Editorial

A roadmap for optimal care of the patient with hereditary angioedema

The United States **Hereditary Angioedema Association (HAEA)** and *Allergy and Asthma Proceedings* have joined forces to publish an *HAE Primer*, which focuses on the diagnosis and management of hereditary angioedema (HAE), a rare, debilitating, life-threatening genetic condition that causes significant morbidity in individuals who are affected and their families. Founded in 1999 and staffed by people with HAE and caregivers, the HAEA is a nonprofit organization that works to help people with HAE live life to the fullest, ultimately unburdened by symptoms. The HAEA achieves its goals by leading a nationwide advocacy movement that focuses on increasing HAE awareness and education, empowering access to suitable treatment, and fostering ground-breaking research. This mission overlaps with that of *Allergy and Asthma Proceedings,* which is to distribute timely information with regard to advancements in the knowledge and practice of allergy, asthma, and immunology to clinicians entrusted with the care of patients. The wide variety of effective on-demand and prophylactic HAE therapies challenge clinicians to make a correct diagnosis and tailor treatment plans that best fit an individual's lifestyle and needs. In this spirit, we are grateful to the HAEA for having provided funding to support the development and publication of this *HAE Primer*.

The *HAE Primer* commences with a review of the definition and classification of HAE by Proper *et al.,*[1] who emphasize the importance of a thorough clinical history and differential diagnostic evaluation to ensure that patients are accurately diagnosed and classified. A presentation by Lumry and Settipane[2] follows, with a review of the extent and degree to which treatment advances have not only lowered disease and treatment burdens but which have also improved the quality of life of patients with HAE. Wedner[3] provides an overview of HAE pathophysiology by focusing on the central role of uncontrolled production of the vasoactive peptide, bradykinin, which is the flashpoint molecule that ignites the majority of cases of HAE. Hsu *et al.*[4] reviewed the variable presentations of HAE that can make the diagnosis of HAE challenging. Manning[5] reviewed the importance of differential diagnosis, diagnostic tests, and family screening in determining the correct diagnosis.

He emphasized that it is critical to develop an appropriate differential diagnosis, work through the various conditions, and obtain the pertinent laboratory results required to confirm or exclude the diagnosis of HAE.[5] In transitioning to treatment, Christiansen and Zuraw[6] reviewed options with regard to on-demand treatment of acute attacks, Craig[7] reviewed choices for short-term prophylactic treatment, and Li[8] reviewed alternatives for long-term prophylactic treatment. Paige *et al.*[9] addressed essential elements of an individualized comprehensive management plan of patients with HAE by focusing on the need for access to an HAE specialist, continuing patient education, availability of effective treatment options, coordination of care and management of treatment logistics with other health care specialists, ongoing monitoring of attacks and treatments, and other resources for patient support. Women and children with HAE are particular populations known to have unique challenges and vulnerabilities that require specialized needs. Yakaboski *et al.*[10] addressed these special considerations in women; and Johnston and Smith[11] addressed these unique requirements in children. In looking toward the future, Kaplan[12] provided a prescient view of the latest research that involves investigational therapies for HAE. In a concluding presentation, Settipane *et al.*[13] highlights the importance of shared decision-making and development of related aids in facilitating the interrelated and interdependent interaction of practitioners and patients required for success of HAE management.

In summary, this *HAE Primer* is dedicated to assisting health care providers with a comprehensive roadmap to deliver optimal care to patients with HAE. The **HAEA** and the *Allergy and Proceedings* are pleased to be a part of this important educational process.

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Definition and classification of hereditary angioedema

Steven P. Proper, D.O., Ph.D.,[1] William J. Lavery, M.D., Ph.D.,[1] and Jonathan A. Bernstein, M.D.[2,3]

