

Hereditary angioedema: Historical aspects, classification, pathophysiology, clinical presentation, and laboratory diagnosis

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ABSTRACT

Hereditary angioedema (HAE) is a rare disorder first described in 1888 by Sir William Osler. Since then, our understanding of this condition has increased tremendously. This article reviews the historical aspects, classification, pathophysiology, clinical presentation, and laboratory diagnosis of HAE. A review was performed of historical and current literature of HAE. HAE I and II are related to insufficient production of C1-esterase inhibitor (C1-INH) or production of a dysfunctional C1-INH protein, respectively. HAE III is not related to C1-INH deficiency and the pathogenesis is unknown. Bradykinin appears to be the main mediator responsible for angioedema in patients with C1-INH deficiencies. Angioedema of the extremities, face, and upper airway along with gastrointestinal angioedema are the most common clinical features in HAE. The laboratory tests that are most commonly used in the diagnosis of HAE include C4, C1-INH concentration, and C1-INH function. Advances in our understanding of the pathogenesis of HAE have led to several advances in the therapy of this disease. Despite our more thorough understanding of the genetics and pathophysiology of HAE, many questions remain unanswered.

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Although the earliest description of angioedema has been credited to Marcelo Donati who in 1586 reported on a young count who was sensitive to eggs and developed lip swelling, it was not until the late 1800s that more detailed descriptions of angioedema first appeared in the medical literature. John Laws Milton has been credited with the first description of angioedema in 1876, which was described as “giant urticaria.”¹ He described one of his patients very descriptively: “SO soon as ever she came into the room I recognized the affection, for there lay, across the face from temple to temple, an oblong tumor almost closing both eyes.” Six year later, the famous Swiss physician, Heinrich Quincke, documented acute, circumscribed edema of the skin and introduced the term “angioneurotic edema.”²

In 1888, Sir William Osler reported an inherited form of angioedema, which he named “hereditary angioneurotic edema.”³

The initial index case was a 24-year-old woman, “Mrs. H.” On September 20, 1887, she was admitted to the Infirmary for Nervous Diseases. She noted a history from childhood of “attacks of transient swelling in various parts” including her extremities and face. The more severe attacks were accompanied by “colic,” nausea, and vomiting. She noted that several members of her family were similarly affected. In his report, Osler went on to describe five generations of affected family members, two whom died of the disease. One patient died of laryngeal edema (edema glottidis) and was found dead by the time the family physician arrived. Osler made three key observations. First, “The occurrence of local swellings in various parts of the body, face, hands, arms, legs, genitals, buttocks, and throat.” Second, “Associated with the edema, there is almost invariably gastrointestinal disturbance: colic, nausea, vomiting, and sometimes diarrhea.” Third, “A strongly marked hereditary disposition...” Osler further commented on the lack of effective therapy (other than “morphia” for abdominal pain) as well as comparisons with a pediatric disease of painfully swollen joints, a purpuric or urticarial eruption, and intense colic, which was described by Henoch 14 years earlier. Recently, this landmark article has been reprinted along with a historical perspective.^{4,5}

By the mid-20th century, most of the clinical features of hereditary angioedema (HAE) were well known.

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Attacks of abdominal pain were recognized as an important feature of the disease and these manifestations were attributed to mucosal edema of the gastrointestinal tract, a point that Osler had already surmised. Trauma was a well-recognized precipitant of attacks and in many patients emotional stress was recognized as a common trigger.

In 1961, Lepow and colleagues had discovered a naturally occurring inhibitor of C1 esterase, a heat-labile α -globulin, C1-esterase inhibitor (C1-INH).⁶ They went on to show that purified human C1 esterase enhances vascular permeability in guinea pig skin and this phenomenon could be prevented by purified C1-INH.⁷ Landerman and colleagues reported a patient with HAE who had decreased amounts of serum inhibitor of kallikrein and suggested that kallikrein might initiate edema formation.⁸ Seventy-five years after Osler's description of HAE, Donaldson and Evans described three families with HAE who had no detectable levels of C1-INH, whereas sera from unaffected relatives contained normal amounts.⁹ During attacks of superficial swelling, laryngeal edema, or abdominal pain, C1-esterase activity was readily detectable in both serum and plasma.

In the last 50 years, additional advances have been made in the understanding of the genetics and pathogenesis of HAE, which has led to increasingly effective therapies. In addition to hereditary C1-INH deficiency, acquired forms of C1-INH deficiency (acquired angioedema [AAE]) have been discovered and, more recently reported, another form of HAE, which is not caused by C1-INH deficiency but may be related to estrogen.

