# Severity of Hereditary Angioedema, Prevalence, and Diagnostic Considerations

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## ABSTRACT

Hereditary angioedema (HAE) is a rare disorder, characterized by intermittent attacks of swelling in any part of the body, without the presence of hives. This lifelong disease typically presents in the first 2 decades of life, and is commonly associated with a deficiency in functional C1 esterase inhibitor (C1-INH) activity. C1-INH levels may be decreased or normal, with an accompanied decrease in functionality, depending on the type of HAE present. The frequency and severity of attacks are highly variable among patients with HAE, but can have a significant impact on a patient's quality of life, and may be fatal if not properly managed. Early diagnosis of the disease can lead to the development of an individualized treatment plan to assist with prevention and management of angiodema attacks. Delays in diagnosis remain, as healthcare professionals often fail to include HAE in the differential diagnosis when patients present with attacks, and patients therefore often go undiagnosed or are misdiagnosed for several years before a diagnosis of HAE is made. It is important for providers to recognize the most common clinical features of HAE and how to evaluate patients to effectively diagnose, prevent, and treat future attacks.


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Hereditary angioedema (HAE) is a rare but potentially life-threatening disease affecting approximately 1 in 67,000 individuals, with no identified differences in prevalence due to sex or ethnicity.[1,2] There is a genetic component of autosomal dominant inheritance in approximately 75% of patients, while 25% of patients present with a spontaneous mutation and therefore no evident family history of disease.[3,4] Most patients begin to see initial symptoms in the first or second decade of life (mean age of onset is approximately 11 years), with symptoms persisting throughout their lifetimes.[5,6] The disease commonly presents with recurrent attacks of swelling in any part of the body, without hives present.[7] The pathophysiology generally involves a sudden increase in skin and submucosa vessel wall permeability mediated by excessive bradykinin, leading to extravasation of plasma and subsequent swelling in the tissue.[8]



## Types of Hereditary Angioedema

Hereditary angioedema is most commonly associated with a quantitative or qualitative deficiency in C1 esterase inhibitor (C1-INH), due to a mutation in the C1-INH *SERPING1* gene, located on chromosome 11q.[8] C1-INH is a key inhibitor of 3 enzymes in the kallikrein-kinin cascade: factor XIIa, factor XIIf, and plasma kallikrein. Loss of functionality of C1-INH results in activation of the entire cascade and most notably excessive cleavage of high-molecular-weight kininogen, leading to increased bradykinin production. Bradykinin is a peptide that binds to the bradykinin B2 receptor on vascular endothelial cells. The binding of bradykinin to its receptors induces vasodilation and increased endothelial permeability.[8] This increase in bradykinin levels leads to increased vascular permeability, which results in the classic symptoms of localized swelling and inflammation.[2,8]

Deficiency of functional C1-INH activity is an autosomal dominant genetic disorder that can be further classified into 2 types. Type I HAE, which accounts for approximately 85% of cases, occurs due to a genetic mutation leading to a reduced quantity of secreted functional C1-INH.[1,7] In type II HAE, which occurs in approximately 15% of patients, the C1-INH is present in normal to elevated quantities but is dysfunctional and therefore unable to inhibit target proteases.[1,7]

More recently, HAE has been identified in patients who present with normal C1-INH levels and activity, classified as HAE with normal C1-INH (previously known as type III HAE).[9] Symptoms of HAE-normal C1-INH appear to be estrogen sensitive and therefore frequently identified in women.[9] HAE-normal C1-INH can further be divided into HAE due to mutations in the factor XII gene (HAE-FXII), plasminogen (HAE-PLG), angiopoetin-1 (HAE-AGPT1), or an unknown genetic cause (HAE-unknown).[9]

## Clinical Presentation

Symptoms of HAE often begin during childhood or adolescence, worsen around puberty, and persist throughout a patient's lifetime.[4,6] A retrospective analysis conducted by Bork and colleagues found a mean age of onset of symptoms of 11.2 years, with approximately 50% of patients experiencing their first attack before age 10 years.[6]

