

Angioedema Due to Bradykinin Dysregulation



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Learning objectives:

1. To understand the pathophysiology of bradykinin-mediated angioedema.
2. To recognize how angioedema is classified on the basis of underlying mechanisms.
3. To diagnose patients who present with bradykinin-mediated angioedema.

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Angioedema is an acute swelling of the deeper layers of the skin or mucosa resulting from a transient increase in vascular permeability. Angioedema can occur in the absence or presence of hives, be hereditary or acquired, and be caused by various potential mediators, including histamine and bradykinin. Bradykinin-mediated angioedema can be difficult to diagnose but is responsible for a disproportionate percentage of the serious

morbidity and mortality associated with angioedema. Our understanding of the basic biology of angioedema has dramatically expanded over recent years. The classification of angioedema has correspondently undergone major changes. Optimal management of patients with angioedema requires that an accurate diagnosis be established and that treatment be tailored to the patient's specific form of angioedema. In this article, we review the biology of bradykinin-mediated angioedema as well as the clinical approach to the evaluation of angioedema with a focus on bradykinin-mediated angioedema. Recognizing how the underlying pathophysiology and mechanisms of bradykinin dysregulation contribute to angioedema can help guide the clinical approach to the patient. © 2018 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2018;6:1132-41)

Key words: Angioedema; Hereditary angioedema; Acquired angioedema; Bradykinin; Histamine; C1 inhibitor; Angiotensin-converting enzyme inhibitor

INTRODUCTION

Angioedema is a consequence of transiently increased vascular permeability that can occur in various disorders. To successfully manage patients with angioedema, the clinician must understand

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Abbreviations used

AAE- Acquired angioedema
ACE- Angiotensin-converting enzyme
ACEI- ACE inhibitor
ANGPT1- Angiotensin-1
ARB- Angiotensin receptor blocker
BDKRB1- Bradykinin B1 receptor
BDKRB2- Bradykinin B2 receptor
C1INH- C1 inhibitor
DPPIV- Dipeptidyl peptidase IV
FXII- Coagulation factor XII
HAE- Hereditary angioedema
HAE-ANGPT1- HAE associated with ANGPT1 mutation
HAE-C1INH- HAE due to a deficiency in C1INH function
HAE-FXII- HAE associated with F12 mutation
HAE-nl-C1INH- HAE with normal C1INH
HAE-PLG- HAE associated with PLG mutation
HMWK- High-molecular-weight kininogen
LMWK- Low-molecular-weight kininogen
PLG- Plasminogen
VE-cadherin- Vascular-endothelial cadherin

the underlying pathophysiology of angioedema and be able to tailor the treatment to the correct and specific disorder. At least 4 different mediators have been linked to angioedema: histamine, bradykinin, substance P, and leukotrienes. Histamine and bradykinin are the best-documented mediators of angioedema. However, distinguishing bradykinin-mediated angioedema from histamine-mediated angioedema remains the most important and frequent dilemma faced by the clinician during an evaluation of angioedema.

Although less common than histamine-mediated angioedema, bradykinin-mediated angioedema is responsible for a disproportionate percentage of the serious morbidity and mortality associated with angioedema. Over the last decade, a number of specific and effective medications have been developed to treat bradykinin-mediated angioedema. Therefore, correctly diagnosing bradykinin-mediated angioedema is a key step toward preventing morbidity and mortality and optimizing patient outcomes when treating patients with recurrent angioedema.

In this article, we will review the pertinent aspects of bradykinin-mediated angioedema, including the underlying pathophysiology, how bradykinin dysregulation may contribute to swelling, and the diagnostic approach. Current treatment options for bradykinin-mediated angioedema have been recently reviewed.¹⁻⁴ Although some of the diagnostic and therapeutic tools are limited to specialized centers, all physicians who diagnose angioedema must be familiar with bradykinin-mediated angioedema and be able to recognize when to refer these patients to a specialized center.

NOMENCLATURE OF ANGIOEDEMA

The many forms of angioedema require some precision in the nomenclature to avoid causing confusion. Angioedema must be clearly distinguished from wheals or hives. Angioedema that occurs independently from hives is referred to as primary angioedema, a term that recognizes that even a patient with hereditary angioedema (HAE) can experience hives under certain conditions. The diagnosis of HAE must also distinguish whether the angioedema is associated with a C1 inhibitor (C1INH) deficiency. HAE due to a deficiency in C1INH

function is often called HAE-C1INH, whereas HAE with normal C1INH is often called HAE-nl-C1INH. There are minor differences in the exact lexicon of angioedema; for instance, the Gargagno consensus article⁵ uses the terms C1INH-HAE and nl-C1INH-HAE, but these differences are minor and readily understood. It is, however, crucial to appreciate that the term “type III HAE” is obsolete and misleading, and so should not be used.

GENERATION AND CATABOLISM OF BRADYKININ

Bradykinin and its related kinins are small peptides with pleiotropic biologic effects, including vascular effects of dilatation and enhanced permeability. Kinins are generated from cleavage of kininogen, a large plasma protein that contains bradykinin. The protease releasing kinin from kininogen is called kallikrein. There are 2 distinct kinin-generating systems: the plasma contact system and the tissue kallikrein system.

Plasma contact system

The plasma contact system consists of 3 plasma proteins: coagulation factor XII (FXII), plasma prekallikrein, and high-molecular-weight kininogen (HMWK) (Figure 1).⁶⁻⁸ When activated, the zymogens FXII and plasma prekallikrein reciprocally cleave each other to generate the active proteases FXIIa and plasma kallikrein. Plasma kallikrein then cleaves HMWK, releasing bradykinin. Plasma kallikrein can also cleave FXIIa, releasing a smaller active protease FXIIf (aka β FXIIa), which can activate the classical complement pathway. Plasma kallikrein, FXIIa, and FXIIf are inhibited by C1INH, the protein that is deficient in type I and type II HAE.

The contact system is activated *ex vivo* by contact with negatively charged surfaces, notably glass, kaolin, celite, and dextran sulfate.^{9,10} In *in vivo* activation, components of the contact system assemble on the surface of endothelial cells in a zinc-dependent manner.¹¹ The physiologic activators of the contact system are unknown but have been suggested to include nucleosomes,¹² extracellular nucleic acids,¹³ platelet-derived inorganic polyphosphate,¹⁴ pathogen-released long polyphosphates,¹⁵ aggregated or misfolded proteins,^{16,17} mast cell heparin,^{18,19} and endotoxin.²⁰ In addition, plasmin has been reported to be capable of activating the contact system,^{21,22} whereas the lectin complement pathway protease MASP-1 has been reported to be capable of directly cleaving HMWK and generating bradykinin.²³

Tissue kallikrein system

The tissue kallikrein system consists of a large family of tissue kallikreins, which are not closely related to plasma kallikrein.²⁴ Most tissue kallikreins cannot generate kinins. Tissue kallikrein type I, however, can cleave low-molecular-weight kininogen (LMWK), releasing Lys-bradykinin. LMWK is an alternatively spliced product of the same gene that codes for HMWK. Lys-bradykinin is identical to bradykinin except for a lysine residue at its N-terminus and has essentially the same biologic effects. Importantly, tissue kallikrein is not regulated by C1INH,^{25,26} and there is no evidence that this pathway contributes to angioedema.