EPIDEMIOLOGY OF HAE

The precise prevalence of HAE is unclear. Estimates range from 1 in 10,000 to 1 in 150,000.^{10,11} With the advent of new therapies for HAE, anecdotally there appears to be an increase in patients seeking therapy and allergists may encounter more HAE patients than in previous years. Support groups and greater awareness may contribute to this phenomenon.

CLASSIFICATION OF C1-INH DEFICIENCY AND OTHER HAE TYPES

In the past, HAE was classified as type I or type II, based on either deficient levels of C1-INH (type I) or normal levels of the protein but abnormal function of the C1-INH protein (type II). Recently, a new form of HAE has been described that is not related to either low levels or abnormal function of C1-INH protein. The appropriate terminology and classification for this new form of HAE has been challenging and has evolved over time.



Figure 1. Typical extremity swelling in a patient with hereditary angioedema.

HAE Types I and II

HAE is a well-defined autosomal trait and is caused by deficiency of C1 inhibitor gene production. The disease results from a large number of mutations to the *C1INH* gene. Two types of HAE have been described depending on whether the *C1INH* gene produces no antigenic protein or a dysfunctional protein. In both types, functional activity of C1-INH is low. Clinically, patients with both types of HAE are identical, experiencing episodic attacks of angioedema (Fig. 1); however, laboratory values of C1-INH levels vary between the two types.

Type I HAE, which accounts for ~85% of patients, is associated with defective expression of one allele and results in low antigenic and functional activity of C1-INH. In type II HAE, ~15% of patients, the gene product produces a dysfunctional protein but has normal or increased antigenic levels of C1-INH.

HAE Type III

In 2000, Binkley and Davis reported a family who had histories of episodic HAE-like angioedema.¹² The family originated from southern Italy but members and their descendants resided in Canada and Italy. Angioedema attacks consisted of extremity, face, or laryngeal edema and episodic severe abdominal pain and nausea in several members. Several unique aspects were identified in this family. First, the disease only occurred in women, and, specifically, episodes only occurred during pregnancy, oral contraceptive use, or with estrogen therapy. Symptoms began typically within 14–21 days after conception or 5–14 days after endogenous estrogen therapy and lasted 48–72 hours. In affected individuals, symptoms occurred with all pregnancies and with each course of estrogen therapy. There were eight affected women from three generations with one obligate male carrier.¹³ The transmission was consistent with an autosomal dominant inheritance. These authors initially referred to this syndrome as estrogen-dependent inherited angioedema.

Several other investigators have described patients with hereditary forms of angioedema, mimicking HAE but with normal C1-INH levels and function.^{14–17} This rare form of HAE is now referred to as HAE type III. Although the exact pathogenesis of HAE III is unclear, some patients have been discovered who have mutations in the FXII gene.¹⁸ The key features of HAE III include autosomal dominant transmission, similar clinical features but more frequent facial edema, normal C1-INH levels, and function, and a female predominance with exacerbation by estrogen.

Pathophysiology

C1-INH Structure and Function. C1-INH belongs to the family of serine protease inhibitors (serpin family), which includes α 1-antitrypsin and antithrombin III. Unlike most other serpins, which have only one or a few target proteases, C1-INH is the major inhibitor for several proteases including (1) C1s and C1r (classic complement pathway); (2) mannin-binding lectin-associated serine proteases; and (3) FXIa, FXIIa, and kallikrein (contact system proteases).¹⁹ In addition, C1-INH interacts with other proteases including thrombin, plasmin, and tissue plasminogen activator (fibrinolytic system).²⁰

Mechanisms of Angioedema in HAE. As discussed earlier, C1-INH regulates the classical and mannin-binding lectin pathways of complement activation, the contact system, and the intrinsic pathway of coagulation.²¹ Patients with HAE have evidence for activation of complement and the contact systems primarily. Typically, patients with HAE have low C4 and C2, but normal C3 values, even while asymptomatic. The low C4 and low C2 results from uncontrolled activation of activated C1. Activation of C3 is typically low or absent, presumably because of efficient control of activation at the level of C4 by C4 binding protein and factor I.¹⁹ Activation of the contact system typically occurs during attacks as indicated by findings of decreased levels of prekallikrein (a substrate for FXII) and reductions in high-molecular-weight (HMW) kininogen (a substrate for plasma kallikrein).²² Increased amounts of cleaved HMW kininogen are found in the vast majority of patients with HAE during attacks.²³ C1-INH has only a limited effect on coagulation. Clinical observations do not support that C1-INH deficiency leads to increased risk of thromboembolic disease, although some thrombin may be generated in attacks.²⁴ C1-INH is a relatively weak inhibitor *in vitro* of plasmin and tissue plasminogen activator¹⁹; nonetheless, one can find evidence of elevated plasmin formation (as determined by plasmin- α 2-antiplasmin complexes) during attacks in HAE patients.²³

Clinically, acute attacks of HAE are sometimes triggered by trauma. Factor XII can be activated by phospholipids microparticles *in vivo*.²⁵ Damaged or apoptotic cells may generate such microparticles, and one could postulate that this could occur with minor trauma, explaining why trauma is a trigger for HAE.