The severity and frequency of swelling in patients with HAE is highly variable.[7] Swelling is characteristically episodic rather than continuous, with many patients experiencing swelling episodes every 10 to 20 days if not treated.[4] However, when examining individual patient experiences, the incidence of swelling can vary from more than 1 swelling per week to fewer than 1 per year.[10,11] The frequency and severity of attacks also varies considerably in affected families with the same C1 inhibitor mutation.[6,10,12]

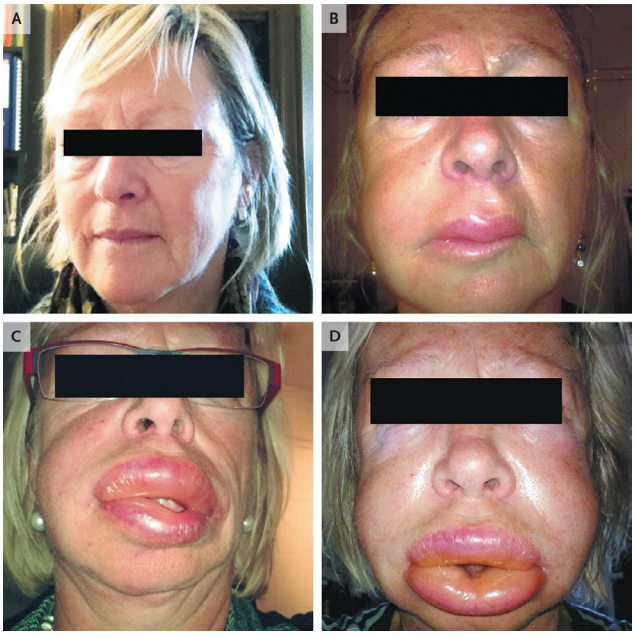
Hereditary angioedema typically presents as recurrent episodes of nonpitting, nonpruritic edema affecting 3 main areas: subcutaneous tissue (face, upper or lower extremities, genitals), abdominal organs (stomach, intestines, bladder), and the upper airway (larynx, tongue).[7,13] The most frequent sites of swelling include the skin (100%), the abdomen (97%), and the larynx (54%), although any of the above sites alone or in combination may also be involved.[6]

Subcutaneous attacks typically progress and evolve over several hours, last for approximately 2 to 4 days if untreated, and are described as a nonpruritic, nonerythematous, and circumscribed swelling of the skin, as seen in **Figure 1**.[12-14] The swelling is not typically accompanied by urticaria, as would be seen with allergic angioedema, and is most commonly seen in the upper and lower extremities, with the upper extremities most often affected.[6,13] Approximately one-third of attacks may be preceded by erythema marginatum, which is a nonpruritic, serpiginous rash producing a map-like pattern on the skin.[1,15] It occurs more often in children, and is often mistaken for similar rashes that accompany childhood viral or bacterial illnesses, or is misdiagnosed as urticaria.[15] Subcutaneous angioedema typically resolves spontaneously but causes substantial disability.[13]

Abdominal attacks in HAE are caused by transient edema of the bowel wall, with clinical symptoms including diffuse continuous pain, vomiting, diarrhea, and abdominal cramping.[10,13,16] Cases of hypovolemic shock resulting from fluid loss, plasma extravasation, and vasodilation have been reported in severe attacks.[10] Notably, there is usually no fever, which can be an important diagnostic indicator.[13] Recurrent abdominal pain has been reported to occur in 70% to 90% of patients diagnosed with HAE.[6,17] Attacks are often preceded by a prephase composed of nonspecific symptoms, such as irritability, aggressiveness, fatigue, or hunger.[16] Symptoms of an abdominal attack in HAE mimic those of acute abdominal emergencies, such as acute appendicitis, mesenteric lymphadenitis, and intussusception, and patients often undergo unnecessary emergency surgery.[12,15,17] In 1 study, 34% of patients with HAE had been misdiagnosed during an abdominal attack and underwent an appendectomy, exploratory laparotomy, or both.[10] Abdominal ultrasound and computerized axial tomography scan can help with the differential diagnosis in these patients by detecting free peritoneal fluid, edematous intestinal mucosa, and abnormalities in liver structure; however, these are not clearly specific for angioedema.[15,17] Symptoms in an abdominal attack typically spontaneously subside within 24 hours of peak symptom expression, with a total time from presentation to resolution of approximately 2 to 5 days.[10,12]

