



Contents lists available at ScienceDirect



Review

Current update on cellular and molecular mechanisms of hereditary angioedema

Hannah H. Walford, MD^{*}; and Bruce L. Zuraw, MD^{*,†}^{*} Department of Medicine, University of California–San Diego, La Jolla, California[†] San Diego Veteran's Administration Healthcare, San Diego, California

ARTICLE INFO

Article history:

Received for publication August 12, 2013.

Received in revised form December 11, 2013.

Accepted for publication December 22, 2013.

ABSTRACT

Objective: To provide an update on the molecular mechanisms of hereditary angioedema (HAE).**Data Sources:** MEDLINE and PubMed databases were searched to identify pertinent articles using the following key terms: *hereditary angioedema, angioedema, C1 inhibitor, bradykinin, contact system, factor XII, mechanism, pathophysiology, severity, permeability, and estrogen*.**Study Selections:** Articles were selected based on their relevance to the subject matter.**Results:** Although the biochemical basis of “classic” HAE is known to result from C1 esterase inhibitor (C1INH) deficiency, a new form, HAE with normal C1INH, has been identified. HAE types I and II are caused by mutations in the *SERPING1* gene that result in decreased plasma levels of functional C1INH. In HAE with normal C1INH, mutations in the *F12* gene have been identified in a subset of individuals, but the genetic defect remains unknown in most patients. The primary mediator of swelling in HAE is bradykinin, a product of the plasma contact system that increases vascular permeability. HAE disease severity is highly variable and may be influenced by polymorphisms in other genes and other factors, such as hormones, trauma, stress, and infection.**Conclusions:** Hereditary angioedema is a heterogeneous disorder with a complex pathophysiology. Implicated genes include *SERPING1* and *FXII* in patients with HAE from C1INH deficiency and HAE with normal C1INH levels, respectively. Disease severity is highly variable.

© 2014 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Hereditary angioedema (HAE; OMIM 106100) is a rare life-threatening disorder characterized by recurrent episodes of angioedema localized to subcutaneous or mucosal tissues without associated pruritus or hives. Although first described clinically more than 130 years ago by Quincke and Osler,^{1,2} it was not until 1963 that the biochemical basis of “classic” HAE was defined by Donaldson and Evans³ as a deficiency in C1 esterase inhibitor (C1INH). Since that time, a growing body of scientific literature has provided further insight into the molecular mechanisms, genetic basis, and treatment of the disease. This article briefly summarizes the clinical features, diagnosis, and management of HAE, also reviewed elsewhere,^{4–9} with special emphasis on the current understanding of the disease mechanisms.

Clinical Summary

Hereditary angioedema can be broadly divided into 2 major categories: decreased and normal C1INH activities.⁶ HAE from

decreased C1INH (HAE-C1INH) can be subdivided into quantitative (type I) and qualitative (type II) defects in C1INH. Type I HAE represents approximately 85% of patients with HAE and is characterized by low antigenic and functional C1INH levels. Type II HAE represents approximately 15% of patients with HAE and is characterized by normal or elevated C1INH concentrations with low C1INH functional activity owing to the secretion of a dysfunctional protein. A distinct form of familial angioedema with normal C1INH protein and function has recently been identified.^{10,11} HAE with normal C1INH (HAE-nlC1INH) can be divided further into 2 subcategories: with *F12* mutation and of unknown cause.¹¹ The diagnosis of HAE-nlC1INH requires the demonstration of a lack of response to high-dose antihistamines plus a mutation in the *F12* gene (found in only a minority of patients) or a positive family history of angioedema.

Patients with HAE typically experience recurrent episodes of nonpitting, nonurticarial edema that commonly include tissues of the face, extremities, gastrointestinal and genitourinary tracts, and oropharynx and may include the hypopharynx and larynx.⁴ Typical attacks of HAE follow a predictable course, often preceded by a prodrome marked by an erythematous serpiginous rash (erythema marginatum) or sometimes fatigue, weakness, local discomfort, or a tingling sensation.¹³ Progressive swelling develops over hours and may start in one location and then spread to another before subsiding spontaneously after 2 to 5 days. Attacks may be disabling, with a substantial burden of disease and impact on quality of life;

Reprints: Bruce L. Zuraw, MD, 9500 Gilman Drive, Mailcode 0732, La Jolla, CA 92093-0732; E-mail: bzuraw@ucsd.edu.

Disclosures: Dr Zuraw has worked as a consultant or speaker for Dyax, CSL Behring, Isis, and BioCryst; received a grant from Shire; and served as chair and on the medical advisory board of the US Hereditary Angioedema Association.

Funding: This work was supported by Training Grant T32 AI 07469 from the National Institutes of Health.