Bradykinin catabolism

Bradykinin is catabolized by various peptidases (also called kininases), of which the most important is angiotensin-converting

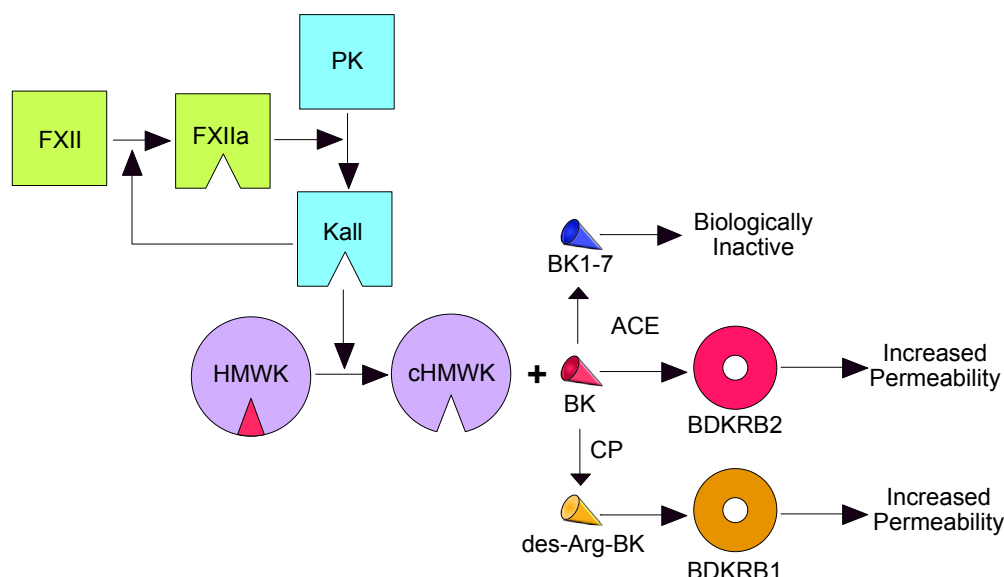


FIGURE 1. Generation, action, and catabolism of bradykinin in angioedema. Schematic of contact system activation with generation of bradykinin, which induces angioedema by binding to bradykinin receptors. BK, bradykinin; cHMWK, cleaved HMWK; CP carboxypeptidase; Kall, kallikrein; PK, prekallikrein.

enzyme (ACE; kinase II) (Figure 1).²⁷ Other important peptidases involved include aminopeptidase P, carboxypeptidase N, carboxypeptidase M, neutral endopeptidase, and dipeptidyl peptidase IV (DPPIV). Cleavage of the C-terminal arginine of bradykinin or Lys-bradykinin by carboxypeptidase generates des-Arg-bradykinin or des-Arg-Lys-bradykinin, respectively. Under normal conditions, the half-life of bradykinin in plasma is measured in seconds.

BRADYKININ RECEPTORS IN ANGIOEDEMA

Kinins transduce their biologic effects through 2 separate G protein-coupled kinin receptors: bradykinin B2 receptor (BDKRB2) and bradykinin B1 receptor (BDKRB1) (Figure 1). These receptors are located at adjacent loci on chromosome 14q32.2, but demonstrate many structural and functional differences.²⁷ Bradykinin and Lys-bradykinin bind to and activate the BDKRB2, which is constitutively expressed on many cells including endothelial cells.²⁷ Once activated, the BDKRB2 is rapidly desensitized and downregulated.²⁷

The agonists for the BDKRB1 are des-Arg-bradykinin and des-Arg-Lys-bradykinin, which are generated by cleavage of the C-terminal arginine from bradykinin or Lys-bradykinin by carboxypeptidase. In contrast to the BDKRB2, the BDKRB1 is not expressed in normal tissue, but is rapidly induced by various inflammatory stimuli. Unlike the BDKRB2, the BDKRB1 signals in a constitutively active manner, which is amplified by binding to its agonists. A final important functional distinction between the kinin receptors is that the BDKRB1 is only slowly and partially desensitized and downregulated after binding to its agonist.²⁷

Kinin receptors and angioedema

Both kinin receptors are capable of increasing vascular permeability; however, the BDKRB2 has generally been

considered to be the major kinin receptor responsible for bradykinin-mediated angioedema attacks. This assumption is based on several considerations: (1) endothelial cells constitutively express BDKRB2 but not BDKRB1; (2) the des-Arg metabolite of bradykinin has been reported to be a poor ligand for the cloned human BDKRB1²⁷; (3) although des-Arg-Lys-bradykinin is a potent agonist for the human BDKRB1, there is no evidence that it is generated during angioedema attacks; and (4) treatment with a specific BDKRB2 antagonist abrogates both the increased vascular permeability seen in a murine model of C1INH deficiency²⁸ and attacks in patients with HAE.²⁹

Although there is strong evidence supporting a key role for the BDKRB2, several lines of evidence point to the possibility that the BDKRB1 may play a role in angioedema.³⁰ The relatively long course of swelling in HAE relative to other forms of angioedema is difficult to reconcile with the rapidly attenuating signaling from the BDKRB2. This has led to the suggestion that prolonged signaling from the BDKRB1 plays a role in sustaining the swelling during episodes of bradykinin-mediated angioedema.³⁰ To signal, however, the BDKRB1 must be expressed, and the BDKRB1 is not expressed in normal tissue. It appears likely that local BDKRB1 expression is upregulated during attacks of angioedema. *Ex vivo* induction of BDKRB1 in cultured endothelial cells by plasma obtained from patients with HAE during an attack supports a role for this receptor in angioedema.³¹ Furthermore, signaling through the BDKRB2 itself has been shown to induce expression of the BDKRB1.³² It is also interesting to consider whether stress, trauma, or infection upregulates BDKRB1 and influences susceptibility to swelling. Finally, although des-Arg-bradykinin has virtually no effect on cloned BDKRB1, evidence suggests that it may have biologically relevant effects on human BDKRB1 *in vivo*.^{33,34} Taken together, the role of the BDKRB1 in bradykinin-mediated angioedema is uncertain but worthy of further research.

EFFECT OF BRADYKININ ON VASCULAR PERMEABILITY

Angioedema results from a transient increase in vascular permeability that is largely determined by the pore size between endothelial cells, and is normally tightly controlled through the dynamic opening and closing of interendothelial junctions.³⁵ An increase in the pore size allows fluid to move more freely across the endothelial barrier, from the higher pressure vascular space into the lower pressure interstitial space. Once in the interstitial space, the fluid must be resorbed, which is a slower process typically mediated through the lymphatic drainage.

The major junctional component limiting permeability outside of the central nervous system is the adherens junction, which maintains the permeability barrier through homotypic associations between transmembrane vascular-endothelial cadherin (VE-cadherin) molecules.³⁶ Signaling cascades downstream from the kinin receptors phosphorylate VE-cadherin as well as its associated intracellular catenins, resulting in internalization and degradation of VE-cadherin and contraction of the actin cytoskeleton.³⁷ These changes increase the effective pore size and the permeability. Signaling from kinin receptors also stimulates the release of the vasodilator nitric oxide, contributing to endothelial dysfunction and enhanced vascular permeability.³⁸

Four different genes have been identified as responsible for HAE.³⁹⁻⁴³ The common denominator for these 4 genes is the possibility to amplify the vasopermeabilizing effect of bradykinin. Other genes may influence angioedema phenotypes reducing bradykinin catabolism.^{44,45} The network providing genetic control of vasopermeability is just emerging. Large-scale, in-depth genetic studies may elucidate unmet aspects of angioedema pathogenesis and heterogeneity.⁴⁶

BRADYKININ DYSREGULATION IN ANGIOEDEMA

The nature of the bradykinin dysfunction that results in angioedema varies among the different angioedema types (Figure 2). The potential causes of bradykinin dysregulation in angioedema due to C1INH deficiency, HAE-nl-C1INH, and ACE inhibitor (ACEI)-associated angioedema are briefly described herein. Although each of these forms of angioedema is thought to be bradykinin-mediated, the strength of the supporting evidence is markedly different.