Angioedema of the upper airway is a less common, although potentially life-threatening, site of attack in patients with HAE. Although less than 1% of all swelling attacks involve the larynx, approximately 50% of all patients with HAE have a laryngeal attack at some point in their lifetime.[6,17] Laryngeal edema can be fatal because of the risk of potential suffocation without alleviation of symptoms and is a significant cause of death in patients with HAE.[16,18] Before the availability of specific treatment agents

**FIGURE 1.** Progressive Swelling Resulting From Angioedema Attack[14]




Images used with permission. Ebo DG, Bridts CH. Images in clinical medicine. Disfiguring angioedema. *N Engl J Med*. 2012;367(16):1539. doi: 10.1056/NEJMicm1200960.

for patients with HAE, mortality associated with laryngeal edema was approximately 30%.[17] Laryngeal edema typically occurs later in life than other types of swelling in HAE, with results of 1 study finding the mean age of first laryngeal edema to be 26.2 years, with nearly 80% of laryngeal edemas occurring between 11 and 45 years.[18] Pediatric patients represent a significant challenge in the diagnosis of laryngeal edema. Timely diagnosis in a pediatric patient is critical because asphyxiation in a pediatric patient presenting with angioedema can happen quickly, due to their smaller airway diameter.[15] An important diagnostic differentiation is that standard medications used to treat acute airway edema in children (antihistamines, corticosteroids, and epinephrine) are ineffective in laryngeal edema attacks in HAE.[15]

Clinical symptoms of laryngeal edema include hoarseness, stridor, dyspnea, dysphagia, voice changes, and a globus sensation.[6,13] In some patients, these symptoms may be accompanied by swelling of the soft palate, including the uvula and tongue.[6,18] The time from onset of laryngeal edema to maximum swelling has been reported to range from 8 to 12 hours, but may be considerably shorter or longer.[18]

Less common manifestations of HAE include neurologic, pulmonary, renal, urinary, and musculoskeletal symptoms.[6] Edema has also been noted in the soft palate, uvula, and tongue, both separately and in conjunction with laryngeal edema. Severe headaches accompanied by other neurologic symptoms, such as vision disturbances, impaired balance, and disorientation, have also been reported. Recurrent pulmonary and esophageal symptoms have been documented, including chest pain, shortness of breath, and severe pain while swallowing food. Urinary symptoms of HAE include urinary retention, bladder spasm, anuria, or pain at micturition. Pain and swelling of the shoulder and hip joints, and muscles of the neck, back, and arms have also less commonly been reported in patients with HAE.[6]

A number of potential attack triggers have been proposed with HAE; the well-recognized triggers include minor physical trauma, prolonged sitting or standing, exposure to certain foods, medications (especially angiotensin-converting enzyme [ACE] inhibitors), estrogen-containing contraceptives, and hormone replacement therapies), chemicals, surgery, infection, and emotional/psychological stress.[4,6,17] Results of a recent study by Caballero and colleagues showed that of the 395 patients who reported having attacks related to HAE, 42.5% of these patients reported an identifiable trigger. The most common triggers associated with attacks included emotional distress, followed by physical trauma and infection.[19] However, many attacks occur without the presence of an identified trigger; the same trigger may not always provoke an attack in an individual patient; and triggers may change for an individual patient over time.[1,4] Known triggers do not seem to directly result in swelling, but rather reduce the threshold for the initiation of an attack.[12]