Table 1

Complement levels and distinguishing features in the diagnosis of HAE

Type of angioedema	C1INH antigenic level	C1INH functional level	C4 level	C1q level	Distinguishing features
HAE-C1INH type I	low	low	low	normal	usually family history; young age of onset; angioedema of bowel frequent; may have prodrome of erythema marginatum; longer duration; unresponsive to antihistamines and corticosteroids
HAE-C1INH type II	normal	low	low	normal	same as HAE type I
HAE-nC1INH	normal	normal	normal	normal	usually family history; more severe in female patients; predilection for face, mouth, upper airway
Acquired C1INH deficiency	low	low	low	low	older age of onset; underlying lymphoproliferative disorder, malignancy, or C1INH autoantibody may be present
Idiopathic or allergic angioedema	normal	normal	normal	normal	may be accompanied by hives; typically responsive to antihistamines and corticosteroids
Angioedema from ACE inhibitor	normal	normal	normal	normal	typically within first 3 mo of medication use but may occur anytime; more often affects face, mouth, upper airway

Abbreviations: ACE, angiotensin-converting enzyme; C1INH, C1 esterase inhibitor; HAE, hereditary angioedema; HAE-C1INH, hereditary angioedema from decreased C1 esterase inhibitor activity; HAE-nC1INH, hereditary angioedema with normal C1 inhibitor.

and all patients with HAE are at risk for laryngeal attacks, which can be fatal if untreated.¹⁴ HAE attacks are often unpredictable, but known triggers include trauma, dental or surgical procedures, emotional or physical stress, menstruation, oral contraceptive use, or infection.¹⁵ Angiotensin-converting enzyme (ACE) inhibitors can worsen disease and are contraindicated.

The mean age of onset of symptoms in patients with HAE is 8 to 12 years. Untreated patients may have attacks every 7 to 14 days on average, but the frequency and severity of attacks can vary significantly between individuals and even within the same kindred.⁴ HAE attacks are classically distinguished from allergic or idiopathic angioedema by their longer duration (typically 72 to 96 hours), absence of accompanying urticaria, and failure to respond to antihistamine or corticosteroid therapy. Although HAE usually presents in childhood and progresses during puberty, there is often prolonged delay in diagnosis; therefore, it is important for clinicians to consider the disease in the differential diagnosis of episodic cutaneous or abdominal swelling.

The clinical characteristics of HAE-nC1INH are similar to those of HAE-C1INH, except that women appear to be more severely affected than men and these patients tend to experience fewer abdominal attacks and more cutaneous and facial swellings.¹²

The differential diagnosis of HAE and the distinguishing clinical and laboratory features are listed in Table 1 and have been recently reviewed elsewhere.^{4–9} All forms of HAE are inherited in an autosomal dominant pattern; however, a substantial minority of patients may present without a family history because of a *de novo* mutation and HAE-nC1INH has a significantly lower penetrance than HAE-C1INH.

Laboratory analysis of circulating complement components is a key diagnostic tool in the workup of angioedema and should begin with measurement of serum C4 levels, which will be low in cases of HAE-C1INH (types I and II) and acquired C1INH deficiency but normal in cases of allergic angioedema, ACE inhibitor–induced angioedema, HAE-nC1INH, and chronic idiopathic angioedema.⁷ Decreased C4 during an attack is found in nearly 100% of HAE-C1INH cases and, if normal, essentially rules out the diagnosis.¹⁶ Confirmation requires measurement of circulating antigenic or functional C1INH. If C1INH deficiency or dysfunction cannot be demonstrated but the clinical features are suggestive of HAE, genetic testing for *F12* mutation may be considered.⁴ In acquired C1INH deficiency, C1q levels are low in most cases, which differentiate it from HAE-C1INH. Acquired C1INH deficiency may develop from C1INH autoantibodies, underlying malignancy, or lymphoproliferative disorder.¹⁷

Hereditary angioedema is a complex, chronic disease requiring a highly specialized, multidisciplinary approach to care. Treatment of HAE has been revolutionized in the past 10 years with the development of multiple new drug therapies.⁷ The goal of HAE treatment should be to allow patients to achieve a normal life with minimal

disruption from acute attacks and minimal side effects. Treatment should consider not only aborting attacks but also preventing swelling in the short and long term. Tailored therapy for each patient requires the consideration of different factors, including frequency and severity of attacks, comorbid conditions, cost, patient preferences, and varying response to available treatments. The treatment of HAE has been recently reviewed.^{4–9} Given the complexity of therapeutic decisions and the high cost of the newer medicines, it is recommended that physicians with substantial experience dealing with HAE be involved in the management of these patients.