Bradykinin dysregulation in C1INH deficiency

Type I and type II HAE. Studies in the early 1960s established that the fundamental defect in type I and type II HAE was a deficiency of functional C1INH.^{47,48} In the case of type I HAE, C1INH protein levels are low, whereas type II HAE is associated with normal or near-normal C1INH protein levels but reduced C1INH function due to a dysfunctional protein.⁴⁹ Subsequent studies proved that type I and type II HAE resulted from mutations in the gene encoding C1INH, *SERPING1*.^{39,50} Type I C1INH mutant proteins are not properly secreted, leading to low plasma levels.⁵¹ The *SERPING1* mutations associated with type II HAE were found to largely cluster around the active inhibitory site, leading to a secreted protein that was incapable of inhibiting its target proteases.

Acquired C1INH deficiency. Unlike type I or type II HAE, acquired C1INH deficiency is not associated with

SERPING1 mutations. Instead, C1INH is secreted normally in these patients, but it is catabolized at a rate faster than it can be synthesized. In most patients with acquired C1INH deficiency, the increased catabolism of C1INH appears to result from an autoantibody against C1INH, an underlying malignancy, or both.⁵²

C1INH deficiency leads to excessive activation of the contact system. C1INH regulates various serine proteases, including early proteases of the classical and lectin complement systems (C1r, C1s, MASP1, and MASP2), contact system protease (plasma kallikrein, FXIIa, and FXIIf), coagulation factor XIa, and plasminogen.⁵³ In the absence of sufficient functional C1INH, these proteases may not be adequately regulated. Although some *ex vivo* studies pointed toward a permeability-enhancing factor released from C2 (C2-kinin), no evidence for *in vivo* generation of C2-kinin has ever been found and some studies have questioned the accuracy of the original C2-kinin results.⁵⁴ In contrast, multiple studies have documented enhanced activation of the contact system with generation of bradykinin in C1INH-deficient patients.⁵⁴⁻⁵⁸

Bradykinin dysregulation in HAE-nl-C1INH

In 2000, Binkley and Davis⁵⁹ and Bork et al⁶⁰ described an unexpected form of HAE characterized by normal C1INH antigenic and functional levels. Several features suggested that HAE-nl-C1INH, like HAE-C1INH, might be bradykinin-mediated, including the lack of response to antihistamines, corticosteroids, and epinephrine as well as the favorable response to medications targeting the bradykinin pathway.

The evidence linking HAE-nl-C1INH with bradykinin is not as strong as that for HAE-C1INH. A breakthrough came in 2006 with the finding that a minority of these patients had a mutation in exon 9 of the *F12* gene.^{41,61} This form of HAE-nl-C1INH is now classified as HAE-FXII. More recently, mutations in the genes for plasminogen (*PLG*)⁴² and angiopoietin-1 (*ANGPT1*)⁴³ have been found in some patients with HAE-nl-C1INH (HAE-PLG and HAE-ANGPT1, respectively). The possible mechanism of bradykinin dysregulation in each of these is described herein.

The most common form of HAE-FXII, p.Thr309Lys, was recently shown to cause enhanced susceptibility of the contact system to become activated *ex vivo* and *in vivo*.⁶² The *F12* mutations associated with HAE-FXII were also shown to enhance susceptibility of FXII to activation by plasmin,⁶³ providing a potential explanation for the efficacy of anti-fibrinolytic medications in the treatment of HAE-nl-C1INH, including HAE-FXII.

The mechanism of angioedema in patients with the recently described HAE-PLG is not yet known. However, considering the putative role of plasmin in HAE-FXII, an early target of investigation will be the ability of the mutant plasmin protease to activate the contact system.

The p.Ala119Ser mutation associated with HAE-ANGPT1 was shown to interfere with the ability of mutant *ANGPT1* to assume a multimeric form, which is the most efficient ligand for the Tie2 receptor.⁴³ Because Tie2 signaling has been shown to decrease susceptibility to enhanced vascular permeability, this mutation may put patients at greater risk of developing angioedema from multiple mediators, including bradykinin.

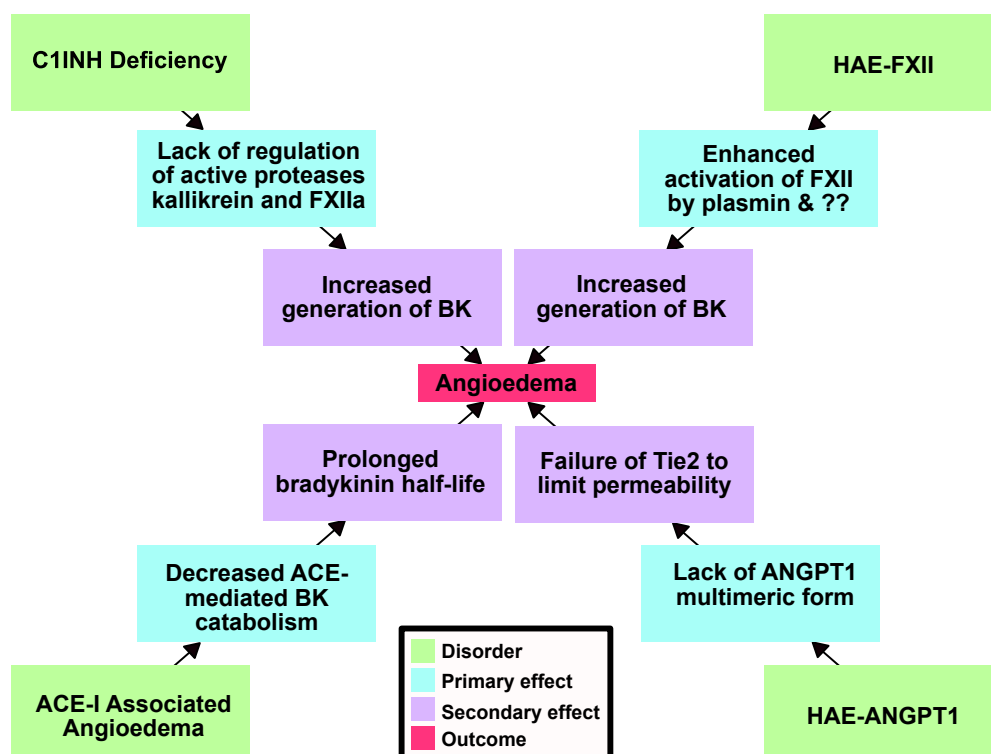


FIGURE 2. Mechanism of bradykinin dysregulation in angioedema. The primary effects, secondary effects, and outcomes of dysregulation are shown for C1INH deficiency, HAE-FXII, ACEI-associated angioedema, and HAE-ANGPT1.

