Update in Novel Therapies for Hereditary Angioedema

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Disclosures

• Speakers Bureau
  – Teva

History

• 1882–Quincke described angioneurotic edema
• William Osler 1888—“hereditary angioneurotic edema”
• 1917–Autosomal dominant inheritance pattern discovered
• 1963–biochemically defined as deficiency in C1 esterase inhibitor by Donaldson and Evans
• 1972–acquired form first described
Epidemiology

- Prevalence 1:50,000
- Described in all races
- No sex predominance
- Autosomal dominant inheritance

Presentation

- Usually presents in second decade and may worsen in adolescence. Rarely occurs 6th-7th decade
- Angioedema (involves inner dermis and subcutaneous tissues) without urticaria
- Painless nonpruritic, nonpitting edema involving face, upper airway, GI tract, and extremities
- Onset within hours and duration 2-5 days
- Upper airway (hoarseness, dysphagia) involvement has mortality of 30-40% in some series
- Hypotension may rarely occur due to fluid shifts
**Upper Respiratory Tract**

- Laryngeal, pharyngeal, and nasal angioedema can lead to asphyxiation
- Asphyxiation can occur as early as 20 min or as late as 14 hours
- Asphyxiation can occur at any age
- Study showed 5 of 6 patients who asphyxiated never had upper airway involvement in previous attacks

**Gastrointestinal**

- Visceral edema results in obstructive symptoms including anorexia, vomiting, and crampy abdominal pain
- Ascites may rarely occur
- Severe isolated abdominal symptoms without cutaneous angioedema can be mistaken for acute abdomen leading to unnecessary exploratory surgery
- Usually resolves in 12 to 24 hours

**Presentation--other**

- Fever and leukocytosis should raise suspicion for another cause of angioedema
- Rarely may have erythematous rash that unlike urticaria is not pruritic, painful, or warm
- Genital swelling can occur with horseback riding, parturition, or intercourse
- Cases reported of migraine-like and TIA-like symptoms during attacks
Triggers

- Minor trauma
  - Dental most common
  - Even writing/typing
- Stress
- Menses or use of OCP’s
- Infection
- Often no precipitating factors identified

C1 Esterase Inhibitor (C1EI)

- Belongs to serine protease inhibitor family and located on chromosome 11 (11q12-q13.1)
- Molecular weight of 105kd
- Produced in liver, monocytes, megakaryocytes, fibroblasts, and placental cells
- Synthesis stimulated by INF gamma
- Biologic half life 64 hours

C1 esterase inhibitor (C1EI)--functions

- C1EI has modulating effect on complement, fibrinolytic, and kinin pathways
- Inactivates C1r, C1s, XIIa, kallikrein, and plasmin by forming irreversible covalent bonds with these substrates
- Inhibits auto-activation of C1q in fluid phase
Classification

- Hereditary (HAE)
  - Hereditary Angioedema Type I--85%
    - Low C1EI level (<30% of normal)
  - Hereditary Angioedema Type II--15%
    - Abnormal functional assay but normal quantitative level
    - Type III--described in women only
- Acquired (AAE)
  - Acquired deficiency Type I
  - Acquired deficiency Type II

Genetic Mutations of C1EI

- Autosomal dominant inheritance pattern
  - 20-25% may have spontaneous mutations
- Over 100 mutations have been described which explain the widely variable clinical differences
- Type I HAE may be due to insertions or deletions of nucleic acids of the C1EI gene
- 70% of Type II mutations result in substitutions at Arg444

Type III HAE

- Described in German study (Lancet 2000;356:213-217)
- Estrogen Associated/Dependent
- Inherited
- Associated with puberty, pregnancy, OCP use or HRT
- Symptoms noted within 14 to 21 days of conception or within 7-14 days of starting estrogen therapy
- Normal C1 inhibitor levels and function
**Type I Acquired Angioedema (AAE)**
- Described 1960’s
- Presents after 4th decade of life
- Synthesis of inhibitor is normal but rate of catabolism of these agents is increased 2 fold
- C1 is thought to be continuously activated which leads to consumption of C1EI

**Type I Acquired Angioedema (AAE)**
- Seen in B cell proliferative disorders, MM, WM, essential cryoglobulinemia, and lymphocytic lymphoma
- Rarely other carcinomas, SLE, Churg-Strauss, infections, and livedo reticularis
- Angioedema may precede development of malignancy by years

