Overview of Epidemiology, Pathophysiology, and Disease Progression in Hereditary Angioedema

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Abstract

Hereditary angioedema (HAE) is an autosomal dominant disease caused by a deficiency in functional C1 inhibitor affecting an estimated 1 in 50,000 individuals in the United States. The disease is characterized by recurrent episodes of nonpruritic swelling of the hands, feet, arms, legs, trunk, face, genitalia, bowels, and larynx beginning in childhood or adolescence and continuing throughout the patient's lifetime. There is significant variability in both the severity and frequency of edema attacks. Untreated patients may suffer an attack as often as every few days, while patients undergoing prophylactic therapy may be symptom free for a decade or more. Although disease awareness has increased following the US Food and Drug Administration approval in 2009 of a new treatment for acute HAE attacks, delayed diagnosis, misdiagnosis, and inappropriate treatment remain significant problems. This article reviews the pathophysiology, symptoms and clinical course, and diagnostic challenges of HAE.

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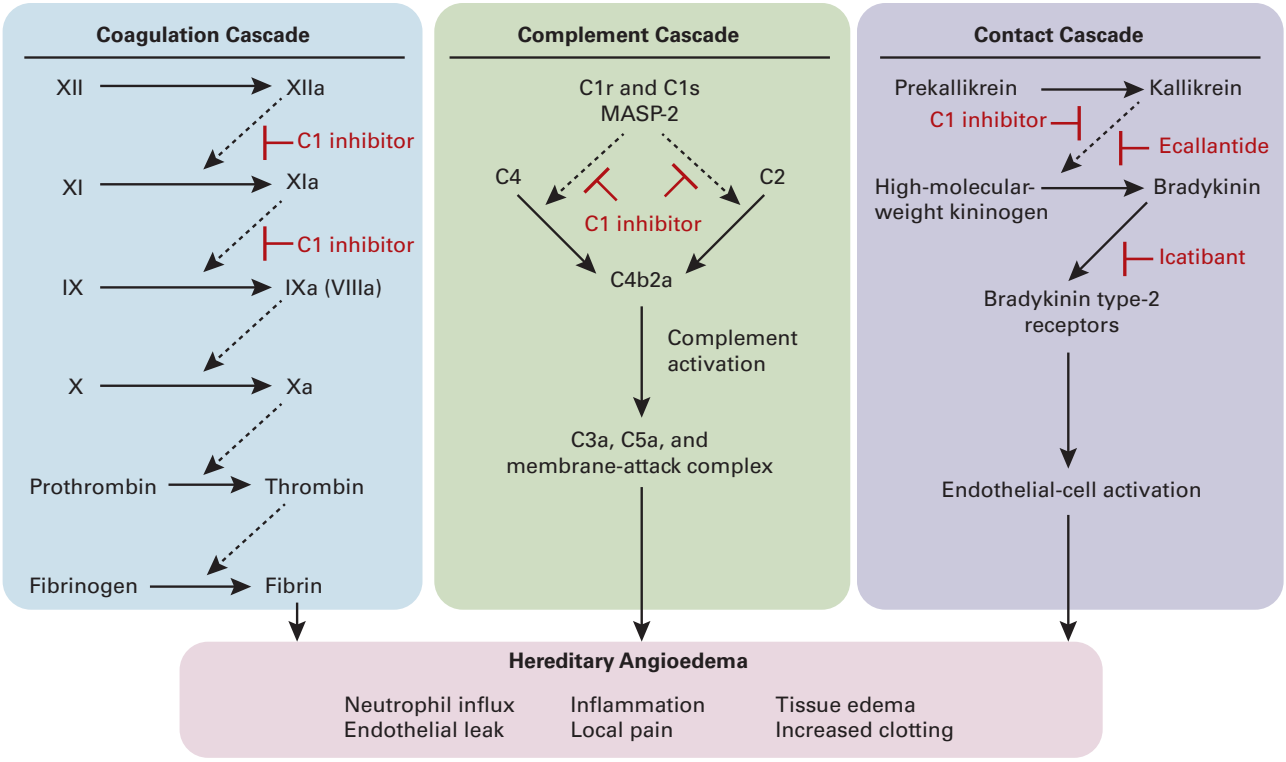
Hereditary angioedema (HAE) is a rare genetic disorder caused by a deficiency in functional C1 inhibitor (C1INH) that results in recurrent attacks of localized subcutaneous or mucosal edema most commonly affecting the skin, intestines, upper respiratory tract, and oropharynx.[1-3] Laryngeal edema, which may occur in 50% of patients, can cause fatal asphyxiation due to obstruction of the upper airways, and is therefore an important clinical feature of the disease.[4] Because of its rarity—an estimated 1 in 50,000 individuals[1] are affected (range: 1 in 10,000–1 in 150,000 worldwide)[5]—there is often a long delay between initial onset of HAE symptoms and a formal diagnosis; misdiagnosis and medical mismanagement is not uncommon in people with the condition.[6]