Bradykinin dysregulation in ACEI-associated angioedema

The antihypertensive effect of ACEIs stems from the physiological role of ACE in cleaving the biologically inactive peptide angiotensin I into the biologically active peptide angiotensin II, which binds and activates the angiotensin I receptor causing vasoconstriction.⁶⁴ By inhibiting the conversion of angiotensin I to angiotensin II, ACEIs lower blood pressure and reduce some pathologic vascular outcomes. Like most peptidases, ACE is promiscuous and cleaves other peptides, including bradykinin. ACE is the primary peptidase responsible for inactivation of bradykinin. ACEIs block the inactivation of bradykinin by ACE, resulting in a longer half-life of bradykinin and potentially enhancing its biologic activity and ability to induce angioedema. ACE also degrades substance P, and inhibition of this activity may also contribute to ACEI-associated angioedema.⁶⁵

APPROACH TO ANGIOEDEMA DIAGNOSIS

Quincke,⁶⁶ in his study “On acute circumscribed cutaneous edema,” gave the first comprehensive description of angioedema as a condition that primarily affects the skin, but may involve the oral mucosa with the possibility to reach the larynx “up to creating severe respiratory problems.” Through the thoughtful observation of a patient with angioedema who had abdominal symptoms, he speculated, “... it is possible that also the mucosa of the stomach and of the bowel could present circumscribed swellings.” In 2008, a capsule endoscopy performed in a patient with HAE-C1INH showed that abdominal symptoms in this patient developed from the obstruction of the bowel, secondary to the swelling of the mucosa.⁶⁷ Going back to the article by

Quincke, he failed in differentiating angioedema from wheals. Today we know that both originate from an increase in permeability of the skin vessels, with angioedema located in the deep layers and wheals in the superficial ones.⁶⁸ The different anatomical location accounts for redness, warmth, and edema demarcation present in wheals and minimal or absent in angioedema. Distinguishing whether angioedema takes place with or without wheals is the first critical step to framing patients with “acute circumscribed edema.”

Angioedema without wheals (primary angioedema)

When angioedema occurs either simultaneously or alternating with wheals, we are in the field of urticaria either induced or spontaneous. However, angioedema without wheals stands as a separate nosologic entity, here identified as primary angioedema. The first classification of primary angioedema was given in 2014 and distinguished 4 acquired angioedema (AAE) types and 3 HAE types (Figure 3).⁵ Aside from distinguishing hereditary and acquired forms, it is crucial to separate angioedema induced by a mast cell mediator from angioedema induced by another principal mediator, such as bradykinin. So far, presence or absence of a response to chronic treatment with antihistamines separates the 2 angioedema forms, named histaminergic and nonhistaminergic.

Histaminergic/mast cell–induced angioedema

Histamine is abundant in mast cell granules, and histaminergic angioedema is mast cell–induced.⁶⁹ This represents the most common form of primary angioedema, accounting for about 70% of cases in a specialized angioedema center.⁷⁰ Nevertheless, a criterion restricting the term histaminergic to

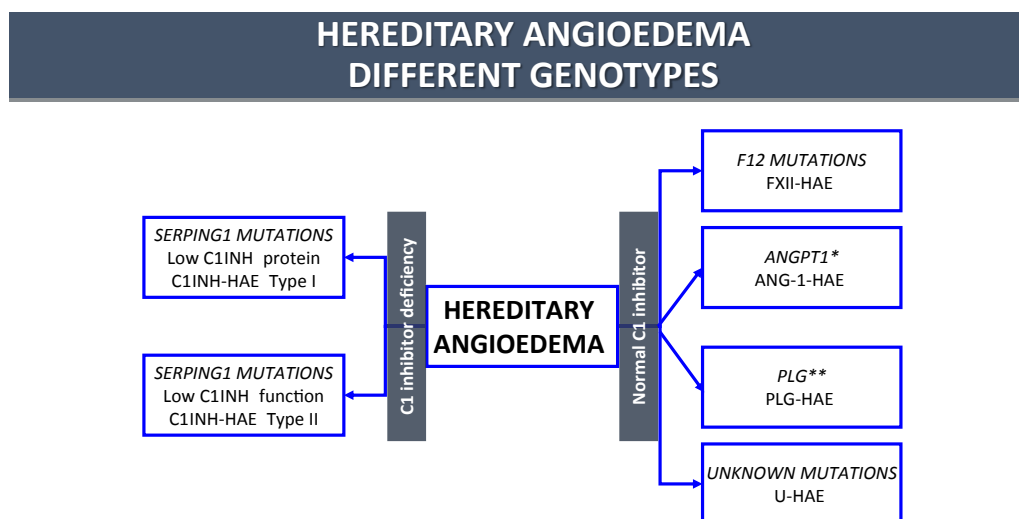


FIGURE 3. Genetic and biochemical abnormalities in HAE.

antihistamine-responsive angioedema excludes from the group types of angioedema that very likely are mast cell–induced, such as those responding to corticosteroids or prevented by omalizumab.⁷¹ Separating mast cell–induced and non–mast cell–induced angioedema is crucial for therapeutic approach, but criteria for these categories remain unclear.⁷² The main problem is defining the response to corticosteroid treatment. The risk/benefit balance of long-term corticosteroids to prevent angioedema is highly questionable, and we have no studies to support this as a criterion. Similarly, using the response to treatment with corticosteroids during attacks would require controlled trials, but these have never been done or seriously contemplated. Although nobody questions the real-life evidence that most angioedema attacks respond to these agents, too many unassessable variables intervene to translate this evidence into a classification criterion.

The clinical features that characterize angioedema induced by mast cells reveal similarities with wheals, including pruritus, erythema, demarcation, eyelid location, and evolution frequently within 24 hours.⁷³ The pathophysiology of histaminergic angioedema looks identical to IgE-mediated allergic reactions with the exclusive but relevant difference, which is the absence of a specific causative factor.⁷⁴

Non–mast cell–induced/bradykinin-induced angioedema

Unifying features in primary angioedema not induced by mast cells first emerge from the clinical presentation that completely loses urticaria-like characteristics.

Angioedema with C1INH deficiency. The prototypes of non–mast cell–induced angioedema are those due to C1INH deficiency. The cutaneous symptoms affect the limbs far more often than the face and they usually last 48 hours or longer.⁷⁵ The redness of vasodilation is not discernable as well as the distinct boundary between swollen and normal skin. Abdominal symptoms occur in more than 90% of the affected subjects and they recur with a frequency similar to that of cutaneous attacks.⁷⁶ Temporary bowel occlusion results in pain, vomiting, diarrhea, dehydration, and even circulatory collapse. The severity

of these symptoms frequently leads undiagnosed patients to unnecessary surgery. Even after diagnosis of C1INH deficiency, distinguishing angioedema from other conditions with acute abdominal pain remains a challenge for emergency departments.⁷⁷ In the absence of precise markers, response to specific angioedema treatment remains the major tool guiding differential diagnosis. The most serious manifestation of this form of angioedema is laryngeal involvement. In 50% of these patients, it occurs at least once in life and accounts for 5% of all angioedema episodes.⁷⁸ In our series of patients with HAE-C1INH, we estimated laryngeal angioedema to be the cause of death in nearly 50% of patients who died without an established diagnosis.⁷⁹ In a series of 983 patients diagnosed with HAE-C1INH in Italy between 1973 and 2015, 63 died, 5 of them from laryngeal edema.⁸⁰ In a study on 182 families with HAE-C1INH, detailed clinical information was available for 728 members, 514 of whom were alive and 214 of whom had died.⁸¹ Among the 13 patients who had a diagnosis of HAE-C1INH at the time of death, 7 died from laryngeal edema. Thus, diagnosis is the first step, but does not *per se* guarantee that there will be no HAE-C1INH-related fatalities.

The diagnosis of HAE-C1INH requires documentation, in the proband or in the family, of angioedema symptoms associated with plasma levels of C1INH less than 50% of normal values. Ninety-six percent of patients with this diagnosis also have plasma levels of C4 less than 50% of normal values. Normal C4 has high negative predicting value for the diagnosis of HAE-C1INH.⁸⁰ The global distribution of HAE-C1INH does not significantly vary with ethnicity or racial characters. Country data indicate HAE-C1INH to have minimum prevalence of 1:64,000.⁸⁰ Two phenotypic variants of HAE-C1INH are recognized: type 1, where C1INH antigen and function are both markedly reduced, and type 2, where C1INH function is reduced, but antigenic levels are in the normal range for the presence of a dysfunctional protein.⁴⁹ No clinical differences are associated with these variants.

