Hereditary Angioedema

A Disease Often Misdiagnosed and Mistreated

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KEYWORDS

• Hereditary angioedema • Bradykinin • C1 inhibitor

KEY POINTS

- Hereditary angioedema (HAE) is often overlooked or misdiagnosed. It is associated with significant morbidity and potential mortality.
- HAE presents with recurrent attacks of subcutaneous and submucosal swelling without urticaria.
- Unlike the more common histamine-mediated causes of angioedema, HAE is bradykinin-mediated and refractory to antihistamines, epinephrine, and corticosteroids.
- Appropriate therapy requires drugs specific to the excess release of bradykinin.

BACKGROUND

Hereditary angioedema (HAE) is a rare, inherited condition characterized by recurrent episodes of nonpruritic, nonpitting swelling typically involving the skin, intestinal wall, genitalia, and upper airway. Generally, angioedema is a clinical syndrome marked by a rapid increase in vascular permeability of submucosal and subcutaneous (SC) tissues. Although angioedema is most commonly mediated by histamine, HAE specifically depends on the release of bradykinin. There are several clinical and pathophysiological features that differentiate HAE from mast-cell mediated swelling typical of allergic reactions.

Lack of physician awareness of HAE and overlapping clinical features of angioedema with histamine-mediated or medication-induced angioedema can make a timely diagnosis challenging. In a 2010 study, 313 patients with HAE reported visiting an average of 4.4 physicians over an average of 8.3 years before receiving an accurate HAE diagnosis.[1] These diagnostic delays have been associated with psychosocial distress, unnecessary surgeries, and even death. In a cohort of 728 patients with a

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family history of HAE, 214 premature deaths were described. One-third of the deaths were from laryngeal edema and subsequent asphyxiation (N = 70) and 63 of those subjects died before HAE was diagnosed.[2]

Although rare, HAE is a debilitating and potentially life-threatening disease. Medications such as epinephrine, antihistamines, or glucocorticoid therapies do not provide relief and often delay care. Through broader physician awareness, earlier diagnosis and initiation of prophylaxis therapy can significantly reduce the morbidity and mortality of HAE. The following discussion reviews the diagnostic and therapeutic considerations in the approach to a patient with HAE.

DISCUSSION

Pathophysiology

HAE is an autosomal dominant disorder without predominance in any ethnicity or gender.[3] With an estimated frequency of 1 per 50,000 Americans, HAE is considered rare.[4] HAE presents with attacks of SC and submucosal swelling in the respiratory and gastrointestinal tracts. These episodes result from either low levels or improper function of a protein called C1 esterase inhibitor (often abbreviated to C1-inhibitor or C1-INH).

There are 3 types of HAE. In type I, which represents 80% to 85% of cases, a deficiency of circulating C1-INH manifests in attacks. In type II, which represents 15% of cases, reduced functional levels of C1-INH cause similar symptoms.[5] HAE with normal C1-INH (previously referred to as type III HAE) is extremely rare. The mechanism for these cases is not well understood and will not be included in this discussion.