**Type II Acquired C1I Deficiency**
- Autoantibody (IgG or IgA) directed against C1EI molecule leading to its inactivation
- An inactive C1EI is cleaved into 96 kd fragment that can be measured in the serum leading to “normal” C1EI measured level
- No known underlying disease
- Nonfunctional C1 Inhibitor
- C1 antigenic level 50-60% of normal
**Diagnosis**

- Presentation and inheritance pattern
- Search for complement abnormalities
  - CH50 may be low
  - C4 level should be low in between attacks but can rarely be normal
  - C4 and C2 are low during attacks
  - C1 inhibitor level low in Type I HAE (<30% less than normal)
  - C1 functional assay abnormal in Type II HAE
  - Distinguishing feature of AAE is low C1q level as opposed to HAE

**Diagnosis**

- Screening test of choice C4 advocated by most authors
- Measure C1EI level and function and C1q
- HAE type 1—decreased C1EI level and normal C1q level
- HAE type 2—decreased C1EI function and normal C1q level
- AAE—decreased C1EI function and C1q level

**Complement Profiles in Angioedema**

<table>
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<tr>
<th>Condition</th>
<th>C1-INH Quantitative</th>
<th>C1-INH Activity</th>
<th>C3</th>
<th>C4</th>
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**Treatment**

- Acute
- Chronic Prophylaxis
  - Short term
  - Long term

**Acute Treatment**

- C1-INH Concentrate
- Plasma Kallikrein Inhibitor
- Bradykinin Receptor Antagonist
- FFP
  - Paradoxical worsening may occur
  - Not recommended for severe attacks
- Supportive therapy during acute attacks until symptoms resolve
  - Airway management
  - Pain management, opioids often required
  - Anti-emetics for nausea/vomiting
  - IVF
- Corticosteroids, antihistamines and epinephrine provide little benefit in most reports

**Chronic Treatment**

- Genetic counseling and testing of relatives and offspring
- C1-INH Concentrate
- Attenuated androgens
  - Danazol
  - Stanazolol
- Antifibrinolytic agents
  - Epsilon aminocaproic acid
  - Tranexamic acid
**Attenuated Androgens**

- Decrease attacks by increasing C1 inhibitor production
- Stanozolol 4 mg TID for 12 wks
  - Taper by 2-4 mg every 12 wks until lowest maintenance dose is reached
  - Typically 2-6 mg/day
  - Alternative is to taper as soon as control is reached
  - Alternate day is also effective
- Danazol 200-300 mg qd
  - 200-300mg every 2-3 days has been successful

**Androgen Contraindications**

Absolute contraindications
- Hepatic, renal, cardiac disorders
- Pregnancy or breast feeding
- Prostate cancer
- Porphyria

Relative contraindications
- Elevated LFT's
- Studies have shown LFT's remain stable even in patients with baseline elevated enzymes

**Androgen Side Effects**

Side effects are dose related
- Weight gain, hirsutism, hair loss, voice changes, abnl menstruation, decreased breast size, decreased libido, HA's, acne, myalgias, abnl lipid panel, polycythemia, elevated LFT's, hepatic necrosis, cholestasis, HTN, possibly increased atherogenesis
- Hepatocellular adenomas and one case of hepatocellular carcinomas in pts taking danazol > 10 yrs
- Stanozolol seems to have fewer adverse effects than danazol
Antifibrinolytic Agents

- Decrease conversion of plasminogen to plasmin and fibrinolysis

- Epsilon aminocaproic acid
  - Dose: 2 g TID
  - Not FDA approved for HAE

- Tranexamic acid
  - Dose: 1 g BID
  - Not FDA approved for HAE

Antifibrinolytic Agents

- Side effects
  - Nausea and diarrhea
  - Vertigo
  - Postural hypotension
  - Fatigue and muscle cramps/weakness
    - Increased muscle enzyme concentrations

- Other concerns
  - Risk of vascular thrombosis
  - Teratogenicity

New Treatment Options for HAE
Treatment - C1 Inhibitors

- C1 inhibitor isolated from plasma:
  - American Red Cross began to make experimental batches in 1974
  - Gadek, et.al. reported effectiveness in NEJM in 1980
  - Became available in Europe in the early 1980’s
  - With the onset of the AIDS epidemic preparation was halted in the US
  - Since then several generations of C1 inhibitors have been developed