## Epidemiology and Financial Burden

Despite the often-reversible nature of HAE attacks, their unpredictability and often association with stressful circumstances lead to increased difficulties for patients, their families, and employers.[12] As with other diseases that are characterized by acute attacks, such as asthma, the burden of HAE is not only economic but also impacts the patient's quality of life, education, relationships, and career.[20]

The economic burden of HAE was analyzed by Wilson and colleagues, who conducted a survey of 457 patients diagnosed with HAE. They estimated the annual per-patient cost of HAE to be $42,000 for the average patient, with annual costs estimated at $14,000 for patients with mild attacks, $27,000 for patients with moderate attacks, and $96,000 for patients with severe attacks. The cost of hospital care accounted for approximately 67% of direct medical costs. Indirect costs (eg, missed work, lost productivity, lost income) totaled $16,000 for the average patient, with these indirect costs increasing with disease severity.[20]

Another patient survey conducted by Banerji and colleagues in 186 patients with diagnosed HAE found that 72% of patients with type I or II HAE and 76% with type III HAE reported that HAE had a significant impact of their quality of life.[21] A survey of 26 patients with diagnosed HAE found that 39% of patients were identified as experiencing depression of mild (50%), moderate (40%), or severe (10%) levels.[22]

Therefore, the effects of HAE spread far beyond the physical effects during a swelling attack and can also lead to significant effects on emotional well-being, negatively impact a patient financially, and lead to a decrease in overall quality of life for a patient and their family.