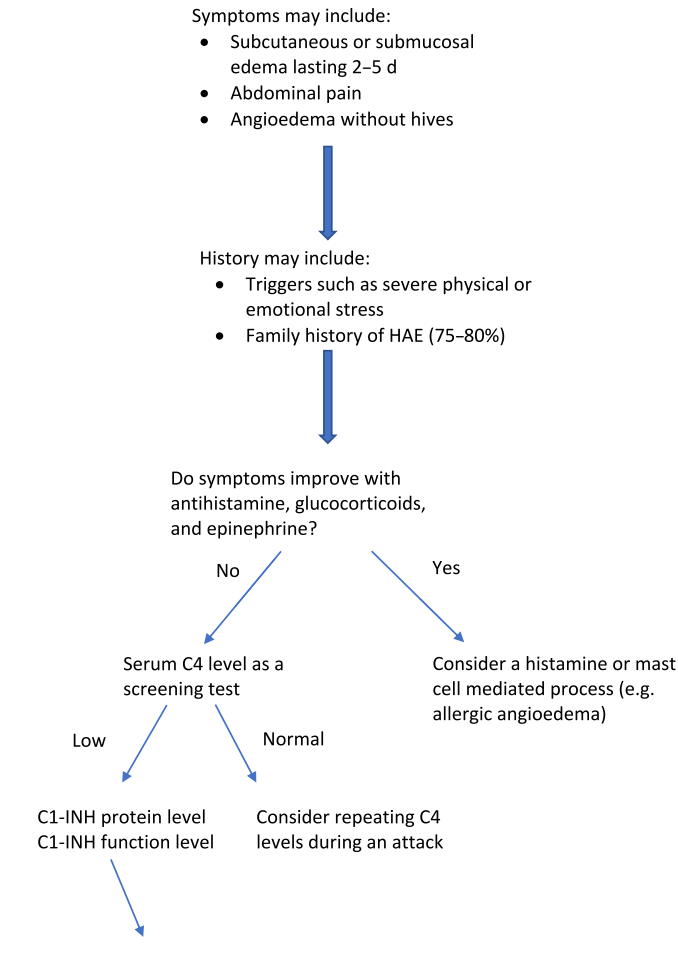
The C1-INH protein acts within many pathways but is most clinically relevant to HAE within the contact activation system and the complement cascade. The contact activation system, also called the contact system or the kinin-kallikrein system, represents a growing area of research during the last 4 decades. The contact system has been implicated in blood pressure control, coagulation, and pain.[6] In the context of HAE, C1-INH normally inhibits kallikrein and activation of factor XII (sometimes called Hageman factor). A lack of C1-INH results in autoactivation of factor XII and activation of prekallikrein to kallikrein. Active kallikrein causes breakdown of high molecular weight kininogen, which subsequently produces a vasoactive peptide called bradykinin. Bradykinin acts on BR2 receptors leading to increased vascular permeability and angioedema.[7] In sum, when C1-INH is deficient or dysfunctional, uncontrolled bradykinin action causes HAE (**Fig. 1**).

In the classical complement pathway, C1-INH blocks activation of C1. C1 goes on to form the C1 complex, which cleaves C4. The result of both C1-INH deficiency (type I HAE) and dysfunction (type II HAE) is a low C4 level. Although C4 is not directly related to the clinical manifestations of HAE, the detection of low C4 levels is a useful and sensitive test (approximately 90%) for HAE.

Briefly, there is an additional role of C1-INH in the fibrinolytic system. The clinical relevance of that pathway to HAE is that D-dimer may be elevated during acute attacks (**Fig. 2**).

Clinical Manifestations

It is hypothesized that the degree of C1-INH deficiency or dysfunctionality plays a role in age of symptom onset, frequency of episodes, and severity of attacks. Approximately one-third of patients with type I or II HAE experience symptoms by age 5. Most cases present before 20 years of age, whereas an estimated 4% of patients will experience their first attack after age 40.[8] Some patients report many attacks



	Type I HAE	Type II HAE
C1- INH Protein	Low	Normal or elevated
C1- INH Function	Low	Low

Fig. 1. An overview of the diagnostic approach to a patient with symptoms suggestive of hereditary angioedema. Notes: Low C4 should be repeated 1 to 3 month apart to confirm diagnosis.

each month, and some patients will go months without an attack. Uncommonly, an individual with HAE may never experience an attack.[3] An individual attack typically lasts 2 to 5 days. Attacks can be triggered by an emotionally or physically stressful circumstance, such as a wedding, athletic event or medical procedure. Older adults with symptoms similar to HAE may have a related condition called acquired angioedema with low C1-INH (AAE). AAE is also characterized by C1-INH deficiency, usually from an autoantibody.