For decades, the mediators and mechanisms responsible for HAE have been the subject of debate. The two mediators that have been debated the most include bradykinin and a peptide referred to as C2-kinin. The majority of evidence points toward the generation of bradykinin as an important feature in C1-INH deficiency. Kallikrein can cleave HMW kininogen to form cleaved HMW kininogen and bradykinin. Bradykinin is a nonapeptide with potent vasodilatory activity and enhances vascular permeability.

Nussberger and colleagues performed important experiments to elucidate the role of bradykinin in HAE.²⁶ During acute attacks of edema, in both HAE and AAE, plasma bradykinin rose to 2–12 times the upper limit of normal. Infusion of C1-INH immediately lowered bradykinin concentrations. In a separate study in which two patients with HAE presented with forearm angioedema, bradykinin levels were measured from the edematous area and from the contralateral unaffected forearm.²⁷ Although bradykinin levels were increased in the systemic circulation (contralateral arm), levels were much greater, three- to eightfold higher, in the blood draining the edematous arm. These data suggest that bradykinin generation is local depending on activation of the kinin-releasing system.

In addition to human data, murine models have also been developed for HAE. In 2002, Han *et al.* published their work on a C1-INH knockout mouse, which further supports the hypothesis that angioedema in these C1-INH-deficient mice is mediated by bradykinin *via* the bradykinin 2 receptor.²⁸

C2-kinin has been debated as the other putative mediator in HAE. This peptide is generated by cleavage from C2b by plasmin. Activation of complement, the contact system (FXIIa), and the fibrinolytic system (plasmin) was required to generate C2-kinin.²⁹ Because C2-kinin is not a vasodilator, it would explain why HAE patients do not have hypotension and angioedema is not painful. Unfortunately, the biological properties of this peptide are not well established, receptors for it have not been identified, and there are no data on concentrations of C2-kinin in patients with HAE. Kaplan has put the data on C2-kinin into perspective: “Nevertheless, the totality of the data we have and the absence of any progress in characterizing a kinin derived from C-2 should lead to the conclusion that the original observation is more likely incorrect than simply questionable.”³⁰

In summary, the preponderance of data suggest that bradykinin is an important mediator in HAE and it is

Table 1 Symptomatology of hereditary angioedema

Symptoms	Frequency (%)
Extremity edema	96
Abdominal pain	93
Nausea/vomiting	88
Facial edema	85
Oropharyngeal edema	64
Laryngeal edema*	50
Diarrhea	22

*Laryngeal edema frequency reported by Bork *et al.*⁴⁸; all other symptom frequency reported by Frank *et al.*⁴⁶

unclear if C2-kinin even exists. The efficacy of bradykinin receptor antagonists may shed further light on the role of bradykinin. It is possible that other, unknown vasoactive mediators may also have a role in the pathogenesis of HAE. Because of their effects on bradykinin metabolism, angiotensin-converting enzyme inhibitors are contraindicated in patients with HAE. In contrast, in a small sample of six HAE patients, angiotensin-receptor blocking agents appear to be well tolerated.³¹

Genetics of C1-INH Deficiency. The C1-INH gene maps to chromosome 11, specifically 11q12-q13.1.³² To date, over 283 mutations have been recorded including 45 gross mutations and 238 micromutations and a mutation database has been created.³³ The structural abnormalities in the C1-INH gene in patients with HAE are very heterogeneous. Based on most clinical data, disease expression can not be attributed to specific mutant proteins. Variable clinical presentation is thought to result from genetic or nongenetic elements distinct from the C1-INH gene.

Cases of angioedema with no family history but with functionally low levels of C1 inhibitor and recurrent attacks are often observed. Pappalardo *et al.* studied their population of HAE patients from Italy.³⁴ Based on their data, *de novo* C1-inhibitor mutations and exon deletions account for at least 25% of all unrelated cases of angioedema. This finding has implications relevant to the genetic epidemiology and genetic counseling of HAE.