Deficiency of C1INH can also be acquired. This diagnosis is made in the absence of a family history of angioedema and of deficiency of C1INH. In the acquired form, symptoms start after

the fourth decade of life,⁸² and patients with AAE-C1INH frequently present low levels of C1q and autoantibodies to C1INH.⁸³ Thirty percent of these patients have non-Hodgkin B-cell lymphoma that seems to cause the consumption of C1INH.^{84,85}

HAE-C1INH results from mutations in *SERPING1*, but the diagnosis does not require genetic testing. Of the 400 *SERPING1* variants resulting in amino acid change, only 1 is associated with normal phenotype.⁸⁶ Relatively few (5%-10%) patients with HAE-C1INH have no detectable pathogenetic variant in the C1INH gene (*SERPING1*).⁸⁷⁻⁸⁹ These variants most commonly derive from point mutations, rarely recur in different families, and represent *de novo* mutations in 25% of index cases.⁹⁰ Their penetrance approaches 100% for biochemical phenotype. Five percent of adults with the biochemical phenotype in families with C1INH-HAE are asymptomatic,⁷⁹ suggesting high penetrance for the clinical phenotype but with variable degrees of severity.^{89,91} The different genotypes only marginally explain this variability.⁹¹ We recently described a woman with genetic C1INH deficiency and no angioedema in her personal and familial history.⁹² The *SERPING1* variant in this woman was identical to the one found in the first patient reported to have homozygous C1INH deficiency. This patient was symptomatic for angioedema, but his heterozygous relatives were not.⁹³ These findings suggest that along with the common dominant pattern, rare HAE-C1INH variant(s) may have low penetrance reminiscent of a recessive character.

Angioedema with normal C1INH. When we exclude that angioedema is induced by mast cells, that there is no C1INH deficiency, and that the patient is not on an ACEI, we are into the group of angioedema with normal C1INH. Patients in this group have HAE if they present a family history of angioedema or 1 of the known HAE-related genetic variants. If there is no angioedema in the family and no genotypic variants, they have AAE. The clinical features of HAE and AAE with normal C1INH are very similar to each other and to that of C1INH deficiency. In a survey of 94 patients with HAE or AAE with normal C1INH, the only difference in clinical presentation was the presence of abdominal symptoms, which was higher in HAE.⁷⁰ Inside the hereditary forms, analysis of the differences has been conducted, distinguishing patients with HAE with and without specific mutations in the *F12* gene.⁹⁴ The main finding is a sex-related difference in the clinical expression. Angioedema-specific *F12* variants have autosomal-dominant transmission, but male carriers almost never express angioedema symptoms.⁹⁵ Furthermore, increases in estrogen levels, whether physiologic or drug-induced, are a potent trigger of angioedema. It is not uncommon that women with this form of angioedema experience symptoms only during pregnancy or estrogen-treatment.^{59,96} Excluding patients with HAE-FXII, there are 3 other recognized forms of HAE-nl-C1INH: the largest, where genetic etiology remains unknown, and the 2 recently described genotypes involving *ANGPT1* and *PLG* genes.^{42,43} The number of patients in the last 2 groups is still too small to elaborate on internal differences.

ACEI-associated/drug-related angioedema. The rapid and large expansion of ACEI for the treatment of hypertension made clear, within a few years after their introduction, that these drugs facilitated the appearance of angioedema, mainly of the lips

and tongue.⁹⁷ Involvement of the larynx with fatalities was also possible.^{65,98,99} Angioedema occurs in less than 1% of all ACEI-treated patients and the risk is higher in women and in blacks.¹⁰⁰⁻¹⁰³ There is no genetic transmission of this form of angioedema, which belongs to AAE, but there is a genetic predisposition likely caused by specific polymorphisms in bradykinin-degrading enzymes.^{44,45} AAE-ACEI differs from other drug-induced angioedema for absence of a relationship between exposure to the drug and appearance of angioedema.⁴⁵ ACEIs facilitate accumulation of bradykinin and therefore act as facilitators of angioedema in a manner repeating C1INH deficiency that facilitates bradykinin release without causing angioedema *per se*. AAE-ACEI is defined as an angioedema that develops during ACEI treatment, and it may start years after the initiation of treatment in absence of other predisposing factors. After the first episode, recurrences occur with different frequencies and severities.⁵ Drug withdrawal stops or drastically reduces angioedema in most patients, but 25% of them continue having recurrences.¹⁰⁴ This finding reinforces the evidence that patients with AAE-ACEI carry established conditions leading to accumulate bradykinin for factors other than ACEI treatment. Why these conditions remain clinically silent before ACEI is unclear.

The possibility that other drugs affecting bradykinin metabolism induce angioedema is highly debated. Angiotensin receptor blockers (ARBs) and other renin-targeted agents are frequently considered to significantly increase the risk of angioedema. There is no evidence that these drugs modify the levels of bradykinin *in vivo*. Data from clinical trial looking at angioedema as a side effect did not confirm that ARBs have significant risk.¹⁰² Case reports associating angioedema with ARBs do not provide definitive evidence.¹⁰⁵⁻¹⁰⁷ Further data are needed to conclude on the risk of angioedema with ARBs.

Alogliptin, an inhibitor of the bradykinin-degrading enzyme DPPIV, is a class of relatively new oral hypoglycemic drugs used in patients with type 2 diabetes.¹⁰⁸ Environmental or genetic factors that reduce DPPIV activity may predispose individuals to angioedema and their use may increase risk.^{108,109} Available evidence confirms an increased risk of angioedema when alogliptin is associated with concomitant ACEIs, but not when used in absence of other angioedema-predisposing factors.¹¹⁰ Inhibitors of neprilysin, a neutral endopeptidase that degrades bradykinin and natriuretic peptides, have been developed on the premise of potential efficacy in the treatment of hypertension and heart failure. Omapatrilat, a dual inhibitor of ACE and neprilysin, was tested versus enalapril alone for efficacy in reducing blood pressure.¹¹¹ In this study, omapatrilat provided broadly superior antihypertensive efficacy, but higher rate of angioedema (2.17% vs 0.68%). Quantification of the risk/benefit ratio hampered its approval.¹¹² In contrast, the combination of the neprilysin inhibitor sacubitril with valsartan (an ARB instead of an ACEI) was approved and is now on the market for heart failure.¹¹³ Present evidence suggests a rate of angioedema for the sacubitril/valsartan combination similar to ACEIs, but future trials and post-market surveillance are critical to understand such risk better.¹¹⁴

CONCLUSIONS

Angioedema was identified at the end of the 19th century. From the first descriptions it has been seen in 2 separate forms: as

a symptom of urticaria and allergic reactions or as a rare genetic disease. Today we recognize primary angioedema as a group of diseases where angioedema stands as a major feature in the absence of urticaria. Genetic conditions, specific therapies, and yet undefined mechanisms create environments where recurrences of the Quincke's acute circumscribed edema, the same that we now call angioedema, develop upon minimum stimuli or spontaneously. The pathophysiology of angioedema has been unraveled enough to provide therapies that in 10 years completely changed the life of patients with HAE.¹¹⁵ Here we did not touch upon the topic of angioedema treatment because it is already covered by a huge amount of literature and excellent recent review articles. However, the present treatment of primary angioedema has a major drawback of being restricted to HAE-C1INH. Development of adequate therapeutic approaches for other forms is the future challenge.