ABSTRACT

Hereditary angioedema (HAE) is defined as a rare genetic disease with recurrent episodes of localized bradykinin-mediated swelling of the deep tissues of the skin, respiratory, and gastrointestinal tracts that can be life threatening. Classification of HAE has evolved over time with our further understanding of clinical phenotypes, underlying causes, and available testing. In most cases, HAE is caused by a deficiency of C1-esterase inhibitor (C1-INH) on the Serpin Family G Member 1 (SERPING1) gene, either through decreased amounts of C1-INH protein (C1-INH–HAE, type 1) or decreased function of C1-INH (C1-INH–HAE, type 2). HAE with normal C1-INH levels and function are divided into unknown cause or into non–C1-INH–HAE forms, which include known mutational defects in factor XII (called FXII-HAE in the Hereditary Angioedema International Working Group consensus), angiopoietin-1, plasminogen, and kininogen 1 genes. It is possible that, after an initial workup, a patient without a family history of HAE could be classified with an acquired form of angioedema (nonhereditary) that may later prove to be HAE due to a de-novo SERPING1 mutation. Because there are forms of nonhistaminergic (H_1-antihistamine unresponsive) angioedema that appear clinically very similar to HAE, it is essential that the patient undergoes a thorough clinical history and diagnostic evaluation to ensure that he or she is properly diagnosed and classified.

DEFINITION OF HEREDITARY ANGIOEDEMA

Angioedema is defined as "a localized, self-limiting, asymmetric and disfiguring non-inflammatory edema of the deep dermis or subcutaneous or submucosal tissues that occurs as a result of vasodilation and increased vascular permeability. HAE [hereditary angioedema] comprises a group of diseases characterized by recurrent angioedema caused by excess bradykinin production, with an autosomal dominant inheritance pattern."[1] Angioedema is seen in ~40% of patients with chronic spontaneous urticaria (CSU) but can appear alone in up to 20% of patients. The initial approach in evaluating a patient who presents with isolated angioedema is to determine if the angioedema is responsive or unresponsive to treatments that control CSU; however, appropriate diagnostic testing, *e.g.*, a serum C4 level, to exclude HAE as a potential cause should be obtained simultaneously. An algorithm for evaluating patients who present with wheals and/or angioedema has been adapted as part of an international guideline for the treatment of angioedema and CSU (Fig. 1).[2] In a patient who presents with isolated angioedema and without a family history, response to treatment with H_1-antihistamines is helpful both therapeutically and diagnostically. However, if a patient is not responsive to high-dose H_1-antihistamines, advocated as step 2 therapy in the urticarial guidelines, it is still possible that a patient may respond to step 3 or step 4 treatments recommended for CSU with or without angioedema. In these circumstances, clinicians should broaden their differential diagnosis to include bradykinin-mediated causes of angioedema.[2,3]

Patients with HAE experience recurrent angioedema attacks anywhere in the body but, most notably, areas that involve the extremities, gastrointestinal tract, oropharynx, face, and genitalia. In addition, they have a reliable family history of angioedema in 75% of cases (usually in a first-degree relative) associated with C1-esterase inhibitor (C1-INH) functional deficiency.[4] However, in 25% of patients with HAE, there may be no family history because of a spontaneous *de novo* mutation.[4] Bradykinin, the mediator involved in HAE, is significantly increased as the result of a deficiency and/or functional abnormality of C1-INH, which is important for regulating bradykinin formation at many sites in the contact pathway.[5]

