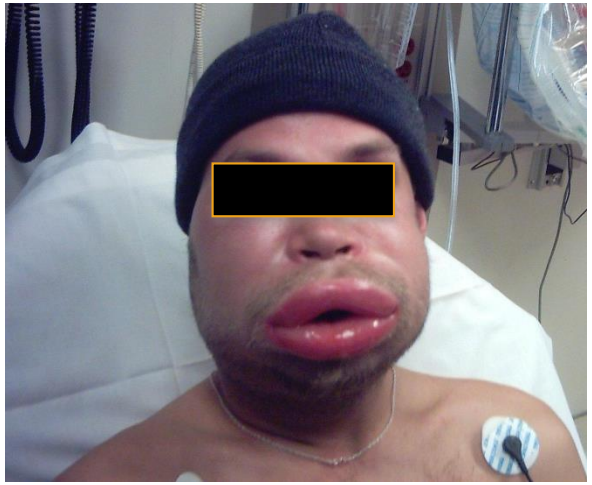
What Is C1-Inhibitor?

Human plasma protein …that mediates inflammation





Key regulator of *four* biochemical pathways

1. Complement
2. Contact
3. Fibrinolytic
4. Coagulation

C1-Inhibitor deficiency can cause:

- debilitating pain
- disfiguring swelling
- asphyxiation & death

Histamine mediated Angioedema

- Classic IgE mediated – Allergic
  - with anaphylaxis
  - with urticaria

- Non-IgE mediated
  - Medications (other than ACE inhibitors)

- Idiopathic
  - Maybe mixed with bradykinin mediated

Moellman, Joseph J., et al. "A consensus parameter for the evaluation and management of angioedema in the emergency department." *Academic Emergency Medicine* 21.4 (2014): 469-484.

Bradykinin mediated Angioedema

- Hereditary Angioedema
  - Type 1: Low C1-inhibitor
  - Type 2: Dysfunctional C1-inhibitor
  - Type 3: Normal C1-inhibitor

- Acquired Angioedema
  - Non-Hereditary

- Angiotensin Converting Enzyme (ACE) inhibitor
  - Iatrogenic

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Bradykinin mediated Angioedema

- Hereditary Angioedema
  - **Type 1: Low C1-inhibitor – 85%**
  - Type 2: Dysfunctional C1-inhibitor
  - Type 3: Normal C1-inhibitor
- Acquired Angioedema
  - Non-Hereditary
- Angiotensin Converting Enzyme (ACE) inhibitor
  - Iatrogenic

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Bradykinin mediated Angioedema

- Hereditary Angioedema
  - **Type 1: Low C1-inhibitor – 85%**
  - **Type 2: Dysfunctional C1-inhibitor – 15%**
  - **Type 3: Normal C1-inhibitor - Rare**

- **Acquired Angioedema - Rare**
  - **Non-Hereditary**

- Angiotensin Converting Enzyme (ACE) inhibitor
  - Iatrogenic

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Epidemiology

- Hereditary:
  - Classic type I and II: 1:30,000 – 1:80,000
  - Type 1 (85%) > Type II (15%)
  - Men = women and all races
  - Autosomal Dominant
  - 50% start in childhood <10 yrs with swelling and abdominal pain increases during puberty

- Acquired:
  - 1:100,000 to 1:500,00 prevalence
  - Middle age to Older

- ACE Inhibiter :
  - African Americans 3-4 x higher incidence than Caucasians
  - Immunosuppressed (transplant)
  - Female gender
  - Smoking

Adkinson Jr, N. Franklin, et al. *Middleton's Allergy E-Book: Principles and Practice*. (p 586-601) Elsevier Health Sciences, 2013.

