Clinical Characteristics of Hereditary Angioedema

William R. Lumry, MD

Angioedema is defined as extravasation of plasma into deeper cutaneous tissues. It may occur with or without urticaria. There are several possible etiologies, including IgE triggers (e.g., food, drugs, inhalants, contactants), non-IgE triggers (e.g., nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme [ACE] inhibitors), physical causes (e.g., delayed pressure urticaria), medical causes (e.g., autoimmune disorders, malignancy), heredity (types I and II [associated with C1 esterase inhibitor deficiency] and III), and acquired C1 esterase inhibitor disorder.

Hereditary angioedema (HAE) is a rare disease, occurring in the range of 1:10,000 to 1:50,000 individuals in the world. It represents about 2% of angioedema cases. The HAE Association in the United States has identified approximately 4000 individuals with HAE. This number is increasing steadily as family members come forward and disease information is disseminated. Angioedema attacks usually begin in the second decade of life, but they have been reported in infants. HAE is often misdiagnosed as an allergic reaction to drugs or foods or as idiopathic angioedema.

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Clinical Characteristics

Clinical characteristics of HAE include recurrent bouts of swelling. It is usually nonpitting, nonerythematous, and nonpruritic. There can be peripheral cutaneous (hands, feet, extremities, trunk) swelling, central cutaneous (face, genitalia) swelling, or mucosal (lips, tongue, larynx, gastrointestinal tract) swelling. Most patients have swelling at all of these sites. About 50% will have laryngeal edema at some point in the course of the disease. The edema is typically precipitated by physical trauma to the skin, psychological stress, menses, or episodes are often misdiagnosed with endometriosis or ovarian cysts.

A family history of HAE is usually present, but the physician must explicitly ask the patient for a family medical history if the disease is suspected. About 25% of patients have a spontaneous genetic mutation.
Improving Outcomes in Hereditary Angioedema: Clinical Cases and Expert Opinion

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drugs (eg, ACE inhibitors, estrogens). The swelling develops slowly over 2 to 24 hours and lasts 24 to 60 hours. Many patients describe a nonpruritic rash called erythema marginatum (a nonpruritic, serpiginous, flat, erythematous rash) that precedes a swelling attack. Patients with HAE do not have urticaria as part of their angioedema attacks.

The cutaneous swelling can be uncomfortable or even disabling (if it occurs in the hands or feet). Abdominal swelling can involve any part of the gastrointestinal tract, such as the esophagus or small or large bowels. Symptoms may include nausea, vomiting, diarrhea, and severe cramping pain. If patients can’t take anything by mouth or have diarrhea dehydration may occur. They may become hemoconcentrated or have leukocytosis.

Facial and upper airway (mouth, tongue, pharynx, hypopharynx, larynx) swelling is potentially life threatening. Symptoms may include dysphagia, voice changes, throat tightness, or stridor. If the airway is not protected or opened, the attack can lead to asphyxia and death.

**Types of HAE**

Two types of HAE are associated with a C1 esterase inhibitor deficiency. In type I HAE (which accounts for 85% of these patients) the C1 esterase inhibitor protein is not present in adequate amounts in the circulation. In type II there are quantitatively normal amounts of C1 inhibitor but it is not functional. There are genetic defects for both type I and type II HAE. Both have autosomal dominant transmission, but there is incomplete clinical expression and variable severity. Spontaneous mutations occur in 25% of patients with HAE. Women tend to be more frequently and severely affected than men.

Type III is not associated with C1 esterase inhibitor deficiency or dysfunction. It is primarily described in women, but a few men have been reported to have this disease. Individuals with type III HAE have normal C1 inhibitor levels and function. The disease predominantly affects the face.

**C1 Inhibitor Sites of Action**

C1 inhibitor is an important regulatory protein in the coagulation, kallikrein-kinin (contact), and complement systems. The kallikrein-kinin (contact) system is involved in the edema that is associated with HAE. Without C1 inhibitor, the system is activated through activation of Hageman factor. The reaction is amplified, producing a large amount of kallikrein. Kallikrein is responsible for converting high-molecular-weight kininogen to bradykinin. Uncontrolled production of bradykinin leads to fluid loss from vessels, edema, and pain. C1 inhibitor blocks the amplification loop and blocks production of bradykinin by kallikrein.

Components of the complement pathway can be measured more easily than components of the contact system. C1 inhibitor controls the activation of the classic complement pathway. When this is uncontrolled, C2 and C4 are consumed and the levels go down. C4 level can quickly and accurately be measured by most laboratories.