CLINICAL FEATURES

Signs and Symptoms

HAE has two common clinical manifestations, angioedema and abdominal symptoms (Table 1). These symptoms are episodic and typically involve a single site but may have contiguous spread. Angioedema and abdominal symptoms may occur independently or in association with one another. In a series of 72 HAE

patients reported by Frank *et al.*, 96% had angioedema of the extremities, 85% had involvement of the face, and 64% had involvement of the oropharynx.³⁵ In the same series, 93% had recurrent abdominal pain with 88% reporting accompanying nausea and vomiting and 22% with watery diarrhea.

Angioedema most commonly involves the face, extremities, genitals, and larynx.³⁶ The angioedema of C1-INH deficiency is identical in appearance to other forms of angioedema. The skin edema is nonpitting, not erythematous, nonpruritic, and has ill-defined margins. It is typically painless, but many patients do complain of "tightness" due to stretching of their skin. Angioedema episodes typically last 2–3 days but may be as brief as 4 hours or persist up to 7 days.³⁵

As opposed to most other forms of angioedema in which accompanying urticaria are typical, HAE is not associated with urticaria. This is an important diagnostic feature in that the presence of urticaria virtually excludes a diagnosis of C1-inhibitor deficiency. Nonetheless, there are other cutaneous rashes that may accompany HAE, which may be mistaken for urticaria. In a survey of U.S. patients, Frank *et al.* noted that 26% of 72 HAE patients may have a variety of erythematous rashes including erythematous mottling, erythema marginatum, or erythema multiforme.³⁵ These rashes are mild and transient and usually preceded or accompanied the angioedema attacks but in some cases occurred independent of the attacks.

Laryngeal edema is a life-threatening complication of HAE. One-half of patients have at least one lifetime episode of laryngeal edema. Bork *et al.* described clinical features of laryngeal edema in a cohort of 123 HAE patients.³⁷ Sixty-one (49.7%) patients experienced a total of 596 laryngeal edema episodes. The ratio of laryngeal edema episodes to skin swellings and abdominal pain attacks was ~1:70:54 in patients who had laryngeal edema. The mean age at the first laryngeal edema was 26.2 years. The mean interval between onset and maximum development of laryngeal edema was 8.3 hours. Laryngeal edema may occur at any age, although young adults appear to be at greatest risk. In contrast to allergic angioedema, which peaks within minutes, in adults with HAE, the interval between onset of symptoms and acute risk of asphyxiation is usually long enough to allow for use of appropriate emergency procedures. In the past, up to 30% of patients with HAE died because of laryngeal edema.³⁵ With improvement in emergency services, and in some countries the availability of effective therapies, fatalities are much less common today. Nonetheless, fatalities still do occur. Bork *et al.* reported on six deaths due to HAE in Germany in the 1990s.³⁸ Three patients were undiagnosed at the time of their fatal asphyxiation. The interval between onset of the laryngeal edema and asphyxiation was 20 minutes in a 9-year-old boy, and

in the other patients, the interval was 1–14 hours (mean for all, 7 hours). The possibility that the first episode of laryngeal edema may be fatal must be emphasized to the relatives of HAE patients.

Recurrent abdominal pain due to bowel wall edema is another common clinical manifestation of HAE occurring in 70–80% of patients.¹⁹ This is another distinguishing feature in that other forms of angioedema, rarely are associated with abdominal pain. Gastrointestinal symptoms of HAE include abdominal pain, which may range from mild to very severe intractable pain and can be associated with nausea, vomiting, and diarrhea. One of my patients with HAE has also gone through labor pains as well as episodes of nephrolithiasis. She rates the pain of her HAE attacks to be much worse than either labor pains or the pain from her nephrolithiasis! In some patients, these symptoms along with plasma extravasation and vasodilatation can lead to hypovolemic shock as reported by Cohen *et al.*³⁹ They proposed that patients with HAE who present with abdominal pain, hypotension, hemoconcentration, and leukocytosis form a distinct subgroup with a high risk of hypovolemic shock. Ascites has also been reported in patients with HAE and is thought to be caused by a combination of effects including fluid extravasation into the peritoneum and changes in the splenoportal axis.^{40,41} Both ultrasound and CT imaging have confirmed bowel wall edema.⁴²

Because of the clinical similarities between abdominal angioedema and an acute abdomen, many patients undergo unnecessary exploratory laparotomies. Patients with acute HAE attacks may have physical findings such as moderate tenderness, normal to increased and high pitched bowel sounds, and, in some cases, rebound tenderness. Moderate-marked leukocytosis (up to 31,000/mm³) may occur with HAE, further confusing the picture.⁴³ Although ultrasound and CT scans may show edematous intestinal mucosa and the presence of free peritoneal fluid, these signs are not specific for angioedema. A history of current or recent body angioedema would be much more suggestive of an attack of HAE. Therapies that are specifically effective for acute HAE may be helpful in differentiating angioedema from other abdominal emergencies.