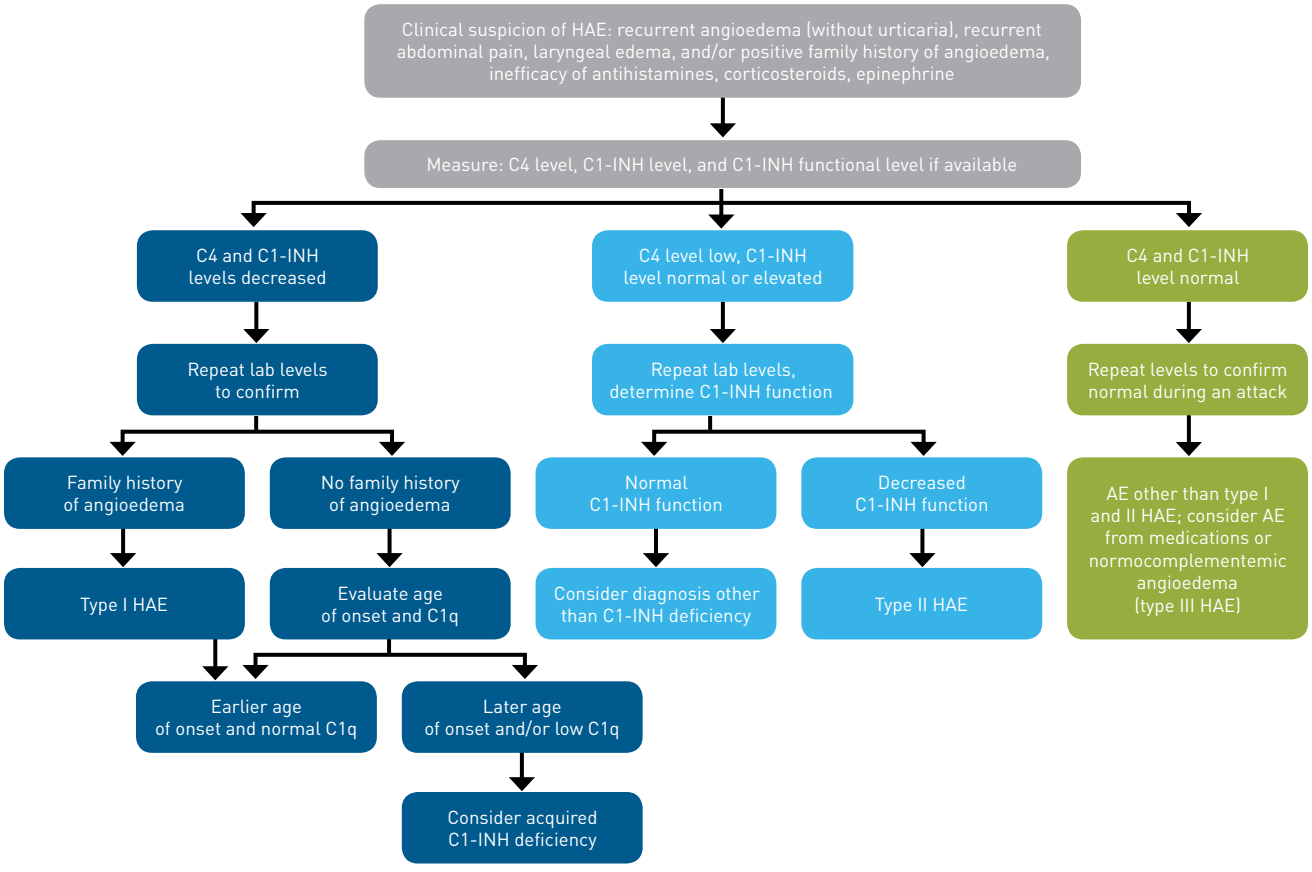
## Diagnosis of Hereditary Angioedema

Early detection and diagnosis of HAE are critical to effectively initiate appropriate patient management and preserve the patient's quality of life. Despite advances in testing procedures and disease recognition, the diagnosis of HAE still presents a considerable challenge for physicians. Diagnosis should be initiated with a careful evaluation of both clinical symptoms and family history, and confirmed using laboratory testing. Clinical symptoms of recurrent abdominal pain or angioedema in the absence of associated urticaria should trigger suspicion of HAE, particularly in patients with a positive family history.[4,7,23]

Obtaining a thorough family history is important in patients presenting with angioedema without urticaria. If there is a positive family history of HAE, the diagnosis can be refined by further investigating laboratory values and genetic testing. The absence of family history is not sufficient to rule out HAE because 25% of patients with HAE will present with a spontaneous C1-INH mutation.[23,24]

Diagnostic confirmation of HAE requires laboratory testing. This testing focuses on an antigenic and functional assessment of C1-INH. Measurement of plasma levels of complement factor 4 (C4) should be the first test performed in a patient presenting with isolated

**FIGURE 2.** International Consensus Algorithm for Diagnosis of HAE[25]




AE indicates angioedema; C1q, complement component 1, q subcomponent; C1-INH, C1 esterase inhibitor; C4, complement factor 4; HEA, hereditary angioedema. Adapted from 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(1):24. doi: 10.1186/1710-1492-6-24.

angioedema and no clear family history of angioedema. However, a clear family history measurement of C4 and C1-INH functional and quantitative levels is the first step in diagnostic evaluation in these patients. (**Figure 2**).[25,26] Nearly all patients with HAE will have persistent low levels of antigenic C4, although approximately 2% to 4% of patients are reported to have normal C4 levels between edema attacks.[1,25,27] Measurement of C4 is considered a valuable, cost-effective test for HAE in patients with unexplained recurrent edema because it can be easily measured in most clinical laboratories.[7] Although a low C4 is indicative of HAE, normal levels of C4 may not exclude the potential for HAE. Results from a study evaluating C4 diagnostic assays found that the sensitivity of low serum C4 for HAE among untreated patients was 81%, and that normal C4 levels were found on 9 separate occasions in 5 untreated patients with HAE.[26] Therefore, C1-INH studies are necessary regardless of C4 levels when there is a high clinical suspicion of HAE.[26]