Treatment - C1 Inhibitors

- 1st Generation
  - Physical separation
    - Risk of viral transmission - HIV and HCV
- 2nd Generation
  - Added dry heat treatment
    - Removed risk for HIV but not HCV
- 3rd Generation
  - Added pasteurization
    - Removed risk of both HIV and HCV transmission
- 4th Generation
  - Added nanofiltration
    - Virtually no risk

Treatment - C1 Inhibitors

- Now FDA approved, but have been used in Europe for many years
- Extensive reports by Bork and colleagues
  - Improvement in laryngeal attacks in close to 100% of patients within 60 minutes
  - 70% of patients with abdominal attacks improved at 60 minutes, and close to 100% improved by two hours

Bork et al. Transfusion. 2005;45(11)
Treatment - C1 Inhibitors

- Two C1 inhibitor preparations purified from pooled human plasma are available
  - Human C1 esterase inhibitor – Berinert
  - Human C1 esterase inhibitor – Cinryze

Berinert

- Pasteurized
- FDA approved for acute therapy of attacks
- First licensed in Germany in 1979
- Approved in Europe since early 1980s

Berinert

- Safety and efficacy not studied for prophylaxis
- Phase III DBPC study in US: Craig et al. JACI. 2009;124(4)
- 125 patients with acute facial or abdominal HAE
- Primary endpoint was time to onset of relief
  - Moderate attacks
    - Median time to symptom relief was 48 minutes compared with 78 minutes with placebo
  - Severe attacks
    - Median time to symptom relief was 30 minutes compared with 810 minutes with placebo.
**Berinert**

- Over 400,000 treatments in Europe and other countries
- Approved in US for adults and adolescents
  - Safety and efficacy for ages 0-12 not established
- 20 units per kg IV

**Berinert**

- Warnings include:
  - Hypersensitivity
  - Thrombotic events
  - Transmission of infectious agents
    - No infections have been observed in decades of use
- Adverse reactions:
  - HA, abdominal pain, nausea, muscle spasm, pain, diarrhea and vomiting

**Cinryze**

- First batches made as early as 1972
- Pasteurized and nanofiltered
- FDA approved for prophylaxis
- Not approved for acute attacks
Cinryze

- Phase III DBPC study in US: Zuraw et al. NEJM. 2010;124(4)
- 22 patients with 2 or more attacks per month
- Reduced attacks by half

- Cinryze is FDA approved for prophylaxis in adolescents and adults
- 1000 units twice a week

Cinryze

- Warnings include:
  - Hypersensitivity
  - Thrombotic events
  - Transmission of infectious agents
- Adverse reactions:
  - URI, sinusitis, rash and HA

Treatment - C1 Inhibitors

- Recombinant transgenic human C1 inhibitor
- Conestat alfa - Ruconest (EU), Rhucin (US) is for the treatment of acute HAE attacks in adults
  - >90% of patients respond within 4 hours
  - Expressed in rabbit milk and then purified
  - Dose: IV 50 or 100 U/kg, shorter half life
- 2 randomized DBPC studies showed rapid improvement
  - European Study (50) and North American Study (50 and 100)
  - Launched in Europe; phase III clinical trials in the US
- Safety
  - The most common adverse event in these studies was headache
  - Contraindicated in patients with rabbit allergy or with IgE antibodies against rabbit epithelium (dander)
Treatment – Drugs Targeting Bradykinin Forming Cascade

• Bradykinin is the mediator of swelling
• Ecallantide (Kalbitor)
  – Plasma Kallikrein Inhibitor
• SQ administration: 30mg (3mL): 3 1mL injections
• Short half life: ~2 hours
• 2 DBPC Phase III studies in the US showed significant improvement vs placebo (N=168)
• FDA approved for acute attacks

Warning:
  – Anaphylaxis in 2.7% to 3.9% of patients
  – Always within the first hour
  – Should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis

Treatment – Drugs Targeting Bradykinin Forming Cascade

• Icatibant (Firazyr)
  – 2nd generation bradykinin B2-receptor antagonist
  – SQ administration
  – Short half life: ~1-2 hours
  – 3 DBPC Phase III studies in US and Europe
  – Europe/Israel trial (FAST-2) – significant decrease in time to relief
  – US trial (FAST-1) showed no benefit; follow-up (FAST-3) trial recently completed and showed significant benefit for icatibant
  – Approved in Europe and in the US the drug was granted FDA approval on August 25, 2011
Conclusion

Bradykinin receptor antagonist
Kallikrein inhibitor