Contemporary medical management of HAE is divided between treatment of acute attacks and short- and long-term prophylaxis to reduce both the frequency and severity of subsequent flare-ups. Until recently, there were no agents approved by the US Food and Drug Administration (FDA) for the treatment of acute HAE attacks in the United States.[7] Purified C1 inhibitor has been available in Europe for at least 3 decades, but was not approved for use in the United States due to concerns about the potential for virus transmission, particularly hepatitis C virus.[2] This changed in October 2009 when the FDA approved a pasteurized formulation of C1INH (Berinert) for the treatment of acute abdominal attacks and facial swelling associated with HAE in patients 12 years and older.[2,8] Pasteurized, nanofiltered C1INH concentrate (Cinryze) has been available for HAE prophylaxis since 2008.[2,9,10] Two randomized, placebo-controlled trials demonstrated efficacy of this agent for treatment of acute attacks (an approved indication in Europe).[2,3] Two other agents—ecallantide (Kalbitor) and icatibant (Firazyr)—are now FDA-approved for the treatment of acute attacks in adults.

Together, these developments mark a major turning point in the management of patients with HAE. In many cases, new treatments have been life altering, allowing people with the condition to pursue academic, professional, and personal interests for the first time in their lives.[7] However, as in the case of many rare genetic diseases, treatments for HAE are expensive and patients do not respond equally to them. Clearly, more research is required to better understand the substantial variability in HAE, and to improve diagnosis of the condition and selection of patients for specific therapies.

For author information and disclosures, see end of text.

Figure 1. Dysregulation of Coagulation, Complement, and Contact Cascades in Hereditary Angioedema[2]



C1 inhibitor controls activation in the coagulation, complement, and contact cascades, and all 3 cascades are dysregulated in hereditary angioedema. Replacement of C1 inhibitor restores homeostasis. Ecallantide and icatibant specifically inhibit the contact cascade but have no direct effect on the complement or coagulation cascade. Dashed arrows indicate enzyme-cleavage steps, and T bars points of inhibition.
MASP-2 indicates mannose-binding lectin–associated serine protease 2.
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Epidemiology and Etiology of Hereditary Angioedema

Hereditary angioedema is an autosomal dominant genetic disorder characterized by a deficiency in functional C1INH. The condition is thought to affect anywhere between 1 in 10,000 and 1 in 150,000 individuals worldwide, but its rarity makes accurate prevalence estimations difficult.[5,6] A registry of patients with HAE in Norway reported a prevalence of 1.75 per 100,000 inhabitants,[11] while a Spanish registration study detected a minimal prevalence of 1.09 per 100,000.[6] Long delays in diagnosis (averaging 13.1 years in the Spanish study) combined with the possibility of misdiagnosis and a general lack of disease recognition mean that the actual prevalence may be higher than estimates suggest.[6] To date, no studies have shown differences in prevalence between ethnic groups.[1]

HAE occurs in 2 primary forms: type I and type II. In type I HAE, which accounts for approximately 85% of cases, mutations throughout the C1INH gene cause the formation of truncated or misfolded proteins that are not secreted efficiently, resulting in low plasma levels of C1INH, leading to low C1INH function.[1,12] Approximately 15% of patients with HAE have the type II form, in which mutations cause the production of a dysfunctional C1INH protein resulting in low C1INH function despite normal levels of antigenic C1INH.[1,12] A third form of HAE (HAE with normal C1INH; formally referred to as HAE type III) was identified 10 years ago.[5] This poorly understood disorder primarily affects women who express normal levels of functioning C1INH but nonetheless suffer the classic recurrent attacks of angioedema that are unresponsive to antihistamines or corticosteroids.[13] These attacks are often preceded by elevated estrogen levels (ie, during pregnancy or estrogen replacement therapy).[13,14] A mutation in coagulation factor XII has been proposed as a possible disease mechanism in the context of elevated hormone levels in a minority of these patients.[13]