In addition to cutaneous, abdominal, and laryngeal edema there are rare case reports of HAE patients experiencing edema in other areas. Frank *et al.* reported 2/72 patients with radiographically confirmed transient pleural effusions with cough and mild pleuritic chest pain with peripheral angioedema episodes.³⁵ A case report from the French literature describes a patient with HAE requiring mechanical ventilation because of pulmonary edema but this appears to be an anomaly. Cicardi has proposed that the lung is protected because of inactivation of bradykinin. Studies comparing the physiological effects of i.v. versus in-

traarterial injections of bradykinin have suggested >95% pulmonary clearance rate of bradykinin.⁴⁴ Although rare, patients have been reported in older literature to have had seizures or hemiparesis,^{8,35} postulated to be caused by cerebral edema; this has not been confirmed. Van Dellen and Myers reported a case of a patient with bladder involvement in HAE.⁴⁵ The patient had documented HAE and presented with episodes of gross hematuria. Cystoscopic examination revealed raised hemorrhagic lesions in the vesical walls and biopsies of the lesions showed submucosal edema. The lesions resolved when the angioedema was better controlled.

Triggers of HAE Attacks

Local trauma and emotional stress are the two most common triggers for attacks of patients with HAE. In the series of Frank *et al.*, trauma precipitated attacks in 54% of patients and 43% had attacks attributed to emotional stress.³⁵ A very common cause of trauma is dental manipulation, which may trigger oropharyngeal or laryngeal edema. Tonsillectomy and other accidental traumas are also common triggers. Other activities that may precipitate extremity edema include: typing, prolonged writing, pushing a lawn mower, hammering, and prolonged standing. Horseback riding and sexual intercourse can precipitate buttock and genitalia swelling. Although both trauma and stress are common triggers, HAE patients can clearly have spontaneous angioedema. Allergic triggers are not a feature of HAE.

Interestingly, many patients may have various prodromal symptoms that precede an attack of HAE.⁴⁶ Prematta *et al.* surveyed a group of 46 HAE patients and reported several prodromal symptoms, the most common including unusual fatigue (63%), rash on arms/legs (48%), myalgias (43%), upset stomach/nausea (41%), arthralgias (41%), abdominal cramps (39%), rash on trunk (33%), and numbness/tingling in the area of the attack (30%).⁴⁷

It is currently known that HAE is influenced by the fluctuation of female hormones, but the effects sometimes appear to vary greatly among women. Estrogen has been shown to increase fibrinolytic proteins, alter the contact system, decrease C1-INH levels, and increase bradykinin.¹⁹ There is general agreement that women taking supplemental estrogens, particularly in the form of oral contraceptives, may have increased attacks of HAE,^{10,48} and estrogen-containing contraceptives are not recommended in HAE patients. Nevertheless, the course of some women's disease seems to be unaffected by estrogen. Progesterone may also have a role in influencing attacks of HAE. The onset of HAE attacks often coincides with the beginning of adolescence or the incidence of attacks can increase during

puberty, perhaps because of the elevation in the progesterone level in the luteinizing phase of the menstrual cycle. Visy *et al.* performed a study to evaluate the relationship between serum levels of sex hormones and the incidence of HAE attacks.⁴⁹ They noted that 13 of 21 female patients experienced an increase in the frequency of attacks at menarche. Overall, the number of attacks was significantly higher (odds ratio = 6.36 in women with high progesterone levels and was even higher, odds ratio = 13.4, for subcutaneous attacks only). The authors suggest that progesterone levels may be useful in predicting the severity of the future clinical course of HAE. In regard to pregnancy, the data are conflicting. Frank *et al.*, in their U.S. series, noted improvement of HAE during the last trimesters of pregnancy, whereas Agostini *et al.*, in their larger Italian series, did not find any reduction with pregnancy.^{10,35}

Age of Onset

C1-INH deficiency is present at birth but only rarely manifests in the 1st few years of life.^{50,51} About one-half of patients become symptomatic before the age of 10 years, and another third by the age of 20 years.^{19,35} This early onset of angioedema may be a helpful diagnostic aid because most idiopathic angioedema typically manifests in adulthood. Although HAE typically manifests in childhood, there are case reports of patients becoming initially symptomatic in their 50s.^{35,52} There does not appear to be any difference between age of onset among male and female subjects. Asymptomatic adults with C1-INH deficiency have been described who were detected by family screening of an affected family member and represent 5% of patients in large series.¹⁹