REFERENCES

- Bork K. A decade of change: recent developments in pharmacotherapy of hereditary angioedema (HAE). *Clin Rev Allergy Immunol* 2016;51:183-92.
- Frank MM, Zuraw B, Banerji A, Bernstein JA, Craig T, Busse P, et al. Management of children with hereditary angioedema due to C1 inhibitor deficiency. *Pediatrics* 2016;138. pii: e20160575.
- Farkas H, Martinez-Saguer I, Bork K, Bowen T, Craig T, Frank M, et al. International consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency. *Allergy* 2017;72:300-13.
- Magerl M, Germent AE, Maas C, Maurer M. Hereditary angioedema with normal C1 inhibitor: update on evaluation and treatment. *Immunol Allergy Clin North Am* 2017;37:571-84.
- Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy* 2014;69:602-16.
- Kerbrin DM, Griffin JH. Human high molecular weight kininogen: studies of structure-function relationships and of proteolysis of the molecule occurring during contact activation of plasma. *J Biol Chem* 1979;254:12020-7.
- Cochrane CG, Griffin JH. The biochemistry and pathophysiology of the contact system of plasma. *Adv Immunol* 1982;33:241-306.
- Colman RW, Schmaier AH. Contact system: a vascular biology modulator with anticoagulant, profibrinolytic, antiadhesive, and proinflammatory attributes. *Blood* 1997;90:3819-43.
- Ratnoff OD, Rosenblum JM. Role of Hageman factor in the initiation of clotting by glass: evidence that glass frees Hageman factor from inhibition. *Am J Med* 1958;25:160-8.
- Ratnoff OD, Pensky J, Ogston D, Naff GB. The inhibition of plasmin, plasma kallikrein, plasma permeability factor, and the C'1r subcomponent of the first component of complement by serum C'1 esterase inhibitor. *J Exp Med* 1969;129:315-31.
- Schmaier AH, Kuo A, Lundberg D, Murray S, Cines DB. The expression of high molecular weight kininogen on human umbilical vein endothelial cells. *J Biol Chem* 1988;263:16327-33.
- von Bruhl ML, Stark K, Steinhart A, Chandraratne S, Konrad I, Lorenz M, et al. Monocytes, neutrophils, and platelets cooperate to initiate and propagate venous thrombosis in mice in vivo. *J Exp Med* 2012;209:819-35.
- Kannemeyer C, Shibamiya A, Nakazawa F, Trusheim H, Ruppert C, Markart P, et al. Extracellular RNA constitutes a natural procoagulant cofactor in blood coagulation. *Proc Natl Acad Sci U S A* 2007;104:6388-93.
- Muller F, Mutch NJ, Schenk WA, Smith SA, Esterl L, Spronk HM, et al. Platelet polyphosphates are proinflammatory and procoagulant mediators in vivo. *Cell* 2009;139:1143-56.
- Puy C, Tucker EI, Wong ZC, Gailani D, Smith SA, Choi SH, et al. Factor XII promotes blood coagulation independent of factor XI in the presence of long-chain polyphosphates. *J Thromb Haemost* 2013;11:1341-52.
- Maas C, Govers-Riemsag JW, Bouma B, Schiks B, Hazenberg BP, Lokhorst HM, et al. Misfolded proteins activate factor XII in humans, leading to kallikrein formation without initiating coagulation. *J Clin Invest* 2008;118:3208-18.
- Shibayama Y, Joseph K, Nakazawa Y, Ghebrehewet B, Peerschke EI, Kaplan AP. Zinc-dependent activation of the plasma kinin-forming cascade by aggregated beta amyloid protein. *Clin Immunol* 1999;90:89-99.
- Oschatz C, Maas C, Lecher B, Jansen T, Bjorkqvist J, Tradler T, et al. Mast cells increase vascular permeability by heparin-initiated bradykinin formation in vivo. *Immunity* 2011;34:258-68.
- Brunnee T, Reddigari SR, Shibayama Y, Kaplan AP, Silverberg M. Mast cell derived heparin activates the contact system: a link to kinin generation in allergic reactions. *Clin Exp Allergy* 1997;27:653-63.
- Morrison DC, Cochrane CG. Direct evidence for Hageman factor (factor XII) activation by bacterial lipopolysaccharides (endotoxins). *J Exp Med* 1974;140:797-811.
- Donaldson VH, Rosen FS, Bing DH. Role of the second component of complement (C2) and plasmin in kinin release in hereditary angioneurotic edema (H.A.N.E.) plasma. *Trans Assoc Am Physicians* 1977;40:174-83.
- Kleniewski J, Blankenship DT, Cardin AD, Donaldson V. Mechanism of enhanced kinin release from high molecular weight kininogen by plasma kallikrein after its exposure to plasmin. *J Lab Clin Med* 1992;120:129-39.
- Dobo J, Major B, Kekesi KA, Szabo I, Megyeri M, Hajela K, 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.
- Kalinska M, Meyer-Hoffert U, Kantyka T, Potempa J. Kallikreins: the melting pot of activity and function. *Biochimie* 2016;122:270-82.
- Christiansen SC, Zuraw BL, Proud D, Cochrane CG. Inhibition of human bronchial kallikrein in asthma. *Am Rev Respir Dis* 1989;139:1125-31.
- Christiansen SC, Proud D, Cochrane CG. Detection of tissue kallikrein in the bronchoalveolar lavage fluid of asthmatic subjects. *J Clin Invest* 1987;79:188-97.
- 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.
- Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE III. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest* 2002;109:1057-63.
- Cicardi M, Banerji A, Bracho F, Malbran A, Rosenkranz B, Riedl M, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med* 2010;363:532-41.
- Hofman ZLM, Relan A, Zeerleeder S, Drouet C, Zuraw BL, Hack E. Angioedema attacks of hereditary angioedema: local manifestations of a systemic activation process. *J Allergy Clin Immunol* 2016;138:359-66.
- Bossi F, Fischetti F, Regoli D, Durigutto P, Frossi B, Gobeil J Jr, et al. Novel pathogenic mechanism and therapeutic approaches to angioedema associated with C1 inhibitor deficiency. *J Allergy Clin Immunol* 2009;124:1303-1310.e4.
- Christiansen SC, Eddleston J, Woessner KM, Chambers SS, Ye R, Pan ZK, et al. Up-regulation of functional kinin B1 receptors in allergic airway inflammation. *J Immunol* 2002;169:2054-60.
- Aptekar E, Lecorvoisier P, Teiger E, Garot P, Dupouy P, Sediame S, et al. Coronary vasomotor response to the selective B1-kinin-receptor agonist Des-Arg9-bradykinin in humans. *J Heart Lung Transplant* 2006;25:187-94.
- Wu H, Roks AJ, Leijten FP, Garrelts IM, Musterd-Bhagoo UM, van den Bogaert AJ, et al. Genetic variation and gender determine bradykinin type I receptor responses in human tissue: implications for the ACE-inhibitor-induced effects in patients with coronary artery disease. *Clin Sci (Lond)* 2014;126:441-9.
- Komarova Y, Malik AB. Regulation of endothelial permeability via paracellular and transcellular transport pathways. *Annu Rev Physiol* 2010;72:463-93.
- Dejana E, Giampietro C. Vascular endothelial-cadherin and vascular stability. *Curr Opin Hematol* 2012;19:218-23.
- Dejana E, Tournier-Lasserre E, Weinstein BM. The control of vascular integrity by endothelial cell junctions: molecular basis and pathological implications. *Dev Cell* 2009;16:209-21.
- Vanhoutte PM, Zhao Y, Xu A, Leung SW. Thirty years of saying no: sources, fate, actions, and misfortunes of the endothelium-derived vasodilator mediator. *Circ Res* 2016;119:375-96.
- Stoppa Lyonnet D, Tosi M, Laurent J, Sobel A, Lagrue G, Meo T. Altered C1 inhibitor genes in type I hereditary angioedema. *N Engl J Med* 1987;317:1-6.
- Cicardi M, Igarashi T, Kim MS, Frangi D, Agostoni A, Davis AE III. Restriction fragment length polymorphism of the C1 inhibitor gene in hereditary angioneurotic edema. *J Clin Invest* 1987;80:1640-3.
- 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;343:1286-9.
- Bork K, Wulff K, Steinmuller-Magin L, Braenne I, Staubach-Renz P, Witzke G, et al. Hereditary angioedema with a mutation in the plasminogen gene. *Allergy* 2018;73:442-50.