Clinical Features of Bradykinin Mediated Angioedema

- Discrete episodes of non-pruritic, non-pitting swelling
- Worsening over 24 hours
- Recovery gradual over 48 to 72 hours
  - May last 5 + days

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- 50% extremities and abdomen
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- 50% at least one laryngeal attack, but multiple possible
- Can be *any* organ or body part
- Maybe life threating: laryngeal, brain
- Third spacing of fluid, hypotension

Possible Triggers

- Usually no clear precipitating cause
  - Emotion/stress
  - Infections
  - Trauma – minor like clapping or sitting down
    - Medical procedures: dental work, surgeries
  - Hormone changes, such as: Birth control with estrogen, pregnancy, and post partum, but not seemly not during delivery

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Laboratory Work-up and Diagnosis

Syndrome	Pathophysiology	C4 Level	C1INH Antigen	C1INH Function	C1q Level
Type I	SERPING1 C1 Inh. Def.	Low	Low	Low	Normal
Type II	SERPING C1 functional Inh. Def.	Low	Normal	Low	Normal
Normal C1inh	Unknown	Normal	Normal	Normal	Normal
Acquired	Consumption of C1 inh. Leading to def.	Low	Low	Low	Low
ACE-Ind.	Inhibition of Bradykinin catabolism	Normal	Normal	Normal	Normal
Idiopathic	Unknown	Normal	Normal	Normal	Normal

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Treatment

- Conceptually divide into three categories
  - Long-term prophylaxis
    - Minimize attack frequency and severity
    - Prevent hospitalizations and emergency room visits
  - Short-term prophylaxis
    - Prevent attacks after trauma
    - Prevent attacks during important life events
  - Treatment of acute attacks
    - Terminate ongoing attack
    - Prevent morbidity and mortality

Example Case 1

- 57 year old African American Female presents to the ED with lip and tongue swelling when she woke up this morning. She recalls mild lip tingling before bed, but is not sure when the swelling started.

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  - Has trouble swallowing, but denies: sob or trouble breathing.
  - Denies: Pruritus, nausea, vomiting, diarrhea, headache, limb swelling, chest pain, family history of swelling, wt loss or unexplained bruising or bleeding.

  - PMH: Hypertension, complete hysterectomy at age 48
  - Medications: Lisinopril for over 5 years

Example Case 1

- 57 year old African American Female presents to the ED with lip and tongue swelling when she woke up this morning. She recalls mild lip tingling before bed, but is not sure when the swelling started.

  - PE: HR 80, BP 132/78, Resp. 18, Pulse OX, 96% RA
  - General: Muffled voice and anxious but otherwise no acute distress
  - HEENT: EOMI, PERRLA**, lips 4 times normal size with enlarged tongue protruding from her mouth, mild drooling**
  - Chest: S1, S2, rrr, no mumurs, CTA B/L
  - Abdomen: soft, NT, ND, BS +
  - Ext: no swelling or pitting edema

Example Case 1: Likely Diagnosis?

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- Angiotensin Converting Enzyme Inhibitor induced

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- Angiotensin Converting Enzyme Inhibitor induced

- Acute Treatment:
  - Cessation of ACE-Inhibitors
  - Steroids and Antihistamines
  - ENT consult to evaluate for laryngeal edema
    - If airway compromised would need intubation
      - Rare with ACEI induced angioedema
- Long term treatment:
  - Avoid ACE-Inhibitors, relapse possible for 1 -2 months. Reports of up to 8 months have been made
  - May consider Angiotensin Receptor Blockers 8 weeks after stopping ACEI. 10% risk of angioedema

Example Case 2

- 59 year old African American Female presents to the ED with lip and facial swelling when she woke up this morning. She recalls mild right facial tingling before bed, but is not sure when the swelling started. She comments that this has been happening for past 6-8 months, but they have been getting worse.

Example Case 2

- 59 year old African American Female presents to the ED with lip and facial swelling when she woke up this morning. She recalls mild right facial tingling before bed, but is not sure when the swelling started. She comments that this has been happening for past 6-8 months, but they have been getting worse.