Testing beyond C4 levels also allows for the potential identification of the specific type of HAE in an individual patient (**Table 1**).[28] C1-INH levels and functional assays should be obtained along with the C4 level. The C1-INH functional assay is a specialized laboratory test and should be done only in experienced reference laboratories.[25] If both C4 and C1-INH levels are low, and C1-INH functional activity is low, this is consistent with type 1 HAE.[25] If C4 levels are low or normal and C1-INH levels are normal, but clinical suspicion of HAE is strong, a C1-INH functional assay can be helpful. Type II HAE will demonstrate a low or normal C4 level, normal C1-INH level, but low C1-INH functional activity.[25] If C4 levels, C1-INH levels, and C1-INH functional activity are all normal, HAE-normal C1-INH may be considered (mutations in the coagulation factor XII gene, plasminogen, AGPT-1, or other unknown defects).[1,25] It is also important to note that routine blood tests, such as a blood count, electrolytes, and C-reactive protein, are unaffected by C1-INH deficiencies.[12]

Because HAE is a genetic disorder transmitted in an autosomal dominant fashion, the child of a parent with HAE will have a 50% chance of inheriting the disease.[15] For infants of an affected parent, testing for C1-INH levels and functionality can be performed at age

**TABLE 1.** Complement Levels in Angioedema[28]

| | C4 Level | C-INH Level | C1-INH Function | C1q Level |
|---|---|---|---|---|
| HAE | | | | |
| Type I | Low | Low | Low | Normal |
| Type II | Low | Normal-High | Low | Normal |
| Normal C1-INH levels | Normal | Normal | Normal | Normal |
| Acquired C1-INH deficiency | Low | Low | Low | Low |
| ACE-I angioedema | Normal | Normal | Normal | Normal |
| Idiopathic angioedema | Normal | Normal | Normal | Normal |

ACE-I indicates angiotensin-converting enzyme inhibitor; C1-INH, C1 esterase inhibitor; c1q, complement component 1, q subcomponent; C4, complement factor 4; HAE, hereditary angioedema.
Adapted from Zuraw BL, Bernstein JA, Lang DM, et al; American Academy of Allergy, Asthma & Immunology; American College of Allergy, Asthma & Immunology. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol*. 2013;131(6):1491-1493. doi: 10.1016/j.jaci.2013.03.034.

6 months or later, when complement levels are thought to reach adult values.[15] As false-positive or false-negative C1-INH results can occur in infants younger than 1 year, repeat testing at a later age is indicated to confirm the diagnosis.[13,15] C1-INH level and function appear to be reliable measures in children younger than 12 months, although C4 levels typically reach adult levels between 2 and 3 years, so are not reliable measurements before that time.[29,30]

## Differential Diagnosis

When a patient presents with angioedema in a primary care setting, a thorough clinical examination in addition to laboratory work will assist in differentiating HAE from other potential causes of angioedema (**Figure 3**).[24]

Allergic Angioedema Allergic or mast cell-mediated angioedema occurs as a result of mast cell degranulation, which may be caused by antigen-specific immunoglobulin E (IgE) antibodies to a specific allergen exposure. The most common allergens include food, insect venom, latex, and drugs.[7,9] However, many cases of mast cell-mediated angioedema do not have a clear identifiable trigger or cause despite comprehensive evaluation. The resulting release of histamine and other vasoactive mediators produces swelling often but not always associated with urticaria and pruritus.[7] Symptoms typically begin within 2 hours of exposure (if an allergen or trigger is involved). It is important to note that, unlike in HAE, the swelling responds to antihistamines, corticosteroids, and epinephrine, because the swelling is mediated by histamine release, unlike the bradykinin-mediated swelling produced in patients with HAE.[7]