Most patients experience swelling in specific parts of the body, although swelling can occur anywhere. Typically, HAE attacks manifest with upper airway, gastrointestinal, or cutaneous symptoms.[4] Laryngeal attacks are the least common but most dangerous type of attack due to airway obstruction with potential of asphyxiation. In

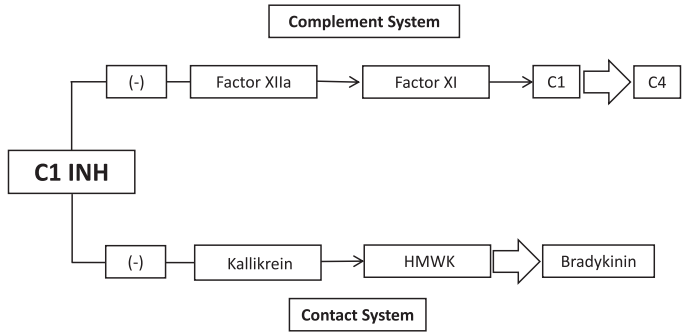


Fig. 2. A simplified summary of the role C1-INH in the contact system (kinin-kallikrein pathway) and the complement system as related to HAE. Dysfunctional or deficient C1-INH results in loss of regulation of factor XIIa and kallikrein. This leads to excess production of bradykinin. Bradykinin is the key molecule that mediates clinical manifestations of HAE.

a series of 138 patients with HAE, approximately half experienced an upper airway attack during their lifetime. This varied from mild tongue swelling to the formidable laryngeal edema. Upper airway edema has been reported to account for up to 33% of mortality in persons with HAE.[9]

Gastrointestinal attacks similarly range from mild to severe in intensity. Symptoms usually resolve without serious complications unless a patient undergoes unnecessary interventions because the disorder is not recognized as HAE. Cutaneous attacks are not associated with high risk of complications or death, although they may cause substantial lifestyle and occupational disruptions from recurrent bouts causing cosmetic concerns and disability (eg, hand swelling and unable to drive, foot swelling and inability to walk, facial disfigurement; **Table 1**).

Evaluation/Diagnosis

A diagnosis of HAE should be suspected in patients with recurrent attacks of angioedema to the face or airway—with or without abdominal pain. Importantly, C1-INH deficiency does not present with urticaria, also known as hives, wheals, or itching. In suspected cases, laboratory investigation should begin with a serum C4 level and then a C1 level and function. The C4 test has been documented to have a 100% sensitivity and a very high negative predictive value during an attack. Between attacks, the sensitivity has been described as 85% to 95%.[10] If C4 levels are low, the next steps are to check C1-INH levels and C1-INH protein functionality.

Although a complement C4 level is a very good screening test, most experts suggest obtaining C4 levels, C1-INH protein, and C1-INH function in all cases suggestive of HAE to avoid diagnostic ambiguity. A normal result on any one test does not rule out HAE as special sample handling requirements can affect results.[11]

Genetic testing is available to confirm the diagnosis of HAE. However, as biochemical tests are very effective in making the diagnosis for type 1 and 2 HAE, genetic testing is rarely necessary. The exceptions are if prenatal diagnosis is desired or if biochemical testing is equivocal during the first year of life. Most type I and II HAE cases are caused by mutations in the C1-inhibitor gene, *SERPING1*.[10] Because there are innumerable mutations in *SERPING1* gene, many that have not been identified, genetic testing is imperfect. In addition, other genes can result in an HAE with normal C1-inhibitor diagnosis, and thus universal genetic testing would have low clinical value. Presently, genetic testing is not recommended in patients with classic symptoms and a strong family history.[11]