Pathophysiology of HAE

C1INH, a member of the serpin family of serine protease inhibitors, is a major regulator of the complement, contact, and coagulation cascades through inhibition of several com-

plement proteases (C1r, C1s, and mannose-binding lectin-associated serine protease 1 and 2), contact proteases (plasma kallikrein and coagulation factor XIIa), and coagulation factors (XIa and XIIa) (**Figure 1**).[2,12,15] In HAE, a deficiency of functional C1INH allows for uncontrolled activation of these cascades, resulting in increased vascular permeability and the classic symptoms of swelling.[12,15] HAE attacks are accompanied by neither inflammatory nor allergic components, and therefore generally do not respond to treatment with antihistamines, epinephrine, or corticosteroids—this clinical feature often provides an important diagnostic clue.[12,15]

The primary mediator of vascular permeability in HAE is bradykinin, a nonapeptide generated through activation of the complement system that binds to receptors (the B2 receptor) on vascular endothelial cells.[12,15] Bradykinin is thought to promote vascular permeability by loosening the junctions between vascular endothelial cells through phosphorylation of vascular endothelial cell cadherin.[12,15] Experiments in C1INH-deficient mice demonstrate a persistent increase in vascular permeability mediated by enhanced bradykinin signaling that is reversible with administration of a B2 receptor inhibitor.[12] By contrast, mice deficient in both C1INH and B2 receptor show no increased vascular permeability.[12] Expression of bradykinin is regulated by kallikrein in the contact cascade.[1,16] B2 receptor and plasma kallikrein are important new drug targets in HAE. In 2009, ecallantide (Kalbitor), a potent and specific inhibitor of plasma kallikrein, became the second agent (following Berinert) to be FDA-approved for the treatment of acute HAE attacks, followed in 2011 by the B2 receptor antagonist icatibant (Firazyr).[17,18]

Symptoms and Clinical Course

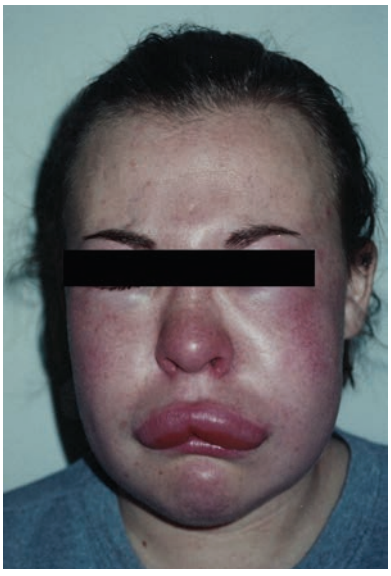
The clinical course of HAE follows a similar pattern in many patients. Symptoms typically first appear during childhood or adolescence, worsen during puberty, and persist throughout the patient's lifetime. A retrospective analysis of 209 patients with HAE by Bork et al reported a mean age at disease onset of 11.2 years (range 1 to 40 years), with approximately 50% of patients having their first attack before age 10.[19] After the onset of clinical symptoms, most patients with HAE have recurrent attacks of edema with symptom-free intervals of less than 12 months, although considerable variability exists in attack frequency—untreated patients may have attacks every 7 to 14 days on average,[1] while patients whose disease is well controlled with long-term prophylactic therapy may be symptom-free for a decade or more.[19] The severity of attacks also varies considerably, even within affected families and even if they have the same genetic mutation.[19]

A number of possible attack triggers have been proposed in HAE, including exposure to cold, minor trauma, prolonged sitting or standing, exposure to certain foods, medications (eg, angiotensin-converting enzyme inhibitors, estrogen-containing contraceptives, hormone replacement therapies), chemicals, infection, and emotional stress.[14,20] However, many attacks occur without an obvious trigger, and the same trigger may not always provoke an attack in a specific individual.[1,14] Elevated levels of female sex hormones have been linked to edema attacks in women in all 3 HAE subtypes.[14,21] Case studies have documented both initiation of and exacerbations of HAE symptoms in women during puberty and after starting estrogen-containing oral contraceptives or hormone replacement therapy (HRT).[21]