43. Bafunno V, Firinu D, D'Apollito M, Cordisco G, Loffredo S, Leccese A, et al. Mutation of the angiotensin-converting enzyme 1 gene (ANGPT1) associates with a new type of hereditary angioedema. *J Allergy Clin Immunol* 2018;141:1009-17.
44. Duan QL, Nikpoor B, Dube MP, Molinaro G, Meijer IA, Dion P, et al. A variant in XPNPEP2 is associated with angioedema induced by angiotensin I-converting enzyme inhibitors. *Am J Hum Genet* 2005;77:617-26.
45. Pare G, Kubo M, Byrd JB, McCarty CA, Woodard-Grice A, Teo KK, et al. Genetic variants associated with angiotensin-converting enzyme inhibitor-associated angioedema. *Pharmacogenet Genomics* 2013;23:470-8.
46. Germeis AE, Speletas M. Genetics of hereditary angioedema revisited. *Clin Rev Allergy Immunol* 2016;51:170-82.
47. Landerman NS, Webster ME, Becker EL, Ratcliffe HE. Hereditary angioneurotic edema, II: deficiency of inhibitor for serum globulin permeability factor and/or plasma kallikrein. *J Allergy* 1962;33:330-41.
48. Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C'1-esterase. *Am J Med* 1963;35:37-44.
49. Rosen FS, Pensky J, Donaldson V, Charache P. Hereditary angioneurotic edema: two genetic variants. *Science* 1965;148:957-8.
50. Cicardi M, Igarashi T, Rosen FS, Davis AE III. Molecular basis for the deficiency of complement 1 inhibitor in type I hereditary angioneurotic edema. *J Clin Invest* 1987;79:698-702.
51. Kramer J, Katz Y, Rosen FS, Davis AE III, Strunk RC. Synthesis of C1 inhibitor in fibroblasts from patients with type I and type II hereditary angioneurotic edema. *J Clin Invest* 1991;87:1614-20.
52. Cugno M, Castelli R, Cicardi M. Angioedema due to acquired C1-inhibitor deficiency: a bridging condition between autoimmunity and lymphoproliferation. *Autoimmun Rev* 2008;8:156-9.
53. Davis AE III, Lu F, Mejia P. C1 inhibitor, a multi-functional serine protease inhibitor. *Thromb Haemost* 2010;104:886-93.
54. Fields T, Ghebrehwet B, Kaplan AP. Kinin formation in hereditary angioedema plasma: evidence against kinin derivation from C2 and in support of "spontaneous" formation of bradykinin. *J Allergy Clin Immunol* 1983;72:54-60.
55. Schapira M, Silver LD, Scott CF, Schmaier AH, Prograis LJ, Curd JG, et al. Prekallikrein activation and high-molecular-weight kininogen consumption in hereditary angioedema. *N Engl J Med* 1983;308:1050-4.
56. Lammle B, Zuraw BL, Heeb MJ, Schwarz HP, Berrettini M, Curd JG, et al. Detection and quantitation of cleaved and uncleaved high molecular weight kininogen in plasma by ligand blotting with radiolabeled plasma prekallikrein or factor XI. *Thromb Haemost* 1988;59:151-61.
57. Berrettini M, Lammle B, White T, Heeb MJ, Schwarz HP, Zuraw B, et al. Detection of in vitro and in vivo cleavage of high molecular weight kininogen in human plasma by immunoblotting with monoclonal antibodies. *Blood* 1986;68:455-62.
58. Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. *Lancet* 1998;351:1693-7.
59. Binkley KE, Davis A III. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol* 2000;106:546-50.
60. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 2000;356:213-7.
61. Cichon S, Martin L, Hennies HC, Muller F, Van Driessche K, Karpushova A, et al. Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. *Am J Hum Genet* 2006;79:1098-104.
62. Björkqvist J, de Maat S, Lewandowski U, Di Gennaro A, Oschatz C, Schonig K, et al. Defective glycosylation of coagulation factor XII underlies hereditary angioedema type III. *J Clin Invest* 2015;125:3132-46.
63. de Maat S, Björkqvist J, Suffritti C, Wiesnekker CP, Nagtegaal W, Koekman A, et al. Plasmin is a natural trigger for bradykinin production in patients with hereditary angioedema with factor XII mutations. *J Allergy Clin Immunol* 2016;138:1414-23.
64. Taddei S, Bortolotto L. Unraveling the pivotal role of bradykinin in ACE inhibitor activity. *Am J Cardiovasc Drugs* 2016;16:309-21.
65. Byrd JB, Adam A, Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am* 2006;26:725-37.
66. Quincke H. Über akutes umschriebenes Hautödem. *Monatsh Prakt Dermatol* 1882;1:129-31.
67. Cicardi M, Zingale L, Zanichelli A. Resolution of bowel obstruction in a patient with hereditary angioedema treated with DX-88 (Ecallantide), a potent human plasma kallikrein inhibitor: a case study. *Mol Immunol* 2007;44:160.
68. Sheffer AL, Craig JM, Willms-Kretschmer K, Austen KF, Rosen FS. Histopathological and ultrastructural observations on tissues from patients with hereditary angioneurotic edema. *J Allergy* 1971;47:292-7.
69. Kaplan AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol* 2004;114:465-74.
70. Mansi M, Zanichelli A, Coerezza A, Suffritti C, Wu MA, Vacchini R, et al. Presentation, diagnosis and treatment of angioedema without wheals: a retrospective analysis of a cohort of 1058 patients. *J Intern Med* 2015;277:585-93.
71. Faisant C, Du Thanh A, Mansard C, Deroux A, Boccon-Gibod I, Bouillet L. Idiopathic non-histaminergic angioedema: successful treatment with omalizumab in five patients. *J Clin Immunol* 2017;37:80-4.
72. Craig T, Pursun EA, Bork K, Bowen T, Boysen H, Farkas H, et al. WAO guideline for the management of hereditary angioedema. *World Allergy Organ J* 2012;5:182-99.
73. Faisant C, Boccon-Gibod I, Mansard C, Dumestre Perard C, Pralong P, Chatain C, et al. Idiopathic histaminergic angioedema without wheals: a case series of 31 patients. *Clin Exp Immunol* 2016;185:81-5.
74. Kaplan AP, Greaves MW. Angioedema. *J Am Acad Dermatol* 2005;53:373-88.
75. Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med* 2006;119:267-74.
76. Bork K, Staubach P, Eckardt AJ, Hardt J. Symptoms, course, and complications of abdominal attacks in hereditary angioedema due to C1 inhibitor deficiency. *Am J Gastroenterol* 2006;101:619-27.
77. Bernstein JA, Cremonesi P, Hoffmann TK, Hollingsworth J. Angioedema in the emergency department: a practical guide to differential diagnosis and management. *Int J Emerg Med* 2017;10:15.
78. Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med* 2008;359:1027-36.
79. Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 1992;71:206-15.
80. Zanichelli A, Arcoleo F, Barca MP, Borrelli P, Bova M, Cancian M, et al. A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy. *Orphanet J Rare Dis* 2015;10:11.
81. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol* 2012;130:692-7.
82. Gelfand JA, Boss GR, Conley CL, Reinhart R, Frank MM. Acquired C1 esterase inhibitor deficiency and angioedema: a review. *Medicine* 1979;58:321-8.
83. Zanichelli A, Azin GM, Wu MA, Suffritti C, Maggioni L, Caccia S, et al. Diagnosis, course, and management of angioedema in patients with acquired C1-inhibitor deficiency. *J Allergy Clin Immunol Pract* 2017;5:1307-13.
84. Cicardi M, Beretta A, Colombo M, Gioffre D, Cugno M, Agostoni A. Relevance of lymphoproliferative disorders and of anti-C1 inhibitor autoantibodies in acquired angio-oedema. *Clin Exp Immunol* 1996;106:475-80.
85. Gobert D, Paule R, Ponard D, Levy P, Fremaux-Bacchi V, Bouillet L, et al. A nationwide study of acquired C1-inhibitor deficiency in France: characteristics and treatment responses in 92 patients. *Medicine (Baltimore)* 2016;95:e4363.
86. Bock SC, Skriver K, Nielsen E, Thøgersen HC, Wiman B, Donaldson VH, et al. Human C1 inhibitor: primary structure, cDNA cloning, and chromosomal localization. *Biochemistry* 1986;25:4292-301.
87. Kalmar L, Hegedus T, Farkas H, Nagy M, Tordai A. HAEdb: a novel interactive, locus-specific mutation database for the C1 inhibitor gene. *Hum Mutat* 2005;25:1-5.
88. Roche O, Blanch A, Duponchel C, Fontan G, Tosi M, Lopez-Trascasa M. Hereditary angioedema: the mutation spectrum of SERPING1/C1NH in a large Spanish cohort. *Hum Mutat* 2005;26:135-44.
89. 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;45:3536-44.
90. Pappalardo E, Cicardi M, Duponchel C, Carugati A, Choquet S, Agostoni A, et al. Frequent de novo mutations and exon deletions in the C1 inhibitor gene of patients with angioedema. *J Allergy Clin Immunol* 2000;106:1147-54.
91. Speletas M, Szilagyi A, Psarros F, Moldovan D, Magerl M, Kompoti M, et al. Hereditary angioedema: molecular and clinical differences among European populations. *J Allergy Clin Immunol* 2015;135:570-3.
92. Caccia S, Suffritti C, Carzaniga T, Berardelli R, Berra S, Martorana V, et al. Intermittent C1-inhibitor deficiency associated with recessive inheritance: functional and structural insight. *Sci Rep* 2018;8:977.
93. 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;118:1330-5.