Original work by Donaldson and Evans[6] revealed, when using complement component antibodies, that patients with HAE had deficient C1-INH and that other complement components were decreased during and/or between swelling attacks. The relevance of these findings has subsequently been confirmed in a number of knockout mouse models and *in vitro* experiments that ultimately led to the development of several novel and effective therapies designed to either replace C1-INH, block bradykinin 2
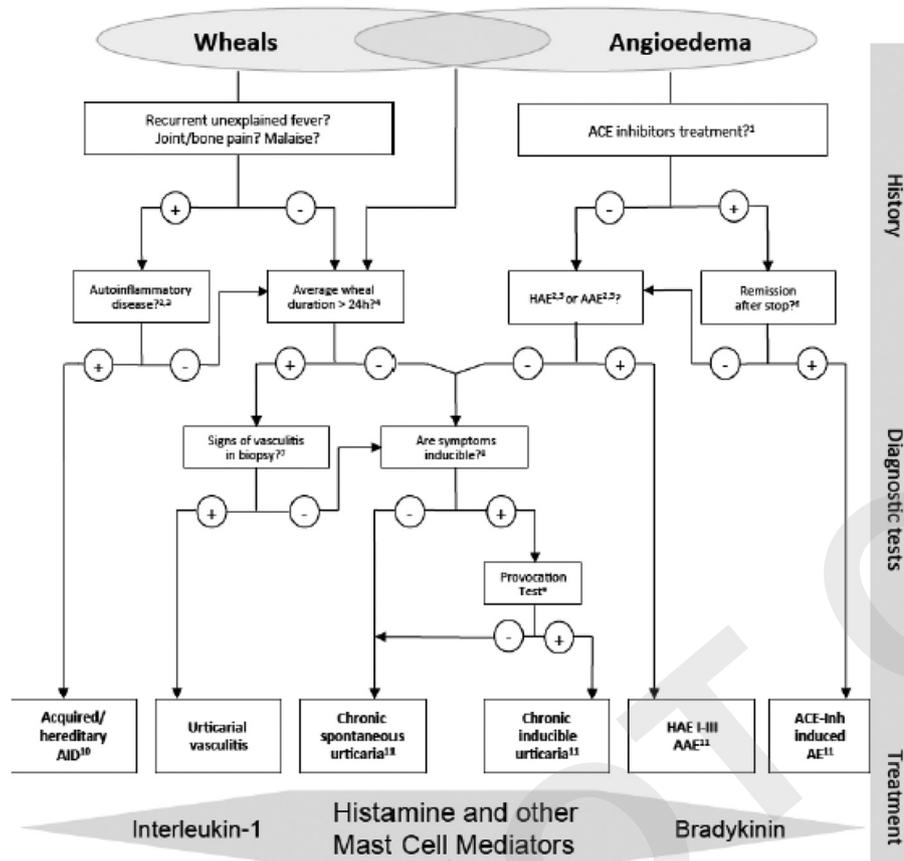
Figure 1. *Algorithmic approach for evaluating patients who present with wheals and/or angioedema (from Ref. 2).*

receptors, or inhibit the critical protein, kallikrein, important for converting high-molecular-weight kininogen to form bradykinin, thereby vastly improving the quality of life of the patient with HAE.[7–13]

CLASSIFICATION OF HAE BY COMPLEMENT TESTING

Although complement testing is considered an important method for classifying patients with HAE, complement consumption has very little involvement in the pathogenesis of HAE. The C1-INH and complement components that differentiate various forms of nonhistaminergic angioedema are summarized in Table 1 and is one approach used to classify different types of non-histaminergic angioedema. For HAE type 1, the patient should have a low C4, C1-INH functional and quantitative level, and a normal C1q, whereas patients with HAE type 2 should have a low C4, low C1-INH functional level, and normal or high C1-INH quantitative level, with a normal C1q level.[4,14] The only difference based on complement testing between HAE and acquired C1-INH angioedema is that the latter will typically have a low C1q level. All the other forms of bradykinin-mediated angioedema will have normal complement levels.[4,14]

Because HAE is a relatively rare disease that occurs in 1:50,000 or fewer patients, obtaining a full battery of

complement testing on every patient with isolated angioedema is costly and not warranted unless there is a clear family history. Therefore, screening with a C4 level is the first step in classifying and diagnosing patients with HAE; however, this test can be normal in a small subset of patients with a C1-INH–HAE deficient if measured when they are asymptomatic. If low, then obtaining a C1-INH functional and quantitative level and a C1q level is appropriate to confirm or exclude HAE and to further classify whether the patient has HAE type 1 or type 2.[4,14]

There are certain caveats that require consideration when ordering complement testing to classify patients with HAE. First, C4 is a good screening tool but sometimes can be slightly or significantly low due to laboratory handling and processing or due to an unrecognized C4 heterozygous or homozygous deficiency. In the former scenario, repeating the test is appropriate, and, in the latter instance, if C1-INH functional and quantitative testing is normal, then genotyping to further confirm a genetic C4 deficiency and a workup for underlying disease processes, such as sarcoidosis, celiac disease, lymphoma, or systemic lupus erythematosus, may be warranted, depending on the patient's clinical presentation.[15,16] In addition, C2 is not a useful laboratory test for screening because it is often normal between attacks.[4] Also, the results of tests for C1-INH

Table 1 **Classification of HAE and other nonhistaminergic angioedema types by C1-INH and complement component levels**