Frequency of Attacks

The frequency of attacks varies greatly in HAE. This variability is seen between patients and also exists within a patient who may be asymptomatic for years and then have a series of attacks. In a survey of the Italian case series, among untreated patients, slightly less than one-third of patients have attacks more than once per month, 40% have 6–11 episodes/year, and 30% range from rarely symptomatic to completely asymptomatic.¹⁹ Perhaps surprisingly, the range of clinical severity and frequency has no correlation with C1-INH concentrations and can vary tremendously among families.³⁵ Recently, a retrospective study of 115 patients from Hungary and Romania showed a correlation between baseline levels of C1-INH function and severity of HAE with more severely affected patients having lower C1-INH function.⁵³

Farkas *et al.* evaluated the potential role of *Helicobacter pylori* in HAE attacks.⁵⁴ They assessed the frequency of *H. pylori* infection in 65 patients with HAE serolog-

ically and using the carbon-14-urease breath test in patients with positive serology. Nineteen of 65 patients had *H. pylori* infection. All 19 patients with infection, and 11 of 46 without infection, had a history of recurrent episodes of acute abdominal pain and the frequency of abdominal symptoms was significantly higher in the infected group ($p = 0.002$). *H. pylori* infection was successfully eradicated in 18/19 patients. In 9 of 19 patients with dyspepsia, the frequency of angioedema episodes decreased from 100 over 10 months before eradication to 19 during the 10-month follow-up period. Based on these findings, evaluation and treatment for *H. pylori* may be reasonable in HAE patients with frequent abdominal attacks.

Disease Associations with HAE

Most patients with HAE are otherwise healthy. However, there are several reports of autoimmune diseases in patients with HAE.^{35,55–65} Frank and colleagues systematically evaluated 157 HAE patients for manifestations of autoimmunity.⁵⁶ Nineteen of these patients (12%) had clinical immunoregulatory diseases including glomerulonephritis (five patients), Sjögren's syndrome (three patients), inflammatory bowel disease (three patients), thyroiditis (two patients), systemic lupus erythematosus (one patient), drug-induced lupus (one patient), rheumatoid arthritis (one patient), juvenile rheumatoid arthritis with IgA deficiency (one patient), incipient pernicious anemia (one patient), and sicca syndrome (one patient). All eight patients with HAE who developed an autoimmune disease with a known human histocompatibility antigen association developed a disease associated with their histocompatibility antigen haplotype ($p = 0.014$). Although only four patients developed Sjögren's syndrome or sicca syndrome, an additional nine manifested part of the sicca complex. They also found patients with HAE with features suggestive of an immune-based abnormality including idiopathic pancreatitis (three patients), Raynaud's disease (two patients), partial lipodystrophy (one patient), chronic chorioretinitis (one patient), and alopecia universalis (one patient).

DIFFERENTIAL DIAGNOSIS

The diagnosis of HAE is fairly straightforward when patients present with symptoms of episodic angioedema and abdominal pain as well as a family history of angioedema. Although a family history may be lacking in approximately one-third of patients, the vast majority of patients have both angioedema episodes and abdominal symptoms. Although other forms of angioedema are more common than HAE, they rarely have associated abdominal symptoms.⁶⁶ Thus, any patient with episodic angioedema who has episodes of abdominal pain should be evaluated for C1-INH deficiency. Urticarial vasculitis

Table 2 Differentiation of hereditary angioedema (HAE) from other forms of angioedema

	Family History	Urticaria	Gastrointestinal Symptoms	Age at Onset	Antihistamine/Steroid Responsive	C4	CH50
HAE	Yes (75%)	No	Yes	Younger	Minimal	↓	NI
Idiopathic angioedema	No	Usually	Rare	Older	Yes	NI	NI
HUVS	No	Yes	Yes	Older	Yes	↓	↓

HUVS = hypocomplementemic urticarial vasculitis syndrome; NI = normal.

is another relatively uncommon condition that may be confused with HAE. Patients with urticarial vasculitis may have both angioedema as well as abdominal pain. Furthermore, a subset of these patients also has low levels of complement. Distinguishing features of urticarial vasculitis include the presence of urticarial lesions, although they differ from typical urticaria in that they may be nonpruritic, bruising, and lesions may persist for a few days. In those patients with urticarial vasculitis with hypocomplementemia, in addition to low C4 and C2 levels, they usually have depressed C3 and CH50 levels, whereas these are normal in HAE. Table 2 contrasts clinical and laboratory features of HAE, idiopathic angioedema, and hypocomplementemic urticarial vasculitis.