In 1 study, approximately two-thirds of women with HAE (either type I or HAE with normal C1INH) experienced an initial edema attack or worsening of both frequency and severity of attacks after starting oral contraceptives or HRT.[21] Changing the formulation of the oral contraceptive had no effect; in a number of cases the attacks continued even when oral contraception was stopped altogether.[21] Like the disease course, symptoms of HAE are quite consistent. Nearly all patients suffer from skin swelling and recurrent abdominal pain; laryngeal edema attacks by contrast are rare but will occur in 50% of patients with HAE at some time in their lives. Attacks are often preceded by nonerythematous rash (erythema marginatum), tingling sensations, anxiety, mood changes, or exhaustion. Symptoms gradually worsen over the first 24 hours and then slowly resolve, usually within 48 to 72 hours, although swelling sometimes persists for up to 5 days.[1,14] While attacks typically involve a single site, some patients may have simultaneous or closely spaced episodes of cutaneous and abdominal involvement.[14]

Cutaneous Edema. Skin swelling, most commonly affecting the extremities, is the defining feature of HAE in the vast majority of patients—upper extremities more than lower—followed by the face and genitals and, more rarely, the trunk and neck.[14,19] In a retrospective analysis by Bork et al, recurrent skin swelling occurred in 201 of the 209 patients observed, of whom 196 (97.5%) had swelling of the extremities.[19] Skin edema in HAE is nonpitting and nonpruritic; blisters and compartment syndromes may accompany particularly severe cases.[1,19] Typically, 1 site is involved, with the edema gradually spreading then receding over a period of days.[19] Approximately one-third of cutaneous HAE attacks are preceded by erythema marginatum, a nonprurutic, serpiginous rash that produces a map-like pattern on the skin.[1,20] This symptom occurs more frequently in pediatric patients

Figure 2. Facial Edema in a Patient With Hereditary Angioedema



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and is a potential diagnostic pitfall, as it can be mistaken for similar rashes accompanying childhood viral or bacterial illnesses, or may be misdiagnosed as urticaria.[20,22] **Figure 2** shows facial edema, characterized by generalized swelling of facial features, in an HAE patient.