### Acquired C1-INH Deficiency

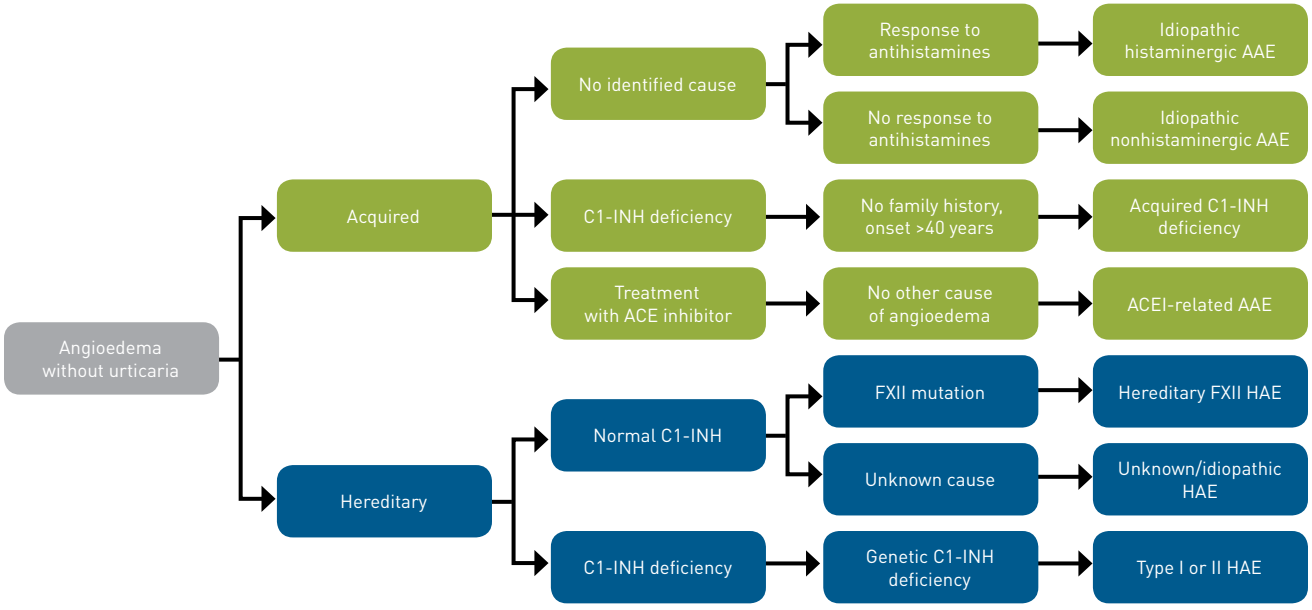
Symptoms of acquired C1-INH deficiency typically resemble those of HAE but do not present until the fourth decade of life or later, and patients will have no associated family history of disease.[7,9] It is often associated with other diseases, most commonly B-cell lymphoproliferative disorders.[24] In some patients, autoantibodies to C1-INH will develop; this does not preclude the presence of an underlying lymphoproliferative disease.[7] Laboratory studies will reveal low C4 and C1-INH levels, as well as low functional activity. Often, C1q levels will also be low, which can be helpful in distinguishing acquired C1-INH deficiency from HAE-C1-INH, because C1q levels are generally normal in HAE. However, C1q can be normal in acquired angioedema (AAE), which can make it difficult to differentiate between HAE occurring as a de nova mutation, as in both situations there is no family history. In this circumstance, it may be necessary to genotype the patient for a SERPING1 mutation, which will be absent in AAE. Due to the link with autoimmune and malignant disorders, a patient diagnosed with acquired C1-INH deficiency should be evaluated for other underlying diseases.[7,24]

### Drug-induced Angioedema

Drug-induced angioedema is most commonly associated with the use of ACE inhibitors.[4,7,9] This type of angioedema most often presents as a well-defined swelling of the tongue, lips, or other parts of the face. Life-threatening airway edema can occur in 25% to 39% of cases.[8,31] Angioedema typically occurs within 1 week after starting the medication; however, there have also been reports of angioedema occurring after several months or years of medication use.[9,31] Risk factors for the development of ACE inhibitor-induced angioedema include black race, female gender, development of a previous drug-related rash, smoking, age older than 65 years, seasonal allergies, obesity, upper airway surgery or trauma, sleep apnea, and immunosuppressive use.[31] The swelling that occurs is not related to histamine release; ACE typically degrades bradykinin, so the inhibition of ACE in these patients leads to an accumulation of bradykinin.[7] Treatment consists of discontinuation of the medication. Because this is a class effect, these medications should be discontinued in any patient who develops isolated angioedema.[7] Angiotensin II receptor blockers (ARBs) appear to have a much lower incidence of recurrent angioedema and are an option for use in patients with a history of ACE inhibitor-induced angioedema.[4,25]