Type of Angioedema	C1-INH Antigen*	C1-INH Function*#	C4	C2§	C1q¶	Autoantibody to C1-INH
HAE type 1 (85% of C1-INH–HAE)#	↓	↓	↓	↓	Nl	Usually absent||
HAE type 2 (15% of C1-INH–HAE)#	Nl or ↑	↓	↓	↓	Nl	Usually absent||
HAE-normal-complement (nC1-INH–HAE or U-HAE)	Nl	Nl	Nl	Nl	Nl	Absent
C1-INH–AAE	Nl or ↓	↓	↓	↓	↓	Present**
ACEI-AAE	Nl	Nl	Nl	Nl	Nl	Absent
InH-HAE	Nl	Nl	Nl	Nl	Nl	Absent

HAE = Hereditary angioedema; C1-INH = C1-esterase inhibitor; ↓ = decreased; Nl = normal; ↑ = increased; nC1-INH–HAE = non–C1-esterase inhibitor form of HAE; U-HAE = HAE-normal-complement of unknown cause; AAE = acquired angioedema; ACEI = Angioedema Converting Enzyme-inhibitor induced; InH = idiopathic nonhistaminergic.

*The C1-INH levels and functional activity when low in C1-INH HAE are usually <50% of normal; marginally low or borderline levels do not confirm C1-INH HAE.

#Results may vary, depending on the whether an enzymatic or chromogenic assay is used.

§Not consistently low between angioedema attacks and, therefore, is an unreliable screening test.

¶May be normal in AAE 30% of the time and low in HAE in some cases.

||C1-INH autoantibodies can generally be found at low titers in some in patients with C1-INH–HAE deficiency and in healthy subjects.

**The presence of a lymphoproliferative disorder or monoclonal gammopathy of unknown significance is also frequently seen with or without a C1-INH autoantibody; whereas, high-titer autoantibodies to C1-INH are supportive of AAE-C1-INH deficiency, they are not required for diagnosis.

functional levels may vary, depending on whether a chromogenic or an enzymatic assay is used.[17]

CLASSIFICATION OF HAE BY GENETIC TESTING

Previously, a consensus classification schema for bradykinin-mediated angioedema was developed by the Hereditary Angioedema International Working Group, which met in 2012 (Fig. 2).[4] This classification differentiates HAE from HAE-normal-complement, acquired angioedema, angioedema converting enzyme (ACE)-induced angioedema, HAE-normal-complement of unknown cause, and idiopathic histaminergic and nonhistaminergic angioedema. HAE types 1 and 2 have genetic mutations in the *SERPING1* gene, which results in a C1-INH functional deficiency. Patients with type 1 HAE have an actual defect in the *SERPING1* gene, with reduced production of functionally normal C1-INH protein, whereas patients with HAE type 2 are believed to have a mutation at or near the active site of the reactive mobile loop of C1-INH, which results in a functionally abnormal C1-INH protein.[7] Very recently, four genetic mutations in patients with HAE and with normal C1-INH levels and/or function have been identified in key non–C1-INH components of the kinin-kallikrein system, including factor XII (*F12*), angiopoietin-1 (*ANGPT1*), plasminogen (*PLG*), and kininogen 1 (*KNG1*). These additional mutations have been included in Fig. 2, our updated version of this classification scheme.[18–21] It is likely that the HAE-normal-complement of unknown cause will narrow as research in this area continues to evolve.[4]

HAE with normal C1-INH function used to be referred to as HAE type 3, but this nomenclature is no longer used and is now replaced by newer precise consensus definitions, in part because of recognition that there are now many examples of HAE-normal-complement associated with non-*SERPING1* gene mutations, as discussed above.[1,18–21] Currently, the HAE-normal-complement group is broadly divided into HAE-normal-complement of unknown cause or due to specific mutations that involve *F12*, *ANGPT1*, *PLG*, or *KNG1*.[18–21] The *F12* gene mutation is believed to result in increased factor XII activity due to a specific mutation in exon 9.[21] This angioedema type seems to affect females more than males, which has been speculated to be due to estrogen playing an important role in precipitating angioedema attacks.[22]