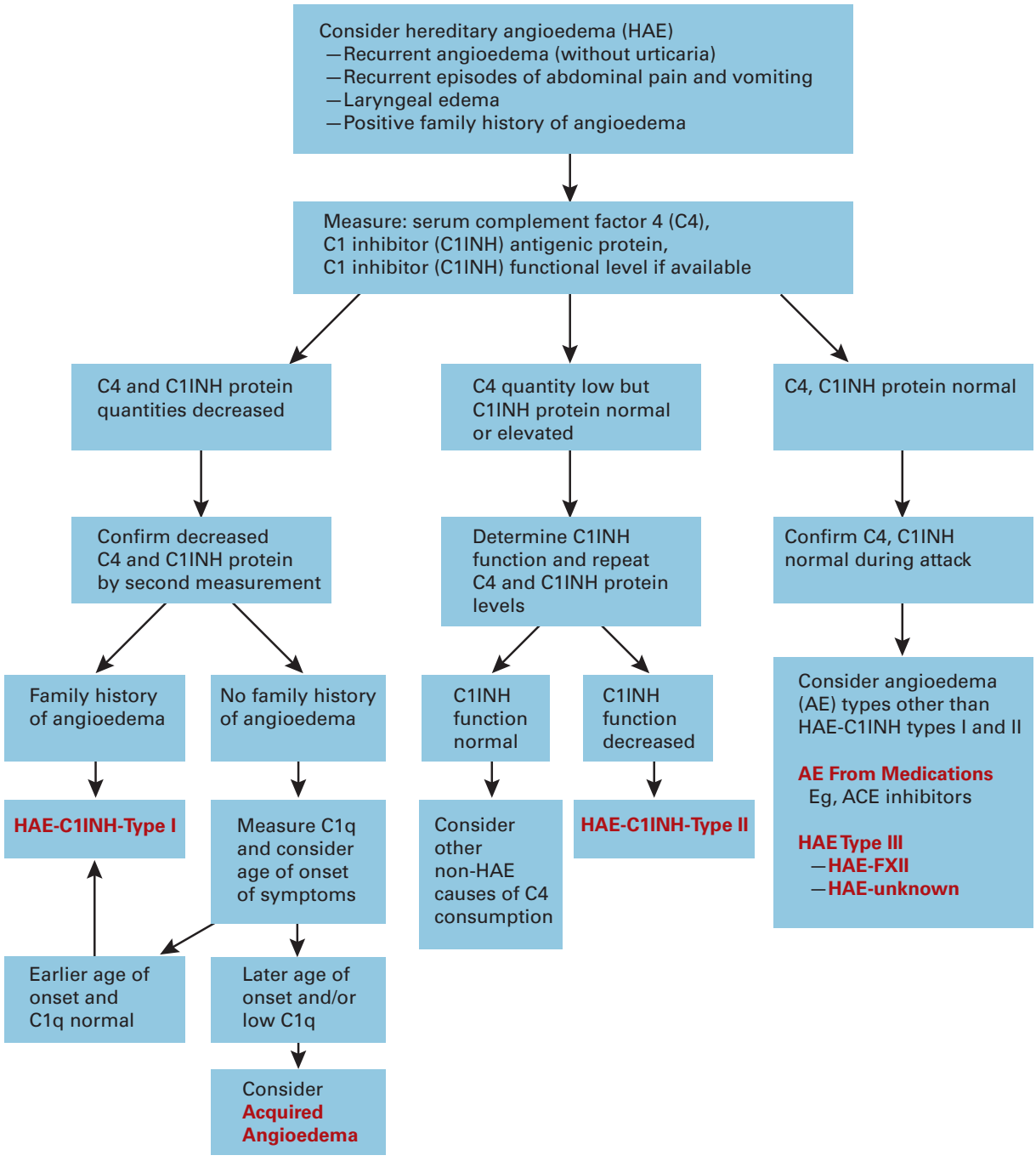
Abdominal Symptoms. Recurrent abdominal pain resulting from edema of the gastrointestinal wall is reported in 70% to more than 90% of patients with HAE.[14,19] Symptoms can range from mild, intermittent abdominal discomfort to severe colicky pain accompanied by vomiting and/or diarrhea. Cases of hypovolemic shock resulting from fluid loss, plasma extravasation, and vasodilation have been reported in severe abdominal attacks.[14] Abdominal episodes of HAE can mimic a number of other conditions, including gastroenteritis, acute appendicitis, mesenteric lymphadentitis, and intussusception, among several less common conditions, which can lead to unnecessary emergency abdominal surgery.[14,20] Abdominal ultrasound and computer-assisted tomography scans help with the differential diagnosis by detecting free peritoneal fluid, edematous intestinal mucosa, and liver structure abnormalities, but these signs are not clearly specific for angioedema.[14,20] Hemoconcentration and leukocytosis are sometimes seen in association with abdominal HAE attacks.[14,23]

Laryngeal Edema. Laryngeal edema is a rare but potentially fatal clinical manifestation of HAE. While less than 1% of all swelling episodes involve the larynx, approximately half of all patients with HAE have a laryngeal attack at some point in their lives.[14,19] Before the availability of agents to specifically treat HAE, mortality associated with laryngeal edema was approximately 30%.[14] Data from 123 patients suggested that, on average, patients experienced their first episode of laryngeal edema at a later age (26.2 years) compared with their first skin swelling (15.4 years) or abdominal pain attack (16.2 years).[4] However, laryngeal edema has been reported in patients as young as 3 years.[4] Pediatric patients present a particular diagnostic challenge because laryngeal edema may be misdiagnosed as allergic asthma or epiglottitis.[20] Further, compared with adults, asphyxiation in children may develop more quickly due to their smaller airway diameter.[20] An important diagnostic clue is that standard medications (ie, antihistamines, corticosteroids, and epinephrine) normally effective for alleviating acute airway edema in children are generally ineffective for laryngeal HAE attacks.[20]