**There are genetic defects for both type I and type II HAE. Both have autosomal dominant transmission, but there is incomplete clinical expression and variable severity.**

In types I and II HAE and acquired C1 inhibitor deficiency, the C4 level is low in about 95% of patients, even if they are not having an attack. C4 levels are low in 100% of patients during an attack. In type I HAE the C1 inhibitor level is low (Table 1). In type II the C1 inhibitor level is normal but its function is low. In acquired C1 inhibitor deficiency there is low C1 inhibitor level, low C1 inhibitor function, low C4 level, and low C1q level (which is normal in type I and type II HAE). For patients with type III HAE, ACE-inhibitor-associated angioedema, or idiopathic angioedema, all of the complement laboratory values are normal.

**Diagnosis**

Clinical suspicion is the key to making the diagnosis. This includes a family history of the disease and measuring C4 level. Low C4, C1 inhibitor, and normal C1q levels indicate type I HAE. If there is a low C4 level but a normal C1 inhibitor level and normal C1q level then functional C1 inhibitor assay should be measured. If C1 inhibitor functional activity is low, the diagnosis is type II HAE.

An international internet survey reported by Lunn et al revealed there often is a delay in diagnosis of HAE. The survey included 313 HAE patients in five countries (average age 37 years). On average, more than one year passed between the first attack and the patient seeking medical attention, and there was an average of 8.3 years from the first attack to the time when an accurate diagnosis was made. These patients saw on average 4.4 physicians before the correct diagnosis was made. The wrong diagnosis was given 63% of the time (eg, allergic angioedema, appendicitis), which led to unnecessary surgery in 21% of patients. Most patients reported two immediate family members and two extended family members with the disease. However, only 48% of the immediate and 26% of extended family members had been screened for the disease.

HAE is a debilitating and potentially life-threatening condition affecting 6,000 to 30,000 individuals in the United States. The diagnosis rests on knowledge of the disease, clinical suspicion, good history taking, and appropriate laboratory evaluation. Making an accurate diagnosis decreases the likelihood of inappropriate treatment and improves the mental well-being of the patient and family. HAE may impose a significant burden of illness on these patients.

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**Table 1. Laboratory Characteristics**

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<thead>
<tr>
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<th>C1 INH Level</th>
<th>C1 INH Function</th>
<th>C4 Level</th>
<th>C3 Level</th>
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An Update on Therapy

Bruce L. Zuraw, MD

Just a few years ago, treatment choices for HAE were limited. This has changed with the approval of newer, more effective drugs.

Case Study
A 16-year-old boy with known HAE complains of abdominal pain. His symptoms began in the middle of the night. In the morning he complains of severe pain and nausea. He vomits every hour and feels lightheaded. On examination, he is in distress, writhing in pain. His blood pressure is 90/60 mmHg and orthostatic to 70/40 mmHg. He is dehydrated. His abdomen is silent, tender to palpation diffusely, with rebound tenderness. In the past, this patient would likely have been sent for surgical evaluation and may have undergone a laparotomy for presumed appendicitis or other surgical emergency.

Conventional treatment for an acute HAE attack (before the availability of the newer drugs) depended on the site of the attack. Typically, no treatment was given for extremity attacks. Gastrointestinal attacks were treated with intravenous hydration, narcotic pain medications, and antiemetic drugs. Oropharyngeal attacks are the most life threatening. Treatment included hospitalization with careful observation and timely intubation (if necessary).

Treatment with fresh frozen plasma (FFP) was available and frequently used for acute attacks. FFP is usually successful, but has some limitations. For example, it occasionally elicits a paradoxical response with rapid worsening of the angioedema.

New Treatment Options for HAE
New treatment options for HAE are derived from scientific advances in the understanding of HAE, particularly two key findings. First, HAE results from a deficiency in C1 inhibitor protein. Second, the major mediator of swelling is bradykinin.

Since C1 inhibitor deficiency is the primary defect in HAE, it was reasonable to assume that replacement of C1 inhibitor with exogenous protein would be beneficial. Data from Bork et al. showed improvement in laryngeal attacks in close to 100% of patients within 60 minutes of receiving C1 inhibitor replacement therapy. Approximately 70% of patients with abdominal attacks improved at 60 minutes and close to 100% improved by two hours. C1 inhibitor therapy, which is a blood-derived product, became available in Europe in the early 1980s, at about the time of the onset of the AIDS epidemic in the United States. Safety was an essential consideration. Since then, several generations of C1 inhibitor concentrates have been developed.