Patients with HAE may have just episodic angioedema without abdominal pain. In the absence of a family history, there are still features of HAE that are somewhat different than other forms of angioedema. With the exception of angiotensin-converting enzyme inhibitor-induced angioedema, which is also bradykinin-mediated, other forms of angioedema typically have histamine as a major mediator. Thus, typical idiopathic or allergic angioedema will often respond somewhat to antihistamines, whereas antihistamines have no effect in HAE. The time from onset to peak of angioedema is typically hours in HAE versus minutes in most other forms of angioedema. The majority of patients with histamine-mediated angioedema will also have associated urticaria. As stated earlier, the age at onset of angioedema occurs earlier in HAE patients. Given all of the aforementioned, in the majority of patients, the history alone is sufficient to make a clinical diagnosis of HAE that can then be confirmed by laboratory tests. According to Frank *et al.* "... the main stumbling block to the proper diagnosis of HAE is its omission as a diagnostic consideration."³⁵ In fact, in their initial series of 30 patients reported in 1976, the average length of time to make the diagnosis after the onset of symptoms was 21 years. A report in 2005 on a large group of HAE patients from Spain indicated a mean delay in diagnosis of 13 years.⁶⁷

LABORATORY DIAGNOSIS

The laboratory tests that are most commonly used to evaluate patients with HAE are C4, C1-INH concentration, and C1-INH function. An additional laboratory

Table 3 Specific laboratory assays in hereditary angioedema (HAE) and acquired angioedema (AAE)

	C1-INH level	C1-INH function	C1q	C4	C3
HAE I	↓	↓	NI	↓	NI
HAE II	NI or ↑	↓	NI	↓	NI
HAE III	NI	NI	NI	NI	NI
AAE I	↓	↓	↓	↓	NI or ↓
AAE II	↓ or NI	↓	↓ or NI	↓	NI or ↓

C1-INH = C1-esterase inhibitor; NI = normal.

test, C1q, is helpful in determining AAE. As shown in Table 3, each type of HAE or AAE has a somewhat different laboratory profile that will be discussed later.

C1-INH Concentration

C1-INH concentration, also referred to as antigenic levels, may be assayed by several different methods including radial immunodiffusion, nephelometry, or ELISA. Based on large sample sizes, the lower limit of normal is 15 mg/dL.⁶⁸ Most patients with HAE I have values well below the normal limits, typically <50% of normal.⁶⁹ Because patients with HAE are heterozygotes, one would expect their C1-INH levels to be ~50% of normal. In contrast, patients with HAE I have serum levels on average of 17% of normal. One mechanism is that lower C1-INH levels result in spontaneous activation of complement and other systems (*e.g.*, contact, fibrinolytic) leading to further consumption of C1-INH.⁶⁹ Cicardi and colleagues using reverse-transcription polymerase chain reaction (RT-PCR) showed that the normal message (C1-INH mRNA) is reduced by >50% when only one allele is expressed functionally.⁷⁰ They also unexpectedly found a similar reduction in HAE II, suggesting that the level at which the C1-INH-producing cell is expressing a functional protein is somehow used to regulate C1-INH.

Patients with HAE II have normal or even elevated concentrations of C1-INH. Higher levels have been attributed to mutated C1-INH proteins binding to other serum proteins.¹⁹ Treatment of HAE I with androgens typically results in only modest if any increase in C1-INH levels. C1-INH levels are normal in HAE III.

Patients with AAE may have either normal or low amounts of C1-INH. Normal antigenic amounts may be seen if C1-INH autoantibodies result in cleaved C1-INH, which is a nonfunctional but antigenic 96-kDa protein.⁷¹

C1-INH Function

C1-INH function may be assessed by several different methods including both enzyme-based chromogenic assays and ELISAs. Enzyme-based chromogenic (colorimetric) assays may use different substrates including Et-CO-Lys or MeCO-Lys. Different types of ELISA tests are also available and measure either C1-INH-C1r or C1-INH-C1s complexes. Depending on the assay, normal ranges for C1-INH function are typically >68–80%.¹⁹ C1-INH function is an extremely sensitive assay and virtually all patients with all types of HAE and AAE have decreased C1-INH function. False positive tests for C1-INH function have been reported to be fairly high with ranges of 54–90%.⁷² The authors of this report suggested this is caused by degradation of the sensitive enzyme used in the assay during prolonged transit of samples to the laboratory. Because of the higher false positive rates, chromogenic assays showed a low positive predictive value of only 36%. A comparison between assays of C1-INH functional assays (C1-INH-C1s complex) and colorimetric assays showed good correspondence (92%) and high sensitivity of both with higher false positives with the colorimetric assay.⁷³ Several reports have suggested that the C1-INH-C1s complex assay is hampered by the manufacturer's reference range and that when laboratories set their own reference range, results are improved.^{73,74} Most European centers specializing in HAE use the chromogenic assay, and based on its higher negative predictive value, the chromogenic C1-INH functional assay has been recommended as the preferred test.⁷⁴

C4 Concentration

C4 levels may be determined by nephelometry or radial immunodiffusion. Functional C4 may be assessed using a hemolytic assay but is not used in clinical practice. As with C1-INH function, all patients with both HAE and AAE usually have low levels. C4 levels have been advocated as a screen by many and some case series have indicated that all patients have low C4 levels.⁷² Nevertheless, not all patients with HAE have low C4 levels while asymptomatic, but during an attack, a normal C4 virtually excludes a diagnosis of HAE.³⁵ Similar to C4, C2 levels are also decreased in patients with HAE but these tests are not as readily available and are not used routinely clinically.