Clinical symptoms of laryngeal edema include voice changes (eg, hoarseness or deepening of the voice), a feeling of tightness or a lump in the throat, and dysphagia.[4,19] Patients with advanced swelling often have aphonia (ie, loss of voice) and fear of asphyxiation with substantial anxiety. Upper airway obstruction is usually caused by laryngeal and glottal edema.[4] In some patients, laryngeal edema may be accompanied by swelling of the soft palate, including the uvula and the tongue.[19] The time from onset of laryngeal edema to maximal swelling has been reported to range from 8 to 12 hours, but may be shorter or considerably longer.[4] Local trauma, such as dental work, endoscopy, and intubation during general anesthesia, has been reported to trigger laryngeal swelling in some patients with HAE.[4]

Other Symptoms. Less common but clinically important manifestations of HAE may include neurological, pulmonary, renal, urinary, and musculoskeletal symptoms, many of these having been only recently identified.[19] As mentioned, edema of the soft palate, uvula, and, rarely, the tongue has occurred, both separately and in conjunction with laryngeal edema. Severe headache accompanied by other neurological symptoms, such as vision disturbances, impaired balance, and disorientation, has recently been reported in patients with HAE.[19] Recurrent pulmonary and esophageal symptoms have been documented in a number of patients, including chest pain, shortness of breath, and severe pain while swallowing food.[19] Because the symptoms resolved relatively rapidly after administration of C1INH concentrate, they were suggestive of an underlying HAE etiology rather than a surgical emergency. Pulmonary involvement in HAE is controversial and

Figure 3. Diagnostic Algorithm for Hereditary Angioedema[25]



C1INH indicates C1 inhibitor; C1q, complement component 1, q subcomponent.
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the underlying pathology is not well understood.[14,19] Urinary symptoms of HAE may include difficulty of urination, pain while urinating, and bladder spasm. Pain and swelling of the shoulder and hip joints and muscles of the neck, back, and arms has been reported in some patients.[19]

Diagnosing Hereditary Angioedema

Early detection and diagnosis of HAE before the onset of clinical symptoms is critical for appropriate treatment, preserving patients' quality of life, and because even the first attack of laryngeal edema can be fatal. Despite advances in

testing procedures and more disease recognition, the diagnosis of HAE still presents considerable challenges for physicians, particularly in the primary care setting. Diagnosis is made through a careful evaluation of clinical symptoms and family history, and confirmed using laboratory testing (**Figure 3**). Clinical symptoms of recurrent abdominal pain or edema in the absence of associated urticaria should prompt suspicion of HAE, particularly in patients with a positive family history. The absence of a family history, however, is not a disqualifying feature, since up to 25% of HAE patients have spontaneous C1INH mutations.[24,25]

Laboratory Findings. Laboratory tests provide the definitive diagnosis of HAE. Measurement of plasma levels of complement factor 4 (C4) and C1INH is the first step in the diagnostic algorithm, as shown in Figure 3. Virtually all patients with HAE have persistent low levels of antigenic C4, although about 2% of patients have been reported to have normal C4 levels between edema attacks.[1,25] Measurement of C4 is generally considered a valuable, cost-effective test for HAE in patients with unexplained recurrent edema because normal C4 levels, particularly at the time of a swelling episode, almost always indicate an alternate etiology.[5] Some clinicians, however, advocate testing for C1INH regardless of C4 levels to avoid possible false negatives—1 study of diagnostic assays for HAE reported a sensitivity of low C4 of just 81%.[26] Despite the best available evidence, 1 recent survey of US allergists/immunologists and primary care physicians who treat HAE found that only 64% of respondents used C4 testing to aid in the diagnosis of HAE.[5] Almost 84% reported that they used C1INH level and function testing.[5]

Low levels of both C4 and antigenic C1INH indicate a diagnosis of type I HAE, which should be confirmed with repeat testing.[25] In cases where there is a strong clinical suspicion of HAE in the context of a low-to-normal C4 test and normal levels of antigenic C1INH, a functional C1INH assay should be obtained.[26] Functional C1INH is a specialized test and should be obtained from an experienced laboratory to avoid sample mishandling or misinterpretation.[25] A normal C4 and functional C1INH result rules out both type I and type II HAE, but does not rule out HAE with normal C1INH.[25] At this point, there is no validated assay for diagnosing this type of HAE. A minority of patients with this form of the disease have mutations in genes encoding coagulation factor XII[13]; testing for this mutation may have some utility in women with recurrent, unexplained edema and an established family history of HAE.[13,25]