If no clear cause of recurrent angioedema can be found, the angioedema is typically labeled as idiopathic.[7] Some patients with idiopathic angioedema fail to benefit from high doses of antihistamines, which suggests that a subset of idiopathic angioedema is mediated by bradykinin.[7]

**FIGURE 3.** Differential Diagnosis in Angioedema without Urticaria[24]




AAE indicates acquired angioedema; ACE, angiotensin-converting enzyme; C1-INH, C1 esterase inhibitor; FXII, factor XII; HAE, hereditary angioedema;
Adapted from Cicardi M, Suffritti C, Perego F, Caccia S. Novelties in the diagnosis and treatment of angioedema. *J Investig Allergol Clin Immunol.* 2016;26(4):212-221. doi: 10.18176/jiaci.0087.

## Delays in Diagnosis of Hereditary Angioedema

Diagnostic delays in patients with HAE have decreased substantially over the past several decades, likely due to a growing awareness in the medical community.[7,13] However, substantial delays still exist in the correct identification and management of patients with HAE. The earlier that HAE can be identified, the sooner that patient-centered management can be initiated to prevent and appropriately treat subsequent attacks.[7]

A Web-based survey of US physicians conducted in 2009-2010 found an average time to diagnosis ranging from 0 to 6 months (5.8%) to more than 10 years (5.8%). Fewer than 38% of physicians reported a time to HAE diagnosis of 1 to 3 years from the onset of symptoms.[32] This delay is important because conventional treatments, such as antihistamines and corticosteroids, are ineffective in undiagnosed HAE, and the majority of deaths occur in patients who are undiagnosed.[12,33]

Another physician survey conducted by Lunn and colleagues found that patients with HAE in the United States visited an average of 4.4 physicians before receiving a diagnosis of HAE; 65% of patients initially received a misdiagnosis; and the average time to diagnosis was 8.3 years. Also, just 63.8% of physicians used C4 levels to aid in their diagnosis.[34] Similarly, a patient-based survey in the United States found that although one-third of patients received a diagnosis of HAE within 1 year of their initial attack, another one-third experienced a delay to diagnosis of more than 10 years.[21] Patients with abdominal symptoms associated with HAE are especially likely to be susceptible to the consequences of misdiagnosis and to undergo unnecessary surgical procedures, such as an appendectomy or exploratory diagnostic procedure.[35,36]

Zanichelli and colleagues found that 44.3% of patients with HAE reported receiving 1 or more prior misdiagnoses, with the most common misdiagnoses being allergic angioedema and appendicitis. It is important to note that patients who had a history of prior misdiagnosis experienced a median delay of 13.3 years to achieve a correct diagnosis versus 1.7 years to diagnosis for patients who did not experience a previous misdiagnosis.[37]

Therefore, in patients with HAE, achieving the correct diagnosis early in the course of symptoms is critical to optimize patient outcomes. Most cases of HAE are still undiagnosed for several years after the initial attack, leading to significant morbidity, frequent emergency department visits, and potential mortality. Improved healthcare provider awareness and understanding of the condition and its differential diagnosis will assist in improving outcomes in patients with HAE.

## Conclusions

Hereditary angioedema is a lifelong disorder that is often misdiagnosed or unrecognized when patients initially present with symptoms of angioedema. It is critical to understand the framework for the diagnosis of HAE, including a deficiency in functional C1-INH, and to recognize the variability in frequency and severity of attacks that may occur among patients. Early and accurate diagnosis

will assist in developing an individual plan to effectively manage, treat, and prevent future attacks. ■

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