  - She has mild nausea and abdominal pain.
  - Denies: headache, limb swelling, chest pain, family history of swelling, or unexplained bruising and bleeding.
  - She has had more wt loss, about 15 pounds and fatigued
  - PMH: Hypertension, complete hysterectomy at age 53 for uterine cancer, diabetes type II.
  - Medications: Lisinopril and metformin

Example Case 2

- 59 year old African American Female presents to the ED with lip and facial swelling when she woke up this morning. She recalls mild right facial tingling before bed, but is not sure when the swelling started. She comments that this has been happening for past 6-8 months, but they have been getting worse.

  - PE: HR 80, BP 132/78, Resp. 18, Pulse OX, 96% RA
  - General: Thin, tired, but no acute distress
  - HEENT: EOMI, PERRLA**, lips 4 times normal size. Full facial swelling extending down the right side of her neck**
  - Chest: S1, S2, rrr, no mumurs, CTA B/L
  - Abdomen: Soft, no organomegly or masses, increased BS, diffuse tender
  - Ext: no swelling or pitting edema

Example Case 2: Diagnosis?

Example Case 2: Diagnosis?

- Acquired verse Idiopathic verse ACEI

- Acute Treatment:
  - Cessation of ACE-Inhibitors
  - Steroids and Antihistamines
  - Consider HAE rescue medication if continuing to worsen
  - HAE labs (C4, C1inh, C1inh function, C1q).
    - Consider Immunology consult

- Long term treatment:
  - Avoid ACE-Inhibitors, relapse possible for 1 -2 months. Reports of up to 8 months have been made
  - May consider Angiotensin Receptor Blockers 8 weeks after stopping ACEI. 10% risk of angioedema

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Example Case 3

- 35 year old African American Female presents to the ED with horrible abdominal pain that have been getting worse since yesterday. She decided to come to the ED after throwing up several times and complains of a horrible headache. She adds that this happens every few months and she is sick of no one taking her seriously.

Example Case 3

- 35 year old African American Female presents to the ED with horrible abdominal pain that have been getting worse since yesterday. She decided to come to the ED after throwing up several times and complains of a horrible headache. She adds that this happens every few months and she is sick of no one taking her seriously.

  - Denies: limb swelling with this episode, chest pain, sob, trouble swallowing, wt loss, unexplained bruising and bleeding, episodes occurring during monthly cycles.
  - PMH: Hypertension
  - Medications: Enalapril
  - FH: Dad and her sister often get periodic abdominal pain and facial swelling. Her dad once had trouble breathing. No one seems to know what they have either.

Example Case 3

- 35 year old African American Female presents to the ED with horrible abdominal pain that have been getting worse since yesterday. She decided to come to the ED after throwing up several times and complains of a horrible headache. She adds that this happens every few months and she is sick of no one taking her seriously.

  - PE: HR 97, BP 146/87, Resp. 20, Pulse OX, 96% RA
  - General: In pain, acute distress
  - HEENT: EOMI, PERRLA, mmm, no facial or lip swelling
  - Chest: S1, S2, rrr, no mumurs, CTA B/L
  - Abdomen: Soft, no organomegly or masses, BS+, diffusely tender
  - Ext: no swelling or pitting edema

Example Case #3: Diagnosis?

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- Hereditary Angioedema verse ACEI verse idiopathic