Prenatal and Postnatal Diagnosis. As HAE is a genetic disorder transmitted in an autosomal dominant fashion, the offspring of a parent with HAE have a 50% chance of inheriting the disease.[20] Prenatal genetic testing for HAE is requested rarely and is only indicated if the mutation of the affected parent is known.[27] Material for genetic testing is obtained from a chorionic villus sample after 10 weeks or amniocentesis after 15 weeks.[20,27] It is generally considered impractical to test for HAE in the prenatal setting because a mutation is not always detected, the same mutation may be associated with different phenotypes, and the severity of the disease is not predictable.[20]

For infants with an affected parent, testing for antigenic and functional C1INH is first performed at the age of 6 months or later, when complement levels typically reach adult values.[20] As false positive or false negative C1INH results can occur in infants under 1 year of age, repeat testing at a later age (usually at 1 year) is indicated to confirm the diagnosis.[20,28] C4 levels typically reach adult values between the ages of 2 and 3 years.[27] Genetic testing can be useful for establishing a diagnosis of HAE in asymptomatic children for whom C1INH and C4 assay results are equivocal.[20]

Diagnosis of HAE in symptomatic children may be impeded by a negative family history, resulting in misdiagnosis. Conversely, a diagnosis of HAE in children has sometimes led to screening and identification of the disorder in a previously undiagnosed parent.[20]

Delayed Diagnosis of HAE—A Persistent Problem With Serious Consequences. Diagnostic delays in patients with HAE have decreased substantially over the past few decades—in 1976 the average time to diagnosis from onset of symptoms was reported to be 21 years.[29] Even today, however, the majority of US physicians estimate that most patients experience symptoms for an average of 7 years before a definitive diagnosis is made,[30] and a few patients completely slip through the cracks. A recent case report from Texas described a 57-year-old man with previously undiagnosed HAE who started experiencing symptoms in his teens—a diagnostic delay of about 40 years.[31] While this case is clearly an outlier, in the Spanish HAE registry study from 2005, the average time to diagnosis from symptom onset was still more than 10 years.[6] A web-based survey of US physicians conducted in 2009 to 2010—The Surveillance Project on Hereditary Edema—reported an average time to diagnosis ranging from 0 to 6 months (5.8%) to more than 10 years (5.8%).[30] Less than 38% of patients with HAE were diagnosed within 1 to 3 years from the first appearance of symptoms.[30]

As mentioned, delays in the diagnosis of HAE can have serious consequences, including impaired quality of life, lost productivity and income, depression, unneces-

sary and/or inappropriate medical procedures, and more frequent utilization of health resources leading to increased healthcare costs.[31,32] An online survey of 63 patients with HAE conducted in 2004 found that patients averaged 4.7 emergency department (ED) visits each year; nearly 21% received treatment for anaphylaxis in the ED.[32] Unnecessary abdominal surgery was not uncommon in patients with undiagnosed HAE, particularly if severe abdominal pain was the presenting or predominant symptom.[33] Appendectomy and exploratory diagnostic procedures, such as colonoscopy, were common procedures.[33]

Conclusion

While diagnostic delays of patients with HAE have lessened substantially over the past few decades due to improved screening techniques and greater disease awareness, there is still substantial room for improvement. Most cases of HAE go undiagnosed for at least several years after the first attack of edema—and in some cases much longer—leading to considerable morbidity, frequent ED visits, and potential mortality. With effective new therapies available for both prophylaxis and treatment of acute attacks, a better understanding of the condition and its differential diagnosis should lead to improved outcomes in many people with HAE.

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REFERENCES

1. Zuraw BL. Hereditary angioedema. *N Engl J Med*. 2008;359:1027-1036.

2. Morgan BP. Hereditary angiogedema—therapies old and new. *N Engl J Med*. 2010;363:581-583.

3. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy*. 2012;67:147-157.

4, Bork K, Ressel N. Sudden upper airway obstruction in patients with hereditary angioedema. *Transfus Apher Sci*. 2003;29:235-238.

5. Lunn ML, Santos CB, Craig TJ. Is there a need for clinical guidelines in the United States for the diagnosis of hereditary angioedema and the screening of family members of affected patients? *Ann Allergy Asthma Immunol*. 2010;104:211-214.

