

Hereditary angioedema: Classification, pathogenesis, and diagnosis

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ABSTRACT

Hereditary angioedema (HAE) is a rare autosomal dominant genetic disorder associated with a deficiency in C1 inhibitor. More than 200 mutations in this gene, located on chromosome 11, have been identified. Although HAE is often inherited, 20–25% of cases are from new spontaneous mutations and they have no family history of swelling. Decreased C1 inhibitor activity leads to inappropriate activation of multiple pathways, including the complement and contact systems and the fibrinolysis and coagulation systems. Reduced C1 inhibitor activity results in increased activation of plasma kallikrein-kinin system proteases and increased bradykinin levels. Bradykinin is felt to be the main mediator of symptoms in HAE. Patients with HAE have recurrent episodes of swelling of the extremities, abdomen, face, and upper airway. Angioedema involving the gastrointestinal tract can lead to intestinal wall edema, which results in abdominal pain, nausea, vomiting, and diarrhea. Laryngeal swelling is life-threatening and may lead to asphyxia. Common triggers of an attack include trauma, stress, infection, menstruation, oral contraceptives, hormone replacement therapy, and angiotensin-converting enzyme inhibitors. Laboratory testing including C4, C1 inhibitor level, and function is needed to confirm or rule out the diagnosis of HAE. The treatment of HAE has improved significantly in recent years with the availability of several safe and effective therapies. Several consensus guidelines have been created to further assist in the management of HAE patients. This review will provide an update on the classification, pathophysiology, clinical presentation, and diagnosis of HAE.

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The clinical features of angioedema were first described by John Laws Milton in 1876 as “giant urticaria.”¹ A few years later, in 1882, Heinrich Quincke introduced the term angioneurotic edema based on his observation of the causal effect of stress on episodes of angioedema.² Although William Osler wrote of the hereditary nature of angioedema in 1888,^{3,4} it was not until 1963 that C1 inhibitor deficiency was discovered as the underlying cause of this condition.⁵ Since that time, significant advances have been made in understanding the pathophysiology, diagnosis, and management of hereditary angioedema (HAE).

HAE is a rare and potentially life-threatening genetic disorder resulting from C1 inhibitor deficiency characterized by attacks of intense and painful swelling. The prevalence of HAE in the literature ranges from

1:10,000 to 1:150,000.⁶ It is estimated that patients can be debilitated by their symptoms for 20–100 days a year.⁷ Acute attacks of HAE account for between 15,000 and 30,000 emergency department visits annually.⁸

CLASSIFICATION

HAE is categorized into type I, which accounts for 80–85% of cases, and type II, accounting for 15–20% of cases. Types I and II are reported in all races with no sex predominance, which is not surprising based on its autosomal dominant inheritance pattern. A low C4 level is found in both types of HAE, but type I HAE is associated with a low C1 inhibitor level. Type II HAE, on the other hand, often has normal levels of C1 inhibitor but the C1 inhibitor protein is biologically dysfunctional. These two types of HAE are clinically indistinguishable.⁹

A third type of HAE has recently been described and is not associated with any known C1 inhibitor abnormalities.^{10–12} It was initially described only in women and led to some initial use of the terms estrogen-related or estrogen-dependent angioedema because it was thought to only be in women with episodes of angioedema during pregnancy, oral contraceptive use, or with estrogen therapy.¹² More recently, a specific mutation in factor XII has

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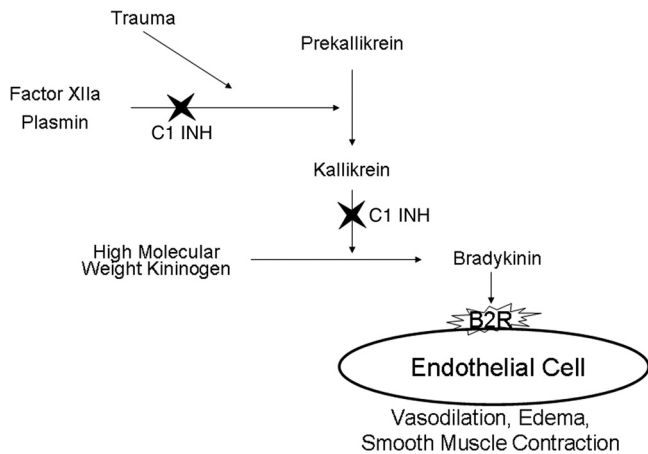