All patients with HAE should have an established action plan in place for treatment of attacks and effective drug therapy immediately available. C1INH concentrates, ecallantide, and icatibant have each been shown effective for the treatment of HAE attacks. Treatment should occur with early onset of symptoms and preferably be self-administered. Short-term prophylaxis can be achieved with the administration of 1,000 to 2,000 U of plasma-derived C1INH several hours before a scheduled surgical or dental procedure.⁷ Alternatively, 2 U of freshly frozen plasma may be used to prevent attacks of HAE when C1INH concentrates are not available. High-dose androgens given for a week in advance of a scheduled procedure also can be used for short-term prophylaxis. Because short-term prophylaxis is not always successful in preventing attacks, on-demand therapy also must be readily available during and after procedures.

The decision to use long-term prophylaxis should be based on attack frequency, attack severity, comorbid conditions, access to emergency treatment, and patient experience and preference.⁷ Before the approval of C1INH, 17 α -alkylated androgens and antifibrinolytics were used for HAE prophylaxis. Antifibrinolytics, including *ε*-aminocaproic acid and tranexamic acid, are not always effective in preventing angioedema episodes.^{7–18} Androgens are generally considered more efficacious than antifibrinolytics but are contraindicated in patients younger than 16 years, women who are pregnant or breastfeeding, and men with a history of prostate cancer.^{5,7} In addition, their use is limited by dose-dependent adverse side effects. Purified C1INH replacement therapy is highly effective for long-term prophylaxis. Because their use has been associated with adverse events,¹⁹ indwelling venous ports should be avoided.

Mechanisms of Disease

Determinants of C1INH Levels in HAE-C1INH

C1 esterase inhibitor, an α_2 globulin of approximately 105 kDa, is a member of the serine protease inhibitor (SERPIN) superfamily that also includes α_1 antitrypsin and antithrombin.²⁰ C1INH regulates different proteases, including C1r, C1s, mannose-binding lectin-associated serine protease-1 and -2, (MASP-1 and MASP-2) of the complement system; plasma kallikrein and activated factor XII

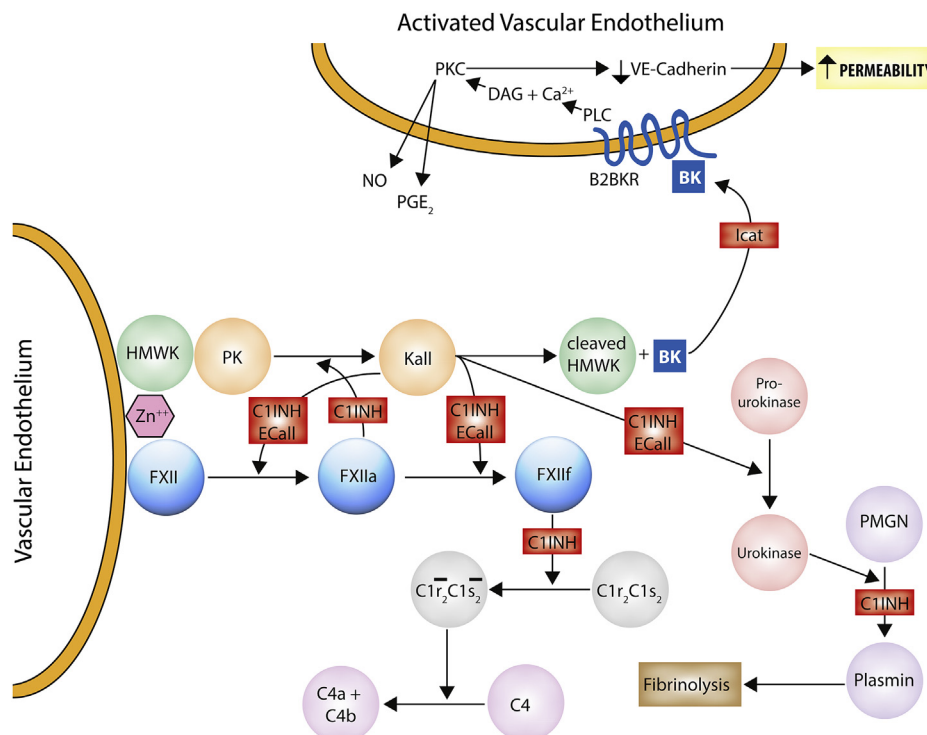


Figure 1. Contact system activation generates bradykinin, which acts on B2 bradykinin receptors to increase vascular permeability. Deficiency of C1INH also leads to activation of the complement and fibrinolytic systems. B2BKR, B2 bradykinin receptor; BK, bradykinin; C1INH, C1 esterase inhibitor; DAG, diacylglycerol; ECall, ecallantide; FXII, coagulation factor XII; FXIIa, factor XIIa; FXIIf, coagulation factor XII fragment; HMWK, high-molecular-weight kininogen; Icat, icatibant; Kall, plasma kallikrein; NO, nitric oxide; PGE₂, prostaglandin E₂; PK, plasma prekallikrein; PKC, protein kinase C; PLC, phospholipase; PMGN, plasminogen; VE-cadherin, vascular endothelial cell cadherin.

of the contact system; activated factor XI of the coagulation system; and plasmin of the fibrinolytic system (Fig 1). As a result, patients who are deficient in C1INH function exhibit evidence of continuous activation of the plasma complement, contact, and fibrinolytic systems. Functional C1INH levels are generally 5% to 30% of normal in HAE despite the presence of 1 functioning gene. Therefore, additional mechanisms must be at play to account for C1INH levels below 50% of normal.