Table 1
Characteristics of different types of angioedema

Differential Diagnosis of AE	Clinical Characteristics	Laboratory Abnormalities	Treatment
Type I HAE	~85% of HAE cases are Type I ~15% of HAE cases are Type II	Low levels of complement C4 Low levels of C1-INH but it functions properly	Intravenous or subcutaneous C1-INH (recombinant or plasma-derived)
Type II HAE	Both types present with recurrent bradykinin-mediated attacks of swelling Episodes last 2–5 d Urticaria or pruritis do not occur Abdominal pain is common	Low levels of complement C4 Normal/high levels of C1-INH but it does not function properly	Ecallantide, icatibant Danazol Lanadelumab Berotralstat Fresh frozen plasma
ACEi-induced AE	Slow onset (hours to days) of symptoms can occur any time after ACEi exposure (not just with initial dose) Up to 5 times more common in people with African descent[20] Bradykinin-mediated swelling often affects lips, tongue, face, and upper airway Abdominal pain is not common	No definitive laboratory tests	Acute airway management Discontinue ACEi Some studies suggest icatibant, others suggest antihistamines and corticosteroids
Allergic AE	Rapid onset of symptoms (within minutes to 2 h) after ingesting or contacting an allergen Histamine-mediated swelling and itching. Urticaria (hives) are extremely common Bronchospasm and hypotension are fairly common Abdominal pain and laryngeal edema are possible but not common	Normal serum complement C4 Normal C1-inhibitor function Tryptase may be elevated Treatment may include avoidance	H1 antihistamines, corticosteroids, epinephrine
Spontaneous AE	Rapid onset of symptoms (within minutes to 2 h) Histamine-mediated swelling and itching. Urticaria (hives) are often present	Normal serum complement C4 Normal C1-inhibitor function Tryptase may be elevated	H1 antihistamines, corticosteroids, and in severe cases epinephrine

Abbreviations: ACEi, angiotension converting enzyme inhibitor; AE, angioedema; HAE, hereditary angioedema.

Treatment/Management

To counteract the unregulated release of bradykinin caused by deficient or dysfunctional C1-INH, treatment of HAE includes management options for acute attacks, short-term prophylaxis (STP), and long-term prophylaxis (LTP).

Acute Attack Treatment

To deploy immediately during acute attacks, all patients with HAE should have 2 doses of on demand therapy (ODT) available. ODT focuses on reversing and preventing further angioedema. There are intravenous (IV) and SC options for ODT. The 2 IV ODT options presented are therapeutic C1-INH and fresh frozen plasma (FFP). ODT with recombinant (50 mg/kg) or plasma-derived C1-INH (20 units/kg) can be given as soon as symptoms develop.[12] It can be used in all ages and even during pregnancy and lactation. In areas where C1-INH ODT is not available due to cost, FFP can be used IV as well. FFP is not as effective as CI-INH; time-to-resolution is slower and adverse events are more frequent.[13]

The 2 SC options presented are a bradykinin-receptor antagonist called ecallantide and a kallikrein inhibitor called icatibant. Both are effective and have less clinical burden than IV therapy. Ecallantide has a 3% risk of allergic reaction and cannot be self-administered. If appropriate, a trained health-care professional can give the injection in a patient's home. Icatibant is approved only in the United States for patients aged 18 years and older. In the E.U., icatibant is approved down to 2 years of age. Because of storage ease, generic availability and injection ease, icatibant is the preferred therapy for ODT by most doctors and patients.[14]

Short-Term Prophylaxis

STP is often referred to as preprocedural; however, it can be used before any other known triggers of HAE attacks such as emotionally or physically significant events. The preferred STP is IV C1-INH an hour before the relevant surgical, medical, or dental procedure. STP is especially recommended if the procedure is adjacent to the airway (eg, molar extraction or upper endoscopy). As with acute attack treatment, if therapeutic C1-INH is unavailable, 2 units of FFP is an acceptable alternative for adolescents and adults.[15]

An alternative to C1-INH for STP is attenuated androgen. The most commonly used androgen is danazol 200 mg PO every 8 hours for 5 to 7 days before the procedure and 2 days after. Due to their short half-lives, ODT medications C1-INH, icatibant and ecallantide are not recommended for STP. In lower income areas, tranexamic acid (TXA) has been used for STP, but high-quality data are lacking to determine the efficacy of this intervention.[16]

Long-Term Prophylaxis

LTP aims to prevent attacks and reduce episode frequency. Akin to ODT, there are SC and IV therapies but unique to LTP is an oral (PO) option. LTP choices include IV C1-INH, SC C1-INH, SC lanadelumab, PO berotralstat, and PO danazol.[15] Additional PO options are currently being investigated.