Figure 1. Bradykinin generation and inhibition by C1 inhibitor.

been described in these patients and the term HAE with normal C1 inhibitor has been used.^{10,11} Interestingly, estrogen has been found to up-regulate a gain of function mutation in factor XII.¹¹ However, there are also cases reported that are not related to any specific mutation in factor XII.

PATHOPHYSIOLOGY

HAE is inherited as an autosomal dominant trait and results from mutations in the gene controlling synthesis of C1 inhibitor.¹³ However, it has been estimated that 20–25% of cases are the result of spontaneous mutations. More than 200 mutations in this gene, located on chromosome 11q11–q13.1, have been reported.^{14–16} Type I HAE is caused by mutations leading to a truncated or misfolded protein. Mutations leading to secretion of a dysfunctional protein cause type II HAE.

C1 esterase inhibitor, an α_2 -globulin of ~105 kD, is a normal constituent of human plasma and belongs to a class of protein enzyme inhibitors called serpins (*serine protease inhibitors*). Serpins are known as “suicide” inhibitors because they inactivate proteases, forming an irreversible bond with its substrates.¹⁷ The primary biological role of C1 inhibitor, a serine protease inhibitor, is to regulate activation of the complement, contact, and intrinsic coagulation systems.

Without C1 inhibitor, there is unregulated activation of the contact system resulting in uninhibited kallikrein. This leads to subsequent increased production of bradykinin (Fig. 1), which is mainly responsible for the symptoms of angioedema in an acute attack: increased vascular permeability, vasodilation, and constriction of nonvascular smooth muscle.^{6,17} Unrestricted activation of the complement system may also initiate and perpetuate an attack by further depleting the low C1 inhibitor levels.^{6,17} During acute attacks of angioedema, together with decreasing levels of C1 inhibitor, the complement and contact systems are activated, C2 and C4 levels fall, and high-molecular-

weight kininogen is cleaved. It is usually the reduced C4, rather than deficient C1 inhibitor levels, which is detected in laboratory analysis when screening for HAE patients. The low C4, even when asymptomatic, results from uncontrolled activation of activated C1.¹⁵ As such, laboratory measurement of serum C4 in addition to C1 inhibitor levels and C1 inhibitor activity should be measured when confirming the diagnosis of HAE.⁶

The initial molecular events in the generation of an angioedema attack in individuals with HAE remain unclear. Some investigators speculate that the activation of clotting factor XII, possibly by phospholipids released from damaged cells, can trigger an attack, while others suggest that endothelial cell-generated kallikrein in an instigating factor.^{18,19}

CLINICAL PRESENTATION

During an HAE attack, patients most often complain of swelling of extremities, abdomen, face, or upper airway. The swelling is nonpitting with ill-defined margins and not pruritic. Patients do not have associated urticaria but can have a seriginous rash known as erythema marginatum often as a prodromal manifestation.²⁰ Most patients can recognize their prodrome several hours in advance of an HAE attack starting.