However, the role of estrogen has not been definitively confirmed, partly because males have also been identified with this mutation and, therefore, the lack of a relationship between increased estrogen and attacks should not discourage a workup for this mutation.[23] In
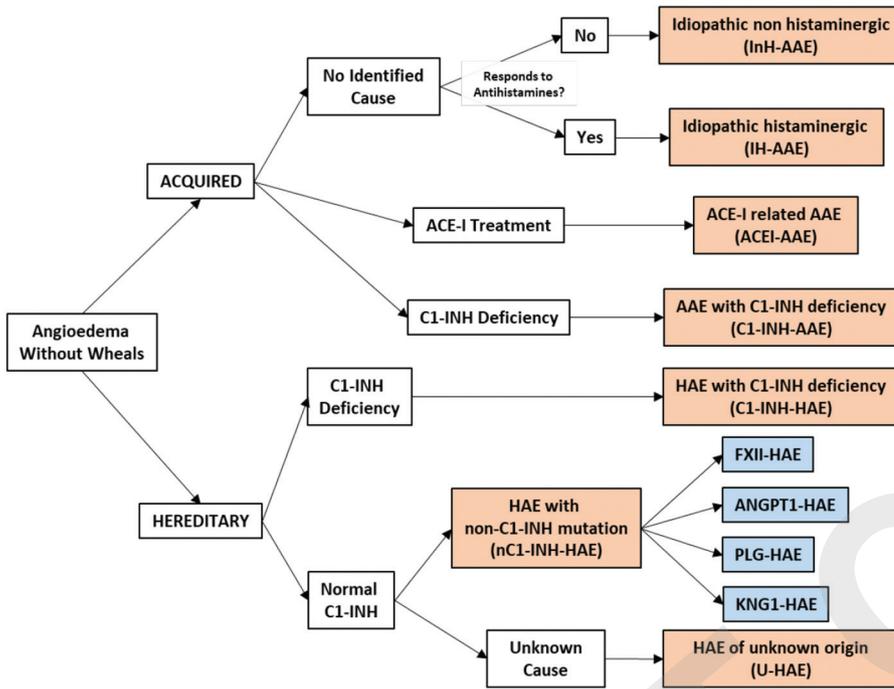
Figure 2. Specific classification of angio-edema without wheals, which has been modified to incorporate some of the newer known mutations in non–C1-esterase inhibitor forms of HAE (nC1-INH–HAE) (from Ref. 4).

2018, a family that exhibited a mutation in the gene encoding for *ANGPT1* was identified.[18] *ANGPT1* is important for endothelial function, and it is believed that the mechanism in *ANGPT1*-HAE likely involves disruption of endothelial integrity.[18] Also discovered that same year in families with HAE-normal-complement was a *PLG* gene mutation.[20] The mechanism responsible for *PLG*-HAE is believed to be related to the conversion of *PLG* to plasmin, which results in activation of a contact system as well as factor XII.[20] The latest of these HAE-normal-complement mutations was identified in 2019 in a single family with a pathologic variant of *KNG1*, which suggests that changes in the N-terminal cleavage site of kininogen could result in a more active protein.[19] Research is ongoing to better characterize the mechanisms that underlie these genetic mutations that lead to angioedema.

In summary, HAE can be classified by C1-INH with complement component testing, and genetic testing. Our understanding of HAE types 1 and 2 bradykinin-mediated forms of angioedema is reflected by the rapid development of effective therapies. In contrast, our understanding of HAE-normal-complement forms of angioedema is still slowly evolving, which is evident by current gaps in diagnosis and treatment.

Clinical Pearls

- HAE is caused by C1-INH deficiency due to a defect or mutation in *SERPING1.* A clear family history of angioedema in present in ~75% of cases of HAE due to C1-INH deficiency.

- Of patients with HAE, ~85% who have C1-INH–HAE have type 1, which is associated with a defect in the *SERPING1* gene, which results in decreased functional levels of normal C1-INH, whereas ~15% of patients with C1-INH–HAE have type 2, believed to be the result of a mutation at or near the active site of the reactive mobile loop of C1-INH, which results in a C1-INH protein lacking functional activity.

- All patients with recurrent angioedema or recurrent unexplained abdominal pain without urticaria and/or wheals should be screened for HAE with a C4 level and, if low, additional screening for C1-INH quantitative level and functional assay should be pursued. If there is a family history of angioedema, then a C1-INH quantitative level and functional assay should be obtained at the initial visit in conjunction with a C1q level.

- Rare forms of HAE-normal-complement that involve non–C1-INH genetic mutations involve *F12*, *ANGPT1*, *PLG*, and *KNG1* genes, although more may be identified.

- When a genetic cause is not identified for a patient with HAE-normal-complement in the presence of a family history, the patient is classified as HAE of unknown origin.

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