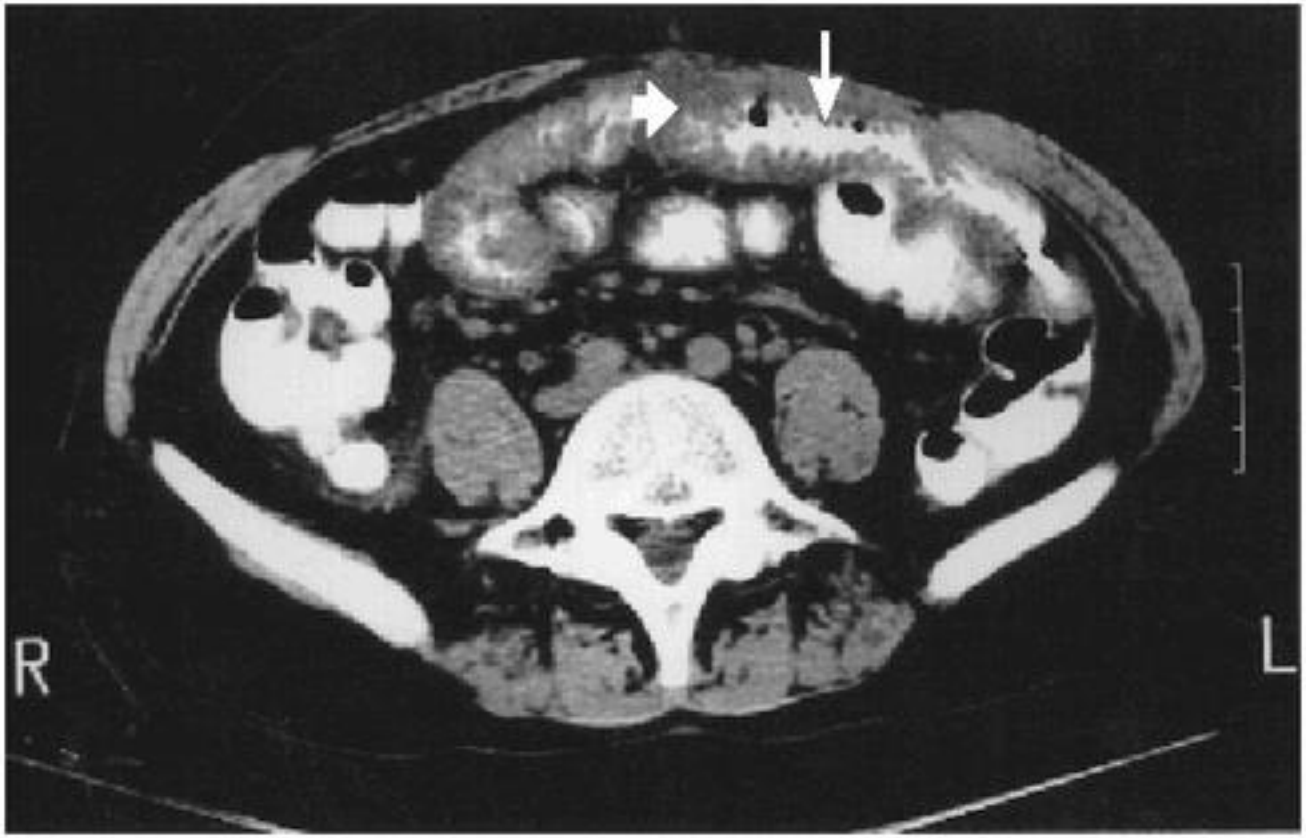
Example Case #3: Diagnosis?

- Hereditary Angioedema verse ACEI verse idiopathic

- Acute Treatment:
  - CT scan of abdomen
  - Steroids and Antihistamines
  - HAE rescue medication
  - HAE labs (C4, C1inh, C1inh function, C1q)
  - Cessation of ACE-Inhibitors

- Long term treatment:
  - Depends on cause and frequency of attacks

Results of Abdominal CT Scan



Gregory, Kate WP, and Rufus C. Davis. "Angioedema of the intestine." *New England Journal of Medicine* 334.25 (1996): 1641-1641.

Medication Options

Drug	Advantages	Disadvantages	Best use	Brand Name
Plasma-derived C1-INH	• Extensive clinical experience • long half-life	• Infectious risk • Needs IV access • Limited supply	• Acute attacks • Short-term • Long-term prophylaxis	• Berinert: Rescue • Cinryze: Prophylaxis
Recombinant C1-INH	• No human virus risk • Scalable supply	• Needs IV access • Short half-life • Potential for allergic reactions	• Acute attacks • Short prophylaxis	• Ruconest
Ecallantide Kallkren inhibitor	• More potent than C1-INH • No infectious risk • Subcutaneous administration	• Antibodies may cause allergic reaction or neutralization • Short half-life	• Acute attacks in office	• Kalbitor
Icatibant Bradykinin B2 receptor antagonist	• No infectious risk • Stable at room temperature • Subcutaneous	• Short half-life • Local pain or irritation	• Home treatment of acute attacks?	• Firazyr

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Example Case #3: Diagnosis?