The first-generation C1 inhibitor concentrates used physical separation to remove impurities. Treatment of HAE was possible, but there was risk for viral transmission, especially of hepatitis C and HIV. These drugs were not available in the United States. The second-generation C1 inhibitor concentrates added dry heat treatment, which removed the risk for HIV transmission but not for hepatitis C transmission. The third-generation C1 inhibitor concentrates added pasteurization, which removes risk for transmission of both HIV and hepatitis C. The fourth-generation adds nanofiltration to pasteurization, resulting in virtually no risk of viral transmission.

Plasma-Derived C1 Inhibitors
The purified plasma C1 inhibitor concentrate (C1 esterase inhibitor [human]; Berinert) is widely used in Europe. A Phase III double-blind, placebo-controlled study conducted in the United States involved 125 HAE patients with acute facial or abdominal HAE attacks. The primary endpoint was time to onset of relief. The C1 esterase inhibitor at a dose of 20 U/kg was statistically significantly better than placebo and has been FDA approved in the United States.

When the data from this study was broken down by attack severity, it was shown that for moderate attacks the difference in time to onset of symptom relief was relatively modest between placebo and active treatment (78 min vs. 48 min). For severe attacks, the impact was markedly different ($80 min vs 30 min).

The C1 esterase inhibitor (human) Cinryze is also pasteurized and nanofiltered. A Phase III study involved 68 patients given 1000 U C1 inhibitor or placebo for facial, abdominal, or genitourinary attacks. The primary endpoint was time to onset of relief. The study showed that it was beneficial to receive the C1 inhibitor (P=0.019). However, this drug was not approved by the FDA for acute HAE attacks.

C1 esterase inhibitor (human) (Cinryze) was also studied for long-term prophylaxis in a Phase III double-blind, placebo-controlled trial involving 22 patients with two or more HAE attacks per month. They were given 1000 U C1 esterase inhibitor every 3 to 4 weeks in this 24-week crossover study. The primary endpoint was number of attacks during each 12-week phase. In the treatment group, the median number of attacks was reduced by half compared to the placebo group. Results on outcomes, including number of attacks, severity of attacks, number of rescue treatments, duration of attacks, and days of swelling, favored prophylaxis with C1 esterase inhibitor. The drug was approved by the FDA for routine prophylaxis against HAE attacks.

Drugs Targeting Bradykinin Forming Cascade
The drug ecalticante was developed based on the understanding that bradykinin is the mediator of swelling. The drug is a Kunitz-type plasma kallikrein inhibitor that is administered subcutaneously and has a short half-life. Two randomized, double-blind, placebo-controlled Phase III studies conducted in the United States showed statistically significant improvement versus placebo. The drug was approved by the FDA for treatment of acute HAE attacks. Because of a risk of allergic reactions to ecalticante, it must be administered in a medical facility.

Drugs in Clinical Trials
Two new drugs for HAE are awaiting FDA review. The first one is a recombinant transgenic human C1 inhibitor. The human C1 inhibitor protein is expressed in rabbit milk and then purified. The preparation, which is administered intravenously, has a shorter half-life than plasma-derived C1 inhibitor. To induce an adequate response a dose of 50 or 100 U/kg is required. Two studies of rhC1 inhibitor showed rapid improvement with both the 50 and 100 U/kg doses compared to placebo.

The second drug that recently completed clinical trials is icatibant, which is a bradykinin B2 receptor antagonist. It has a short half-life and is administered subcutaneously. It has undergone three Phase III trials in the United States and Europe. In the FAST-2 trial, which was largely conducted in Europe and Israel, the compara-
Individualization of Therapy

Richard G. Gower, MD

HAE is an autosomal dominant disease with heterogeneous genetic and phenotypic expressions. Affected persons can have highly variable presentations. Now that effective treatment modalities are available for HAE, it is necessary to diagnose the condition early, diagnose it accurately, and treat it effectively. For some patients, no therapy may be necessary. Episodic treatment is appropriate for infrequent acute attacks. Short-term prophylactic therapy may be indicated in some cases, such as before dental or surgical procedures. Long-term routine prophylaxis is indicated for patients with frequent or severe attacks and in patients whose quality of life is significantly impaired. Several effective therapies now available allow individualization of treatment.

HAE imposes significant economic burden in the United States. A study by Wilson et al found that the total annual per patient cost for HAE attacks of mild severity is $14,000, for moderate attacks $27,000, and for severe attacks $96,000 (average $42,000). Direct costs are about $26,000 per patient and over 80% of these direct costs are related to treatment of acute attacks. Indirect costs are $16,000 per patient, mostly from lost income.