Like other classic SERPINS, C1INH functions as a suicide inactivator in which 1 molecule of C1INH is consumed by forming an irreversible complex with 1 of its target proteases.²¹ Excessive activation of these proteases, particularly the contact system proteases, can result in cleavage of C1INH into an inactive fragment.²² These mechanisms would be expected to result in enhanced consumption of C1INH in cases in which there is evidence of excessive activation of its target proteases.²³ Evidence of increased clearance of radiolabeled normal C1INH injected into patients with HAE-C1INH has indeed been demonstrated.²⁴ In addition, there is evidence that mutated C1INH proteins may be capable of interfering with the biosynthesis or secretion of normal C1INH protein in the same cell through a process called *transinhibition*.²⁵

Genetics of HAE

Hereditary angioedema with decreased C1INH is fundamentally a consequence of a mutation in the gene encoding C1INH (*SERPING1*), which is located on chromosome 11 (11q12.1).²⁰ HAE-C1INH is inherited in an autosomal dominant; however, up to 25% of cases may be the result of *de novo* mutations.²⁶ With an estimated prevalence of approximately 1 in 50,000 in the general population, it appears to affect all ethnic groups equally. To date, more than 200 genetic mutations have been identified in the *SERPING1* gene, distributed across the entire gene.²⁷ Fewer than 20% of these mutations are large insertions or deletions, whereas the majority result

from missense, frameshift, nonsense, or splicing defects owing to changes in one or several base pairs. Patients with HAE-C1INH are almost always heterozygous for the *SERPING1* mutation. In rare cases of homozygous C1INH deficiency, clinical severity has been variable.^{28,29}

The structural consequences of the *SERPING1* mutation determine whether a patient develops type I or type II HAE.³⁰ Several mechanisms may interfere with secretion of the type I mutant protein, including nonsense or frameshift mutations that cause truncation of the protein or instability of the mRNA and missense mutations that affect protein folding and intracellular transport of the mutant C1INH protein.³¹ In type II HAE, mutations have been localized mostly to exon 8 near the Arg444 reactive site. The defective protease is secreted normally but cannot form complexes with proteases, which increases its half-life in the circulation.

Hereditary angioedema with normal C1INH is not associated with a mutation in *SERPING1*.¹⁰ Approximately 25% of European patients with HAE-nC1INH have been identified as having a mutation of the gene *F12* (chromosome 5q35.3) encoding coagulation factor XII (Hageman factor).⁶ The mutation is most often a threonine-to-lysine substitution (Thr328Lys) in exon 9, which is not associated with the proteolytic site of the coagulation factor XII protein.³² Although genetic studies have shown that the mutations co-sort with inheritance of the disease, the functional consequences of the *F12* mutations remain unknown. There have been very few reported cases of *F12* mutations in the United States.⁶ The genetic defects associated with HAE-C1INH and HAE-nC1INH are listed in Table 2.

Pathophysiology of Increased Vascular Permeability in HAE

To treat HAE appropriately, it is important to understand the underlying pathogenesis. Patients with HAE-C1INH exhibit

Table 2
Genetic defects associated with HAE

Disease	Mode of inheritance	Gene/locus	Encodes	Complement phenotype
HAE-C1INH	autosomal dominant with high penetrance	<i>SERPING1</i> , chromosome 11q12.1	C1INH	
Type I (85%)		large number of mutations throughout gene		C1INH protein and functional levels <50% normal, C4 low
Type II (15%)		missense mutations mostly within the mobile reactive loop		normal C1INH protein levels; C1INH functional levels <50% normal, C4 low
HAE-nC1INH	autosomal dominant with variable penetrance			normal C4, C1INH protein and functional levels
FXII (rare)		<i>F12</i> , chromosome 5q35.3; mutations in exon 9	coagulation factor XII	
Unknown (rare)		Unknown	unknown	

Abbreviations: ACE, angiotensin converting enzyme; C1INH, C1 esterase inhibitor; FXII, factor XII; HAE, hereditary angioedema; HAE-C1INH, hereditary angioedema from decreased C1 esterase inhibitor activity; HAE-nC1INH, hereditary angioedema with normal C1 inhibitor; SERPIN, serine protease inhibitor.