- Hereditary Angioedema verse ACEI verse idiopathic

- Acute Treatment:
  - CT scan of abdomen
  - Steroids and Antihistamines
  - HAE rescue medication
  - HAE labs (C4, C1inh, C1inh function, C1q)
  - Cessation of ACE-Inhibitors

- Long term treatment:
  - Plasma Derived C1-Inh for prophylaxis and/or Rescue agent

Medication Options

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Example Case 3, Next visit to ED

- 35 year old African American Female presents to the ED with horrible abdominal pain that have been getting worse since yesterday, sob and stridor. She missed her prophylaxis dose of C1-inh for over a week. She has her rescue medication of plasma derived C1-inh, but no IV access.
  - Denies: limb swelling with this episode, chest pain, trouble swallowing, wt loss, unexplained bruising and bleeding, episodes occurring during monthly cycles.
  - PMH: Hypertension, HAE Type I
  - Medications: Amlodipine
  - FH: Dad and her sister recently were tested and confirmed to also have HAE Type I

Example Case #3: Emergency Treatment Plan

- Hereditary Angioedema
- Acute Treatment:
  - Prepare for emergency intubation if unresponsive to rescue medication and showing signs of deterioration
    - Cricothyrotomy maybe required if above is unsuccessful

Example Case #3: Emergency Treatment Plan

- Hereditary Angioedema
- Acute Treatment:
  - Prepare for emergency intubation if unresponsive to rescue medication and showing signs of deterioration
    - Cricothyrotomy maybe required if above is unsuccessful
  - Fresh Frozen Plasma (FFP) can be considered if other rescue medication is not available. FFP may, in rare cases, cause the angioedema to worsen.
  - HAE is poorly responsive to Epinephrine IM
    - If HAE status is unknown Epinephrine IM is always warranted, along with H1, H2 antihistamines and Steriods

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Summary

- Angioedema without signs or history of histamine involvement: Consider Bradykinin mechanism
- Unless Bradykinin mechanism is known, it is appropriate to treat with antihistamines, steroids and epinephrine (life-threatening respiratory angioedema).
- C4 for screening, C1inh, C1 function and C1q are needed to distinguish different forms of HAE
- If HAE is established: HAE specific treatments are required: plasma derived C1-INH, recombinant C1-INH, Kallkren inhibitor (Ecallantide), Bradykinin B2 receptor antagonist (Icatibant) and FFP

Question #1

- Hereditary Angioedema is mediated by?
  A. Histamine
  B. Platelet Activating Factor
  C. Bradykinin
  D. Tryptase

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- Hereditary Angioedema is mediated by?
  - A. Histamine
  - B. Platelet Activating Factor
  - **C. Bradykinin**
  - D. Tryptase

Question #2

- Hereditary Angioedema flare can be life threatening

  True or False?

Question #2

- Hereditary Angioedema flare can be life threatening

  True

Question #3

- Treatment of life threatening hereditary angioedema involves which of the following?

A. Bradykinin B2 receptor antagonist
B. C1 inhibitor
C. Plasma Kallikrein inhibitor
D. Epinephrine
E. All of the above except D

Question #3

- Treatment of life threatening hereditary angioedema involves which of the following?

A. Bradykinin B2 receptor antagonist
B. C1 inhibitor
C. Plasma Kallikrein inhibitor
D. Epinephrine
E. All of the above except D

Acknowledgements

- University Hospitals Cleveland Medical Center, LECOMT and Case Western Reserve University
- **Clinical Fellowship Mentors:**
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- *All of You!!!*