Considerations When Choosing Therapy

The choice of therapy for HAE depends on several factors, including costs of medication and administration, availability of medications, availability of experienced providers, and availability of treatment facilities. The medication efficacy, quality, and safety are important considerations. Currently, there is limited evidence-based consensus regarding management of HAE. One consensus document on the management and treatment of HAE was developed in 2007 (before the newer medications were approved) by the U.S. Academy for Advances in HAE and published by Craig et al. The consensus committee looked at frequency, severity, and location of attacks and considered episodic versus prophylactic therapy. The committee stated that individualized HAE management is the preferred approach and ideal therapy should have proven efficacy with appropriate half-life and a good tolerability profile. Discussion between physician and patient is essential.

The consensus committee described three categories of HAE therapy consideration criteria: description of HAE attacks, nature of HAE attacks, and burden on activities of daily living. In the description of attacks category, the committee recommended episodic therapy for patients with less than one attack per month and prophylactic therapy for those with one or more attacks per month. Patients with rapid progression of attacks were also considered candidates for prophylactic therapy. Patients with timely access to care can be managed with episodic therapy if they do not qualify for prophylaxis.

In the nature of HAE attacks category, a history of laryngeal attacks, more than three emergency visits per year to the physician or hospital, intubation, more than one hospitalization per year, or any intensive care unit visits are indications for prophylactic therapy. Episodic therapy is indicated for less frequent and less severe attacks.

In the burden on activities of daily living category, prophylactic therapy is recommended for patients who miss more than 10 days per year of school or work. Patients with analogic dependency or who experience a large impact on their quality of life from HAE should also receive prophylactic therapy. The presence of any criteria for prophylactic therapy supports the need for prophylactic treatment.

HAE causes variable intermittent disability and, therefore, treatment decisions must be individualized and involve the patient. Patients must be educated to under-
stand the disease and participate in treatment choices. Economic loss for the patient, family, employer, and society must be considered as well as loss of opportunity to those affected.

Episodic Therapy
NZ is a 43-year-old man with type I HAE diagnosed at an early age. Abnormal laboratory values include C1-inhibitor antigen 6 (normal, 11-16), C1-inhibitor function 31% (normal >68%), and C4 level 4 (normal, 15-55). His father died of a laryngeal attack and his brother died at age 20. One brother and three sisters have HAE. Two of his children exhibit signs and symptoms of HAE. For prophylactic therapy he takes danazol 200 mg every day with acute dose increases as needed. He also uses C1 inhibitor episodically.

Therapy options for episodic HAE attacks include plasma-derived, pasteurized C1 esterase inhibitor (human) (Berinert) for intravenous (IV) treatment of acute abdominal or facial attacks in adolescent and adult patients. It is well tolerated. Ecallantide is a kallikrein inhibitor approved for subcutaneous treatment of acute HAE attacks in patients 16 years of age and older. Anaphylaxis has been reported after administration. FFP may be administered when C1 inhibitor or ecallantide are not available. FFP can occasionally exacerbate HAE acute attacks. Supportive therapy involves IV fluids, pain management, intubation, and tracheotomy as indicated.

Prophylactic Therapy
JZW is a 36-year-old man with type I HAE. He has had attacks since age 5, but was not diagnosed until age 18. Abnormal laboratory values include C1 inhibitor antigen 6, C1 inhibitor function 19%, and C4 level 13. His brother, niece, nephew, cousin, and aunt have HAE and his mother and uncle died of HAE. He was treated with danazol for over 18 years and weighs 480 pounds. Acute attacks have been treated with FFP. Noncompliance has also been an issue. A tracheotomy was required in May 2007 and he was also intubated in January 2008 for a laryngeal attack. Overall, he states he has had in excess of 100 upper airway attacks.

Danazol has been inadequate to control this patient’s symptoms and he has experienced side effects of the drug. He was placed on C1 inhibitor prophylaxis and has had no major attacks while on this therapy.

Prophylactic therapy options include plasma-derived, nanofiltered C1 esterase inhibitor (human) (Cinryze), which is approved for routine prophylaxis against HAE attacks in adolescent and adult patients. It is effective for both short-term and long-term use. C1 inhibitor for prophylaxis has been shown to reduce severity and duration of HAE attacks. Adverse reactions were all mild as reported by 87.5% of subjects.

Antifibrinolytics (aminocaproic and tranexamic acid) are another option. They are slow acting and therefore not suitable for treating acute attacks. Long-term use is associated with adverse effects.