abnormalities in the regulation of the plasma complement, contact (kallikrein–kinin), fibrinolytic, and intrinsic coagulation systems.³³ A large body of studies has established that swelling in HAE-C1INH is a consequence of activation of the contact system, with the generation of bradykinin leading to increased vascular permeability (Fig 1).⁴ Circumstantial evidence also suggests that the swelling in HAE-nC1INH is from the generation of bradykinin.⁶ The diagnosis of HAE is dependent on complement measurements, and the pathogenesis of HAE swelling is dependent on the generation of bradykinin through contact system activation; therefore, these 2 pathways are described in more detail below.

Complement system

C1 esterase inhibitor is the main regulator of the early activation of the classic component pathway and may suppress spontaneous activation of C1. It is the only inhibitor of C1r and C1s in the classic pathway and inhibits MASP-1/2 in the lectin pathway.³³ These 2 complement pathways converge to activate complement components C4 and C2. In the absence of adequate C1INH levels, C1 auto-activates and subsequently activates C4 and C2, resulting in lower levels of C4 and C2. The early classic complement pathway is further activated during HAE attacks by the active coagulation factor XII fragment. Interestingly, MASP-1 has been reported to be capable of cleaving high-molecular-weight kininogen and releasing bradykinin, although the significance of this remains unclear.³⁴

Contact activation system

Bradykinin, generated from activation of the contact system, has been shown to be the primary mediator of swelling in HAE-C1INH.⁴ The major components of the contact system are coagulation factor XII, plasma prekallikrein, and high-molecular-weight kininogen. The cascade is initiated when membrane-bound coagulation factor XII auto-activates and is converted to factor XIIa, which then activates prekallikrein to kallikrein.³⁵ Active kallikrein efficiently activates additional coagulation factor XII in a positive feedback loop that results in rapid activation of the contact system in the absence of sufficient C1INH.³⁵ High-molecular-weight kininogen is digested by kallikrein, releasing bradykinin. Coagulation factor XII also is activated by plasmin, which is not thought to contribute significantly unless there is subnormal C1INH activity, as seen in HAE. The contact system also may be initiated through heat shock protein 90 or direct endothelial cell activation of circulating coagulation factor XII.³⁶ Recently, prekallikrein has been shown to have some proteolytic activity, which may become relevant in plasma that lacks sufficient C1INH activity.³⁷

Bradykinin induces angioedema through binding to G-protein–coupled bradykinin receptors expressed on the endothelial cell membrane. Mammalian bradykinin receptors are classified as types B1 and B2.³⁸ The bradykinin B1 receptor is an inducible receptor with slow agonist desensitization, whereas the B2 receptor

is constitutively expressed with rapid agonist desensitization. Bradykinin receptor subtypes can be distinguished by their natural ligands: B1 is preferentially bound by the carboxypeptidase degradation product, des-Arg bradykinin, and B2 by bradykinin. Although the bradykinin B2 receptor appears to mediate most of the bradykinin effects in HAE, some evidence suggests a possible additional role for the bradykinin B1 receptor.³⁹ Activation of the B2 bradykinin receptor enhances vascular permeability in significant part by leading to phosphorylation, internalization, and cleavage of vascular endothelial cadherin, the major protein of the endothelial adherens junction that regulates fluid movement across the barrier.⁴⁰ Bradykinin also stimulates production of the vasodilator nitric oxide and actin–cytoskeleton contraction. These events lead to movement of fluid from the vascular space into the interstitial compartment, which results in the tissue swelling characteristic of HAE.

Bradykinin also is presumed to cause the angioedema in HAE-nC1INH, although the evidence for this is indirect and inconclusive. Antihistamines and corticosteroids consistently fail to alter the swelling in HAE-nC1INH, and there are anecdotal reports that the drugs used to treat HAE-C1INH also work in HAE-nC1INH.⁶ Because factor XII is a major component of the contact system, *F12* mutations have been suggested to result in enhanced contact system activation. *F12* mutations in HAE-nC1INH have involved the proline-rich region of coagulation factor XII rather than its C-terminal catalytic protease domain.⁴¹ This proline-rich region may play a role in the binding of coagulation factor XII to negatively charged surfaces.⁴²

Additional Parameters Affecting Disease Severity

Regulation of the bradykinin B2 receptor and peptidases that degrade bradykinin may influence HAE disease severity. Lung et al⁴³ reported that HAE-C1INH clinical severity may be influenced by genetic polymorphisms in the noncoding first exon of the bradykinin B2 receptor that affects the receptor activity, although a subsequent study failed to observe this pattern in a different cohort of HAE patients.⁴⁴ However, other groups subsequently published evidence that polymorphisms in the bradykinin B2 receptor gene have a modifying role in the expression of other disorders, such as hypertension and ischemic heart disease.^{45,46}