6. Roche O, Blanch A, Caballero T, Sastre N, Callejo D, López-Trascasa M. Hereditary angiogedema due to C1 inhibitor deficiency: patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol*. 2005;94:498-503.

7. Kalfus IN, Gower RG, Riedl M, Bernstein JA, Lumry WR, Frank MM. Hereditary angiogedema: implications of treating a rare disease. *Ann Allergy Asthma Immunol*. 2012;109:150-151.

8. US Food and Drug Administration (FDA). FDA approves Berinert to treat abdominal attacks, facial swelling associated with hereditary angioedema. FDA website. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm186257.htm. Accessed December 16, 2012.

9. US Food and Drug Administration (FDA). October 10, 2008 Approval Letter—Cinryze. http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm093602.htm. Accessed December 16, 2012.

10. Zuraw BL, Busse PJ, White M, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med* 2010;363:513-522.

11. Stray-Pedersen A, Abrahamsen TG, Frøland SS. Primary immunodeficiency diseases in Norway. *J Clin Immunol*. 2000;20:477-485.

12. Davies A III. The pathogenesis of hereditary angioedema. *Transfus Apher Sci*. 2003;29:195-203.

13. Kaplan A. Type III hereditary angioedema: defined, but not understood. *Ann Allergy Asthma Immunol*. 2012;109:153-154.

14. Agostoni A, Aygören-Pürsün E, Brinkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004;114:S51-S131.

15. Zuraw BL. The pathophysiology of hereditary angioedema. *World Allergy Organ J*. 2010;3:S25-S28.

16. Cicardi M, Levy RJ, McNeil DL, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med*. 2010;363:523-531.

17. US Food and Drug Administration (FDA). FDA approves Kalbitor for treating potentially life-threatening attacks of hereditary angioedema. FDA website. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm192687.htm. Accessed December 17, 2012.

18. Firazyr [prescribing information]. Lexington MA; Shire Orphan Therapies, Inc; 2011.

19. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med*. 2006;119;267-274.

20. Farkas H. Pediatric hereditary angioedema due to C1-inhibitor deficiency. *Allergy Asthma Clin Immunol*. 2010;6:18.

21. Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. *Am J Med* 2003;114:294-298.

22. Hubiche T, Boralevi F, Jouvencel P, Taieb A, Leaute-Labreze C. Reticular erythema signalling the onset of episodes of hereditary angioedema in a child. *Ann Dermatol Venereol*. 2005;132:249-251.

23. Calbo L, Quattrocchi P, Ferlazzo B. Abdominal attack of hereditary angioedema associated with marked leucocytosis: a case report. *Ital J Gastroenterol*. 1992;24:464-465.

24. Pappalardo E, Cicardi M, Duponchel C, et al. Frequent de novo mutations and exon deletions in the *C1inhibitor* gene of patients with angioedema. *J Allergy Clin Immunol*. 2000;106:1147-1154.

25. Bowen T, Cicardi M, Farkas H, et al. 2010 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol*. 2010;6:24.

26. Tarzi MD, Hickey A, Förster T, Mohammadi M, Longhurst HJ. An evaluation of tests used for the diagnosis and monitoring of C1 inhibitor deficiency: normal serum C4 does not exclude hereditary angio-edema. *Clin Exp Immunol*. 2007;149:513-516.

27. Caballero T, Farkas H, Bouillet L, et al. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. *J Allergy Clin Immunol*. 2012; 129:308-320.

28. Farkas H, Varga L, Szeplaki G, Visy B, Harmat G, Bowen T. Management of hereditary angioedema in pediatric patients. *Pediatrics*. 2007;120:e713-e722.

29. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med*. 1976; 84:580-593.

30. Riedl M, Gower RG, Chrvala CA. Current medical management of hereditary angioedema: results from a large survey of US physicians. *Ann Allergy Asthma Immunol*. 2011;106:316-322.

31. Maskatia ZK, Orson FM. Delayed diagnosis of hereditary angioedema. *Am J Med Sci*. 2010;340(1):82-83.

32. Huang S. Results of an on-line survey of patients with hereditary angioedema. *Allergy Asthma Proc*. 2004;25:127-131.

33. Bowie KJ, Scarupa M, Li H. Unnecessary abdominal surgeries secondary to undiagnosed hereditary angioedema. *J Allergy Clin Immunol*. 2007;119:S276.