Conclusion
In summary, disease specific therapies that interfere with the mechanisms of HAE are available. The paradigms for acute treatment and for prevention of HAE attacks have significantly changed in the past 3 years. Treatment guidelines are rapidly evolving and unanswered questions remain, such as which treatment is best, how much to give, and for how long.

When monitoring HAE treatment, it is important to understand that there is no known correlation between laboratory values and disease severity. Patients should be treated according to their clinical history of attacks and not their laboratory values. Additionally, frequent laboratory testing is not necessary once the diagnosis is confirmed on at least two occasions. Patients should keep an attack diary and have periodic clinical assessment with appropriate laboratory evaluation for patients on androgen therapy.

References
A CME-Certified Newsletter

Improving Outcomes in Hereditary Angioedema: Clinical Cases and Expert Opinion

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Self-Assessment Test

After reading each item carefully, please select the best response (one) and enter your choice on the reverse.

1. Which of the following is least likely to be seen in a patient experiencing a hereditary angioedema (HAE)-associated swelling attack involving the right leg and abdomen?
   A. Serpiginous erythematous macular eruption (erythema marginatum) on anterior chest
   B. Colicky abdominal pain with nausea and vomiting
   C. Diffuse urticaria
   D. Nonpitting, nonerythematous edema of right foot and lower leg

2. HAE is a rare genetic disorder with an autosomal dominant mode of transmission. Therefore, all patients with proven diagnosis of hereditary angioedema are the offspring of someone who has HAE.
   A. True
   B. False

3. As an initial screening test for HAE, which of the following has a 95% likelihood of being below normal?
   A. C1 Inhibitor quantitative (antigenic) level
   B. C4 level
   C. C1q level
   D. C3 level

4. In a patient with acquired C1 inhibitor deficiency, which of the following laboratory values are low?
   A. C4 level
   B. C1q level
   C. C1 Inhibitor functional activity
   D. A and B only
   E. All of the above

5. Which of the following statements about the drugs used to treat HAE is FALSE?
   A. Ecallantide and icatibant are effective in the treatment of HAE because they target bradykinin.
   B. Ecallantide is administered by subcutaneous injection
   C. Plasma-derived C1 inhibitor has a shorter half-life than recombinant C1 inhibitor.
   D. When administered for the treatment of an acute attack of HAE, fresh frozen plasma has been observed to significantly worsen the attack.

6. Which of the following treatments has been proven to be effective for long-term prophylaxis of HAE?
   A. Recombinant human C1 inhibitor 100 U/kg given twice/week
   B. Plasma-derived C1 inhibitor 20 U/kg given once/week
   C. Plasma-derived C1 inhibitor 1,000 U given twice/week
   D. B and C
   E. A and C

7. Which of the following statements about C1 inhibitor concentrates is true:
   A. Physical fractionation of C1 inhibitor removes the risk of transmission of HCV but not HIV
   B. Dry heat treatment of C1 inhibitor removes the risk of transmission of HIV but not HCV
   C. Pasteurization of C1 inhibitor removes the risk of transmission of HIV but not HCV
   D. Pasteurization of C1 inhibitor removes the risk of transmission of all viral pathogens
   E. Nanofiltration of C1 inhibitor is designed to remove protein aggregates, and has no impact on the risk of viral transmission

8. Which of the following is a therapy option for an acute HAE attack?
   A. Plasma-derived, nanofiltered human C1 inhibitor
   B. Attenuated androgens
   C. Ecallantide
   D. Antifibrinolytic

9. A 21-year-old man with HAE experiences 3 or 4 HAE attacks per year. They generally do not require an emergency room visit, although in the past he was admitted for a laryngeal attack. He missed 4 days of work in the past year due to HAE attacks. Which of the following is the best therapeutic choice?
   A. Plasma-derived human C1 inhibitor, given for prophylaxis
   B. Plasma-derived human C1 inhibitor, given episodically
   C. Ecallantide, given for prophylaxis
   D. Attenuated androgens, given episodically

10. What is the relationship between C1 inhibitor level and severity of disease?
    A. The level allows the clinician to predict how much C1 inhibitor will be required to treat a given attack.
    B. The level allows the clinician to know in general how much C1 inhibitor is likely to be required in the members of a family.
    C. The level allows the clinician to determine the dose of other treatment modalities that will be required to treat an attack.
    D. There is no relationship.
Activity Evaluation

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   If Yes, what specifically? ____________________________________________
   If No, what might be barriers to making any changes? ________________________

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