Bradykinin is catabolized by different peptidases (also called *kininases*), the most important of which is ACE.³⁸ Other important peptidases involved in the metabolism of bradykinin include aminopeptidase P (APP), carboxypeptidase N, neutral endopeptidase, and dipeptidyl peptidase IV. Decreasing the activity of these peptidases, as seen when using an ACE inhibitor, results in decreased catabolism and therefore a longer half-life of bradykinin, resulting in potential worsening of HAE. Patients on ACE inhibitors who develop angioedema have been shown to have decreased

levels of APP, and this may be due to polymorphisms in the promoter region of the *XPNPPE2* gene.⁴⁷ In turn, treatment of HAE with danazol has been shown to increase APP levels.⁴⁸ This suggests that long-term prophylaxis with androgens may decrease HAE attacks in part by increasing the breakdown of bradykinin. Binkley and Davis¹⁰ reported on a family with HAE-nlC1INH in which affected members experienced angioedema in a strictly estrogen-dependent manner. Genetic analysis of the affected individuals showed a mutation in the *F12* gene and 2 kininase polymorphisms, an ACE insertion polymorphism and an APP regulatory polymorphism, either of which can result in decreased kininase activity.⁴⁹

Role of Estrogens

The role of estrogens in women with HAE is well documented but poorly understood. Estrogens have different effects on the kallikrein–kinin system that can increase bradykinin generation and effects. Increased plasma coagulation factor XII levels have been observed in women treated with estrogens.⁵⁰ The promoter region of the *F12* gene contains an estrogen-response element, and estrogens have been shown to increase transcription of coagulation factor XII mRNA.⁵¹ Estrogens also may contribute to the regulation of bradykinin B2 receptor expression. B2 receptor expression in the rat uterus varied during the estrous cycle, increasing at times of high estrogen exposure and decreasing at times of low estrogen exposure.⁵² In female rats, ovariectomy led to a decreased vaso-depressor response to bradykinin and decreased B2 receptor mRNA expression in the aorta and kidneys.⁵³ The vasodilatory effect and the B2 receptor expression were restored with estrogen replacement. In addition, the hypotensive effect of captopril in female rats was more pronounced in the presence of 17 β -estradiol.⁵⁴ Moreover, this effect was attenuated by the blockade of bradykinin B2 receptors or by the inhibition of nitric oxide synthesis, suggesting that bradykinin and nitric oxide are likely involved in the potentiating effect of ACE inhibitors by estrogen.

Clinical observations have repeatedly noted estrogen-mediated worsening of angioedema in most women with HAE, including HAE-C1INH and HAE-nlC1INH.⁵⁵ This estrogen-mediated worsening of disease is seen most clearly in women treated with exogenous estrogen but is sometimes seen during periods of high endogenous estrogen levels. Conversely, androgens have long been established as effective long-term prophylaxis in HAE. The phenomenon by which estrogens provoke angioedema attacks is likely the result of hormonal regulation of the kallikrein–kinin pathway and bradykinin B2 receptor expression and function, but further studies are needed to understand the exact mechanism in human subjects.

Conclusion

Although a great deal is known about the biochemical basis of C1INH deficiency, it is evident that HAE is a heterogeneous disorder with complex biologic and genetic bases of disease. The new classification of HAE-nlC1INH has been defined, with a growing body of knowledge identifying the underlying genetic defects. It is important for clinicians to be able to recognize when to screen for HAE and to distinguish it from other more common forms of angioedema. An understanding of the disease has led to the development and implementation of some innovative and effective therapies for patients, thereby vastly improving treatment options and patient quality of life. Nonetheless, further work is clearly needed to improve the diagnosis and treatment of HAE-nlC1INH. Identification of the molecular mechanisms influencing disease severity and elucidation of the underlying pathophysiology of HAE-nlC1INH should lead to more effective and better-targeted management of HAE in the future.