94. Bork K, Wulff K, Witzke G, Hardt J. Hereditary angioedema with normal C1-INH with versus without specific F12 gene mutations. *Allergy* 2015;70:1004-12.
95. Bork K, Gul D, Hardt J, Dewald G. Hereditary angioedema with normal C1 inhibitor: clinical symptoms and course. *Am J Med* 2007;120:987-92.
96. Bork K, Wulff K, Hardt J, Witzke G, Staubach P. Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. *J Allergy Clin Immunol* 2009;124:129-34.
97. Wood SM, Mann RD, Rawlins MD. Angio-oedema and urticaria associated with angiotensin converting enzyme inhibitors. *Br Med J (Clin Res Ed)* 1987;294:91-2.
98. Brown NJ, Ray WA, Snowden M, Griffin MR. Black Americans have an increased rate of angiotensin converting enzyme inhibitor-associated angioedema. *Clin Pharmacol Ther* 1996;60:8-13.
99. Slater EE, Merrill DD, Guess HA, Roylance PJ, Cooper WD, Inman W, et al. Clinical profile of angioedema associated with angiotensin converting-enzyme inhibition. *JAMA* 1988;260:967-70.
100. Makani H, Messerli FH, Romero J, Wever-Pinzon O, Korniyenko A, Berrios RS, et al. Meta-analysis of randomized trials of angioedema as an adverse event of renin-angiotensin system inhibitors. *Am J Cardiol* 2012;110:383-91.
101. Miller DR, Oliveria SA, Berlowitz DR, Fincke BG, Stang P, Lillienfeld DE. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension* 2008;51:1624-30.
102. Toh S, Reichman ME, Houstoun M, Ross Southworth M, Ding X, Hernandez AF, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch Intern Med* 2012;172:1582-9.
103. Woodard-Grice AV, Lucisano AC, Byrd JB, Stone ER, Simmons WH, Brown NJ. Sex-dependent and race-dependent association of XPNPEP2 C-2399A polymorphism with angiotensin-converting enzyme inhibitor-associated angioedema. *Pharmacogenet Genomics* 2010;20:532-6.
104. Beltrami L, Zanichelli A, Zingale L, Vacchini R, Carugo S, Cicardi M. Long-term follow-up of 111 patients with angiotensin-converting enzyme inhibitor-related angioedema. *J Hypertens* 2011;29:2273-7.
105. Hamasaki H, Hiraishi C, Yanai H. Severe angioedema induced by angiotensin II receptor blocker. *Int J Cardiol* 2013;168:e15-6.
106. Shino M, Takahashi K, Murata T, Iida H, Yasuoka Y, Furuya N. Angiotensin II receptor blocker-induced angioedema in the oral floor and epiglottis. *Am J Otolaryngol* 2011;32:624-6.
107. Bas M, Adams V, Suvorava T, Niehues T, Hoffmann TK, Kojda G. Nonallergic angioedema: role of bradykinin. *Allergy* 2007;62:842-56.
108. Chen XW, He ZX, Zhou ZW, Yang T, Zhang X, Yang YX, et al. An update on the clinical pharmacology of the dipeptidyl peptidase 4 inhibitor alogliptin used for the treatment of type 2 diabetes mellitus. *Clin Exp Pharmacol Physiol* 2015;42:1225-38.
109. Byrd JB, Touzin K, Sile S, Gainer JV, Yu C, Nadeau J, et al. Dipeptidyl peptidase IV in angiotensin-converting enzyme inhibitor associated angioedema. *Hypertension* 2008;51:141-7.
110. Scott SI, Andersen MF, Aagaard L, Buchwald CV, Rasmussen ER. Dipeptidyl peptidase-4 inhibitor induced angioedema—an overlooked and potentially lethal adverse drug reaction? *Curr Diabetes Rev* [published online ahead of print February 14, 2017]. <https://doi.org/10.2174/1573399813666170214113856>.
111. Kostis JB, Packer M, Black HR, Schmieder R, Henry D, Levy E. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens* 2004;17:103-11.
112. Messerli FH, Nussberger J. Vasopeptidase inhibition and angio-oedema. *Lancet* 2000;356:608-9.
113. Rodgers JE. Sacubitril/valsartan: the newest addition to the toolbox for guideline-directed medical therapy of heart failure. *Am J Med* 2017;130:635-9.
114. Tyler JM, Teerlink JR. The safety of sacubitril-valsartan for the treatment of chronic heart failure. *Expert Opin Drug Saf* 2017;16:257-63.
115. Wu MA, Zanichelli A, Mansi M, Cicardi M. Current treatment options for hereditary angioedema due to C1 inhibitor deficiency. *Expert Opin Pharmacother* 2016;17:27-40.

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