Age at onset can vary, but 50% of cases manifest by 10 years of age and 85% manifest by 20 years with rare symptoms in early childhood increasing in frequency after puberty.^{21,22} Symptoms will persist throughout life but with unpredictable severity.²³ There does not appear to be any difference between age of onset among male and female subjects.¹⁵

Attacks of HAE follow a predictable course. The swelling gradually increases in severity over the first 24 hours and then slowly improves over the next 2–3 days. A typical HAE attack usually lasts 2–5 days. Attacks can also start at one location and progress to a different location before resolving.²³ Attacks can vary greatly in frequency, with some individuals experiencing severe symptoms up to several times per week. Interestingly, disease severity differs markedly among affected members within the same family, despite the presence of the same mutation, and a minority of subjects with laboratory-identified C1 inhibitor deficiency remain asymptomatic for reasons that are unclear.^{21,24}

Cutaneous attacks are the most common and usually manifest as temporarily disfiguring, nonpitting, and sometimes painful skin swelling, most commonly affecting the extremities, face, and genitals.^{6,21,23} An episode may begin with a tingling or irritable sensation in the skin followed by swelling and a sense of tightness.^{6,23} Angioedema involving the gastrointestinal tract can lead to intestinal wall edema. Over 90% of patients have gastrointestinal episodes with severe ab-

Table 1 Laboratory abnormalities in hereditary, acquired, ACE inhibitor, and idiopathic angioedema

Diagnosis	C4	C1 Inhibitor Function	C1 Inhibitor Level	C1q
HAE type I	Low	Low	Low	Normal
HAE type II	Low	Low	Normal	Normal
HAE with normal C1 inhibitor	Normal	Normal	Normal	Normal
Acquired C1 esterase inhibitor deficiency	Low	Low	Normal/Low	Low
ACE inhibitor angioedema	Normal	Normal	Normal	Normal
Idiopathic angioedema	Normal	Normal	Normal	Normal

ACE = angiotensin-converting enzyme; HAE = hereditary angioedema.

dominal pain often accompanied by nausea, vomiting, and diarrhea at some time during their life time. Approximately one-half of patients will report at least one episode of laryngeal swelling during their lifetime.²⁴ If left untreated or undiagnosed, airway obstruction is associated with mortality rates as high as 30%.²¹ Asphyxiation can occur at any age and has been documented in individuals as young as 4 weeks and as old as 78 years.⁶

Investigators have documented triggering factors for angioedema attacks in individuals with HAE.^{21,25,26} Common triggers of an attack include trauma, stress, infection, menstruation, oral contraceptives, hormone replacement therapy, and angiotensin-converting enzyme inhibitors. *Helicobacter pylori* infections have been reported to trigger abdominal attacks, and eradication of this infection can lead to a significant reduction in the frequency of abdominal attacks.^{27,28} Others reported triggers include exposure to cold and prolonged maintenance of certain postures.^{21,26} However, it is important to note that many HAE attacks do not have an identifiable trigger.

DIAGNOSIS

Initial diagnosis can be challenging, because many symptoms of HAE overlap with those of other common medical diseases. This has led to a significant delay in initial diagnosis. The average time between initial symptoms of HAE and diagnosis was 22 years in 1977.²⁹ In 2005, the average time was unfortunately still >10 years.³⁰ A diagnosis of HAE should be suspected in any patient with recurrent angioedema and abdominal pain.

Laboratory testing is needed to confirm or rule out the diagnosis of HAE.²³ Almost all patients with HAE have a low antigenic C4 level with normal C3 levels. A low C2 level may be found during an acute attack of HAE.²⁶ A normal C4 level, however, does not completely exclude a diagnosis of HAE. In fact, C4 levels are normal between attacks in <1% of patients with HAE.^{31,32}

C1 inhibitor studies should be performed regardless of serum C4 if a high index of clinical suspicion exists.

The diagnosis is confirmed by low serum levels of C1 inhibitor or detection of a C1 inhibitor mutation altering the gene production or function. Low C1 inhibitor functional activity is also seen in type II HAE (Table 1). C1 inhibitor levels are age dependent³³ and the complement system usually reaches adult levels by 3–36 months. Therefore, it is recommended that testing in children not be performed before 1 year of age. If complement values are not consistent, genetic DNA testing can be performed although because of the multitude of different mutations, genetic testing is available mainly in the research laboratory. Early evaluation will also help family members make informed decisions about future family planning.