References

- Quincke HI. Über akutes umschriebenes Hautödem [About an acute described skin edema]. *Monatshe Prakt Dermatol*. 1882;1:129–131.
- Osler W. Hereditary angio-neurotic oedema. *The American Journal of the Medical Sciences*. 1888;95:362–367.
- Donaldson VH, Evans RR. A biochemical abnormality in hereditary angio-neurotic edema: absence of serum inhibitor of C'1- esterase. *Am J Med*. 1963; 35:37–44.
- Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med*. 2008;359: 1027–1036.
- Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy*. 2012;67:147–157.
- Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. *Allergy Asthma Proc*. 2012;33(suppl 1):S145–S156.
- Zuraw BL, Bernstein JA, Lang DM, et al. A focused parameter update: Hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol*. 2013;131:1491–1493.e25.
- Craig T, Pursun EA, Bork K, et al. WAO guideline for the management of hereditary angioedema. *World Allergy Organ J*. 2012;5:182–199.
- Lang DM, Aberer W, Bernstein JA, et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol*. 2012;109: 395–402.
- Binkley KE, Davis A III. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol*. 2000;106:546–550.
- Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet*. 2000;356:213–217.
- Bork K. Diagnosis and treatment of hereditary angioedema with normal C1 inhibitor. *Allergy Asthma Clin Immunol*. 2010;6:15.
- Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med*. 1976;84:586–593.
- Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol*. 2012;130:692–697.
- Longhurst H, Cicardi M. Hereditary angio-oedema. *Lancet*. 2012;379: 474–481.
- Zuraw BL, Sugimoto S, Curd JG. The value of rocket immunoelectrophoresis for C4 activation in the evaluation of patients with angioedema or C1-inhibitor deficiency. *J Allergy Clin Immunol*. 1986;78:1115–1120.
- Zingale LC, Castelli R, Zanichelli A, Cicardi M. Acquired deficiency of the inhibitor of the first complement component: presentation, diagnosis, course, and conventional management. *Immunol Allergy Clin North Am*. 2006;26: 669–690.
- Frank MM. Hereditary angioedema: the clinical syndrome and its management in the United States. *Immunol Allergy Clin North Am*. 2006;26:653–668.
- Yoo SM, Khan DA. Implantable venous access device associated complications in patients with hereditary angioedema. *J Allergy Clin Immunol*. 2013;1: 524–525.
- Davis AE III, Lu F, Mejia P. C1 inhibitor, a multi-functional serine protease inhibitor. *Thromb Haemost*. 2010;104:886–893.
- Lomas DA, Belorgey D, Mallya M, et al. Molecular mousetraps and the serpinopathies. *Biochem Soc Trans*. 2005;33:321–330.
- Zuraw BL, Curd JG. Demonstration of modified inactive first component of complement (C1) inhibitor in the plasmas of C1 inhibitor-deficient patients. *J Clin Invest*. 1986;78:567–575.
- Lachmann PJ, Rosen FS. The catabolism of C1-inhibitor and the pathogenesis of hereditary angio-edema. *Acta Pathol Microbiol Scand*. 1984;92:35–39.
- Quastel M, Harrison R, Cicardi M, Alper CA, Rosen FS. Behavior in vivo of normal and dysfunctional C1 inhibitor in normal subjects and patients with hereditary angioneurotic edema. *J Clin Invest*. 1983;71:1041–1046.
- Kramer J, Rosen FS, Colten HR, Rajczy K, Strunk RC. Transinhibition of C1 inhibitor synthesis in type I hereditary angioneurotic edema. *J Clin Invest*. 1993;91:1258–1262.
- 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.
- Pappalardo E, Caccia S, Suffritti C, Tordai A, Zingale LC, Cicardi M. Mutation screening of C1 inhibitor gene in 108 unrelated families with hereditary angioedema: functional and structural correlates. *Mol Immunol*. 2008;45: 3536–3544.
- Blanch A, Roche O, Urrutia I, Gamboa P, Fontan G, Lopez-Trascasa M. First case of homozygous C1 inhibitor deficiency. *J Allergy Clin Immunol*. 2006;118: 1330–1335.
- Lopez-Lera A, Favier B, de la Cruz RM, Garrido S, Drouet C, Lopez-Trascasa M. A new case of homozygous C1-inhibitor deficiency suggests a role for Arg378 in the control of kinin pathway activation. *J Allergy Clin Immunol*. 2010;126: 1307–1310.e3.
- Zuraw BL, Herschbach J. Detection of C1 inhibitor mutations in patients with hereditary angioedema. *J Allergy Clin Immunol*. 2000;105:541–546.
- Verpy E, Couture-Tosi E, Eldering E, Lopez-Trascasa M, Spath P. Crucial residues in the carboxy-terminal end of C1 inhibitor revealed by pathogenic mutants impaired in secretion or function. *J Clin Invest*. 1995;95:350–359.