As mentioned previously, diminished C3 levels are extremely rare in HAE, and when present are only minimally depressed. Likewise, CH50 is only occasion-

ally decreased in HAE. In contrast, patients with AAE often have undetectable CH50.⁷⁵

C1q Concentration

In HAE, C1 or its subcomponents are typically normal. In contrast, patients with AAE typically have significantly decreased C1q levels. Patients with AAE have accelerated catabolism of C1-INH with resultant hyperactivation of the classic complement cascade. Studies of patients with AAE have shown increased catabolism of both C1-INH and C1q.⁷⁶ Confusing the picture is the fact that some patients with AAE may have normal values of C1q. Fremeaux-Bacchi *et al.* reported 19 patients with AAE, all of whom had anti-C1-INH antibodies, in which 4 of 19 had normal levels of C1q.⁷⁵ Patients with low C1q also had undetectable CH50 levels, whereas the patients with normal C1q had normal levels of CH50. Patients with hypocomplementemic urticarial vasculitis may also have decreased C1q and C4, and occasionally decreased C1-INH because of consumptive loss.

Diagnostic Strategies

Various algorithms for the diagnosis of HAE and AAE have been proposed.^{19,36} None of the algorithms take into account a careful history, which is the most helpful diagnostic strategy. As discussed earlier, there are several clinical features that are very suggestive of C1-INH deficiency including episodic angioedema with characteristic features (slow to peak and triggered by trauma), recurrent abdominal pain, and in two-thirds of HAE cases, a family history. When patients present with these characteristic features, obtaining C4 and C1-INH function levels would be appropriate. If both tests are normal, C1-INH deficiency can be excluded. If the C4 is low, but C1-INH function is normal, hypocomplementemic urticarial vasculitis should be considered. If both C4 and C1-INH function are low, C1-INH deficiency is confirmed and further tests can be performed. If there is a family history, a C1-INH quantitative level could be obtained to determine whether the patient has HAE I (low C1-INH level) or HAE II (normal C1-INH level). Practically, the value in determining this is unlikely to be of much clinical use at the present time. In the absence of family history and if the patient is >40 years of age, determining a C1q level and obtaining a serum protein electrophoresis would be appropriate. A depressed C1q level in the setting of low C1-INH function would be diagnostic of AAE. Even if the C1q is normal, as discussed earlier, the patient may still have AAE and if the serum protein electrophoresis does not reveal paraproteinemia, further evaluation for occult malignancy should be entertained. Unfortunately, anti-C1-INH antibodies are not widely available, although arguably the presence or absence of anti-C1-INH antibodies is of questionable clinical relevance.

The laboratory evaluation of HAE has been investigated in a systematic fashion to provide sensitivity and specificity data.⁶⁸ The combination of a low C4 and low C1-INH function has a 98% specificity and 96% negative predictive value. The authors caution that the accuracy of diagnosis is significantly improved when repeat samples confirm the results.

It should be stressed that these laboratories often require repeating, particularly when the results are only marginally abnormal. Another good general rule would be not to order C1-INH testing of any sort in patients with histories of urticaria. C1-INH quantitative levels should not be ordered initially, unless one orders them with C1-INH functional tests because patients with both HAE II and AAE II may have normal C1-INH quantitative levels. Furthermore, because these tests are ordered rarely, there is typically a great deal of confusion among laboratory personnel in actually ordering the correct test (quantitative C1-INH versus functional C1-INH). It is imperative to ensure that one obtains the proper test results before making the diagnosis.

CONCLUSIONS

Certainly, many advances have been made in the understanding of HAE since the time of Osler. Despite our more thorough understanding of the genetics and pathophysiology of HAE, many questions remain unanswered, particularly those that relate to the inherent variability of disease expression despite similar biochemical or genetic profiles. Our understanding of other forms of HAE (HAE III) that are unrelated to C1-INH remains in its infancy. Finally, despite our better understanding of this disease, in clinical practice it remains largely unknown or misunderstood with patients being misdiagnosed or inappropriately treated.

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