IV C1-INH at 1000 units twice a week is about 50% effective in reducing attacks. Dosage can be increased to improve efficacy but this increases cost. SC C1-INH at 60 units/kg is about 85% effective and usually well tolerated.[12] Lanadelumab can be given SC every 2 or 4 weeks. At every 2 weeks, it is about 85% effective at decreasing attacks. If attacks are controlled after 6 months, a trial of dose reduction to every 4 weeks should be attempted to reduce cost.[15]

The PO LTP option, berotralstat, can cause gastrointestinal discomfort during the first few weeks and has a dose-dependent risk of QT prolongation. The significant drug burden reduction that comes from a PO option is unfortunately counterbalanced by a reduction in efficacy compared with the IV and SC options. Interestingly, some patients respond very well to berotralstat and have a greater reduction in frequency of attacks than the reported 50% decrease in episodes.

The second-line LTP options are androgens and tranexamic acid. Just as TXA is used without strong evidence for STP, physicians in lower income areas may use TXA for LTP for affordability. Danazol, as discussed with STP, is an oral, effective, and affordable option for LTP as well.[16] Danazol can cause polycythemia, hematuria, hyperlipidemia, transaminitis, and an increased risk of hepatocellular carcinoma. Use should be limited, especially in women because of masculinization. Danazol for LTP is typically used at a dose of 200 mg PO daily or less to reduce toxicity.

Additional Considerations

Beyond the biophysical manifestations of HAE, there are considerable psychosocial and financial consequences of the condition. Patients affected by HAE are often forced to miss work, school, or other social engagements due to frequent attacks. These disruptions can lead to reduction in quality of employment, education, and overall well-being. In one study of 500 patients with HAE, 42% of respondents noted symptoms of depression.[17] In another study, 39% of patients had depressive symptoms and 15% reported features of prominent anxiety.[18] As depression itself is thought to be a trigger for HAE attacks, appropriate management of depression and anxiety in patients with HAE is essential.[19]

SUMMARY

Although angioedema is commonly mediated by histamine, HAE represents a unique form of bradykinin-mediated swelling through the kinin-kallikrein cascade. To reduce morbidity and mortality, early diagnosis of HAE during attacks is extremely important. Patients with a family history of recurrent episodes of swelling without urticaria should be suspected of having HAE. Biochemical testing with complement C4 levels and C1-INH and C1-INH function can confirm the diagnosis. Once diagnosed, specific therapies can be prescribed to treat acute attacks and even prevent future attacks. All patients should be educated about the need for STP, trigger avoidance, self-treatment, LTP, and a referral to an allergy/immunology specialist.

CLINICS CARE POINTS

- HAE is a rare, inherited condition characterized by recurrent episodes of nonpruritic, nonpitting edema to the skin, intestines, and upper airway.
- HAE is commonly mistaken for other conditions such as allergic (mast cell-mediated) angioedema; however, HAE has a unique treatment approach.
- The key distinguishing aspects of HAE are an absence of wheals/urticaria, unresponsiveness to epinephrine, antihistamines, and corticosteroids, and laboratory abnormalities of C1 inhibitor quantity or function.
- The high mortality in patients with undiagnosed HAE underscores a need for broader physician awareness to identify these patients at an early age and initiate appropriate therapy.

DISCLOSURE

Dr T. Craig declares the following conflicts of interest: Research—CSL Behring, Ionis, Biocryst, Takeda, Pharvaris, BioMarin, Kalvista. Speaker—Grifols, Takeda, CSL Behring. Consultant—BioMarin, CSL Behring, Takeda, Biocryst, Spark. Drs A. Sarkar and C. Nwagwu have no conflicts to report.

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