- [32] Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun*. 2006;343:1286–1289.
- [33] Davis AE III. Mechanism of angioedema in first complement component inhibitor deficiency. *Immunol Allergy Clin North Am*. 2006;26:633–651.
- [34] Dobo J, Major B, Kekesi KA, et al. Cleavage of kininogen and subsequent bradykinin release by the complement component: mannose-binding lectin-associated serine protease (MASP)-1. *PLoS One*. 2011;6:e20036.
- [35] Kaplan AP. Enzymatic pathways in the pathogenesis of hereditary angioedema: the role of C1 inhibitor therapy. *J Allergy Clin Immunol*. 2010;126:918–925.
- [36] Kaplan AP, Joseph K. The bradykinin-forming cascade and its role in hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104:193–204.
- [37] Joseph K, Tholanikunnel BG, Bygum A, Ghebrehiwet B, Kaplan AP. Factor XII-independent activation of the bradykinin-forming cascade: Implications for the pathogenesis of hereditary angioedema types I and II. *J Allergy Clin Immunol*. 2013;132:470–475.
- [38] Leeb-Lundberg LM, Marceau F, Muller-Esterl W, Pettibone DJ, Zuraw BL. International Union of Pharmacology. XLV. Classification of the kinin receptor family: from molecular mechanisms to pathophysiological consequences. *Pharmacol Rev*. 2005;57:27–77.
- [39] Bossi F, Fischetti F, Regoli D, et al. Novel pathogenic mechanism and therapeutic approaches to angioedema associated with C1 inhibitor deficiency. *J Allergy Clin Immunol*. 2009;124:1303–1310.e4.
- [40] Bouillet L, Mannic T, Arboleas M, et al. Hereditary angioedema: key role for kallikrein and bradykinin in vascular endothelial-cadherin cleavage and edema formation. *J Allergy Clin Immunol*. 2011;128:232–234.
- [41] Bork K, Wulff K, Meinke P, Wagner N, Hardt J, Witzke G. A novel mutation in the coagulation factor 12 gene in subjects with hereditary angioedema and normal C1-inhibitor. *Clin Immunol*. 2011;141:31–35.
- [42] Citarella F, Misiti S, Felici A, Farsetti A, Pontecorvi A, Fantoni A. Estrogen induction and contact phase activation of human factor XII. *Steroids*. 1996;61:270–276.
- [43] Lung CC, Chan EKL, Zuraw BL. Analysis of an exon 1 polymorphism of the B2 bradykinin receptor gene and its transcript in normal subjects and C1 inhibitor deficient patients. *J Allergy Clin Immunol*. 1997;99:134–146.
- [44] Freiberger T, Vyskocilova M, Kolarova L, et al. Exon 1 polymorphism of the B2BKR gene does not influence the clinical status of patients with hereditary angioedema. *Hum Immunol*. 2002;63:492–494.
- [45] Brull D, Dhamrait S, Myerson S, et al. Bradykinin B2BKR receptor polymorphism and left-ventricular growth response. *Lancet*. 2001;358:1155–1156.
- [46] Van Guilder GP, Pretorius M, Luther JM, et al. Bradykinin type 2 receptor BE1 genotype influences bradykinin-dependent vasodilation during angiotensin-converting enzyme inhibition. *Hypertension*. 2008;51:454–459.
- [47] Cilia La Corte AL, Carter AM, Rice GI, et al. A functional XPNPEP2 promoter haplotype leads to reduced plasma aminopeptidase P and increased risk of ACE inhibitor-induced angioedema. *Hum Mutat*. 2011;32:1326–1331.
- [48] Drouet C, Desormeaux A, Robillard J, et al. Metalloproteinase activities in hereditary angioedema: effect of androgen prophylaxis on plasma aminopeptidase P. *J Allergy Clin Immunol*. 2008;121:429–433.
- [49] Duan QL, Binkley K, Rouleau GA. Genetic analysis of Factor XII and bradykinin catabolic enzymes in a family with estrogen-dependent inherited angioedema. *J Allergy Clin Immunol*. 2009;123:906–910.
- [50] Campbell SJ, Mackie IJ, Robinson GE, Machin SJ. Contact factor mediated fibrinolysis is increased by the combined oral contraceptive pill. *Br J Obstet Gynaecol*. 1993;100:79–84.
- [51] Farsetti A, Misiti S, Citarella F, et al. Molecular basis of estrogen regulation of Hageman factor XII gene expression. *Endocrinology*. 1995;136:5076–5083.
- [52] Murone C, Chai SY, Muller-Esterl W, Mendelsohn FA, Clements J. Localization of bradykinin B2 receptors in the endometrium and myometrium of rat uterus and the effects of estrogen and progesterone. *Endocrinology*. 1999;140:3372–3382.
- [53] Madeddu P, Emanuelli C, Song Q, et al. Regulation of bradykinin B2-receptor expression by oestrogen. *Br J Pharmacol*. 1997;121:1763–1769.
- [54] Gimenez J, Garcia MP, Serna M, et al. 17Beta-oestradiol enhances the acute hypotensive effect of captopril in female ovariectomized spontaneously hypertensive rats. *Exp Physiol*. 2006;91:715–722.
- [55] Bork K. Hereditary angioedema with normal c1 inhibitor. *Immunol Allergy Clin North Am*. 2013;33:457–470.