DIFFERENTIAL DIAGNOSIS OF ANGIOEDEMA

It is important to differentiate HAE from other forms of angioedema because the management approach can be quite different (Table 2). When evaluating patients with unexplained angioedema, a careful history and physical exam is the best tool. For example, the cutaneous or laryngeal edema of HAE can appear similar to manifestations of allergic reactions (*i.e.*, venom hypersensitivity, latex allergy, food allergy, and anaphylaxis), idiopathic angioedema, drug-induced angioedema, various autoimmune conditions, thyroid disorders, or superior vena cava syndromes.³⁴

HAE is differentiated from other forms of mast cell-mediated angioedema by the absence of pruritus and erythema overlying the affected edematous area. The presence of urticaria makes HAE less likely. A diagnosis of HAE should be considered in patients with angioedema that is unresponsive to antihistamines, steroids, or epinephrine. Ocular swelling with features of rhinitis and conjunctivitis could suggest aeroallergen exposure. Symmetric swelling could suggest other types of edema.

Furthermore, distinguishing between abdominal attacks of HAE and other intraabdominal pathologies, including true surgical emergencies, can be difficult. Most case studies report that imaging or exploratory laparotomy findings in patients with HAE-related abdominal attacks are relatively nonspecific (bowel wall

Table 2 Differential diagnosis of angioedema

Bradykinin mediated
Hereditary angioedema
Acquired angioedema
ACE inhibitor angioedema
Histamine mediated
Chronic idiopathic urticaria/angioedema
Food allergy
Drug allergy
Venom hypersensitivity
Latex allergy
Other causes
Autoimmune disease (<i>i.e.</i> , lupus and urticarial vasculitis)
Thyroid disease
Superior vena cava syndrome
Intraabdominal disorders (<i>i.e.</i> , appendicitis and diverticulitis)
Infection (<i>i.e.</i> , cellulitis and parasitic infections)
Well's syndrome
Clarkson syndrome

ACE = angiotensin-converting enzyme.

edema), and as many as one-third of patients with undiagnosed HAE may undergo unwarranted abdominal surgery.^{21,26} On the other hand, automatically attributing acute abdominal complaints to an angioedema attack in a patient with an established history of HAE carries the risk of missing common intraabdominal disorders that require prompt surgical intervention or alternate medical therapy. Some investigators suggest that the presence of fever, peritoneal signs, or an elevated white blood cell count should prompt imaging studies and surgical consultation to evaluate for other causes in patients with HAE.^{26,35} The difficulty of timely diagnosis of HAE is underscored by the fact that, in most cases, initial clinical presentation often precedes actual diagnosis of HAE by years or even decades; thus, a strong degree of clinical suspicion often is required for successful diagnosis.

TREATMENT

Current treatment options for HAE, including attenuated androgens, fresh frozen plasma, and antifibrinolytics, historically have shown either undesirable side effects or limited efficacy. Treatments commonly used for other types of angioedema, such as epinephrine, H₁- and H₂-histamine receptor agonists, and corticosteroids, have not been effective in treating acute attacks of HAE. Newer agents including C1 inhibitor replacement therapy bradykin receptor antagonist and kallikrein inhibitors have recently been Food and Drug Administration approved for the treatment of HAE. A recombinant C1 inhibitor product is still under study.

The medical management of HAE has improved significantly in recent years with the availability of several safe and effective therapies. Consensus guidelines^{25,36–38} have also been published by experts in the field to assist in the management of HAE patients with a focus on individualized care.

CONCLUSION

Despite significant advances in our understanding of HAE, many questions remain unanswered. The mechanisms underlying the initiation and resolution of attacks are not clear.^{23,39} The correlation between C1 inhibitor levels and disease expression remains unknown. The diagnosis of HAE could be facilitated if the assays available for C1 inhibitor function were improved. There are clearly many areas of research needed to further our understanding of this relatively rare disorder.

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