

# Pathophysiology of hereditary angioedema

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## ABSTRACT

**Background:** Laryngeal angioedema may be associated with significant morbidity and even mortality. Because of the potential severity of attacks, both allergists and otolaryngologists must be knowledgeable about the recognition and treatment of laryngeal angioedema. This study describes the clinical characteristics and pathophysiology of bradykinin-mediated angioedema.

**Methods:** A literature review was conducted concerning the clinical characteristics and pathophysiology of types I and II hereditary angioedema (HAE), type III HAE, acquired C1 inhibitor (C1INH) deficiency, and angiotensin-converting enzyme (ACE) inhibitor-associated angioedema.

**Results:** The diagnosis of type I/II HAE is relatively straightforward as long as the clinician maintains a high index of suspicion. Mutations in the SERPING1 gene result in decreased secretion of functional C1INH and episodic activation of plasma kallikrein and Hageman factor (FXII) of the plasma contact system with cleavage of high molecular weight kininogen and generation of bradykinin. In contrast, there are no unequivocal criteria for making a diagnosis of type III HAE, although a minority of these patients may have a mutation in the factor XII gene. Angioedema attacks and mediator of swelling in acquired C1INH deficiency are similar to those in type I or II HAE; however, it occurs on a sporadic basis because of excessive consumption of C1INH in patients who are middle aged or older. ACE inhibitor-associated angioedema should always be considered in any patient taking an ACE inhibitor who experiences angioedema. ACE is a kininase, which when inhibited is thought to result in increased bradykinin levels. Bradykinin acts on vascular endothelial cells to enhance vascular permeability.

**Conclusion:** Laryngeal swelling is not infrequently encountered in bradykinin-mediated angioedema. Novel therapies are becoming available that for the first time provide effective treatment for bradykinin-mediated angioedema. Because the characteristics and treatment of these angioedemas are quite distinct from each other and from histamine-mediated angioedema, it is crucial that the physician be able to recognize and distinguish these swelling disorders.

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Laryngeal angioedema can be associated with significant morbidity or even mortality.<sup>1–3</sup> Treatment of laryngeal angioedema is therefore of critical importance to many physicians, most notably allergists, otolaryngologists, primary care physicians, and emergency medicine physicians. Effective treatment of laryngeal angioedema requires both an accurate diagnosis of the cause of the swelling as well as an appreciation of the underlying pathophysiology of the process. This review will summarize both the clinical characteristics and the pathophysiology of several of the most important causes of laryngeal angioedema.

Laryngeal angioedema, like all angioedema and urticaria, results from increased vascular permeability with movement of fluid from the vascular space to the interstitial space.<sup>4–7</sup> This may occur from either a histamine-mediated process or a bradykinin-mediated process. The current review will focus on the pathophysiology of recurrent angioedema that is believed to be caused by bradykinin. The specific forms of recurrent angioedema covered will be hereditary angioedema (HAE), acquired C1 inhibitor (C1INH) deficiency, and angiotensin-converting enzyme (ACE) inhibitor-associated angioedema (Fig. 1). Most of the discussion will focus on HAE because it is the most completely understood of these conditions. The accompanying article by Christiansen will then review the treatment of laryngeal angioedema.<sup>8</sup>

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## HAE WITH LOW C1INH ACTIVITY

HAE was first accurately described by Dr. William Osler in 1888.<sup>1</sup> Dr. Osler recognized the strong heritable nature of the disease and provided a very comprehensive description of the attacks in multiple generations of a single family. HAE is inherited in an autosomal dominant manner. It affects both male and female gender equally. Approximately 50% of the children of an affected parent will inherit the disease. In addition, the disease does not skip generations. Surveys of HAE patients and their families have revealed that only ~75% of patients with HAE have a positive family history of angioedema, with the other 25% of HAE patients having *de novo* mutations.<sup>9</sup>

HAE is a rare disease, with an estimated prevalence of 1 per 50,000 in the general population.<sup>10–12</sup> There is no known ethnic difference in the prevalence of HAE. Because it is so uncommon, an accurate diagnosis of HAE must begin with the physician having a high index of suspicion based on the clinical characteristics (Table 1).<sup>11,13,14</sup> Patients with HAE typically have recurrent angioedema without urticaria. The most commonly affected locations of swelling in HAE are the extremities, the gastrointestinal tract, the external genitourinary tract, the face, and the oropharynx/larynx. The probability that a given attack will involve the skin or abdomen is nearly 50% each. All other attack locations, including genitourinary and laryngeal attacks, account for only 3.6% of attacks.<sup>15</sup>

Attacks of swelling in HAE patients are usually prolonged, with the swelling typically slowly increasing over ~24 hours and then resolving even more slowly over the subsequent 2–4 days. A clinical observation that is useful for suggesting that a patient might have HAE is the lack of a clear response to the standard medicines used to treat allergic swelling (antihistamines, corticosteroids, and epinephrine).<sup>11,13</sup> Attacks are frequently but not always preceded by prodromal symptoms, most classically a serpiginous nonpruritic rash called erythema marginatum.<sup>13,16</sup>

The swelling in HAE is often quite severe and may be associated with considerable morbidity and even mortality.<sup>11,13,14</sup> The most



Table 1 Distinguishing bradykinin-mediated angioedemas based on clinical characteristics

| Characteristic                           | Type I HAE           | Type II HAE          | Type III HAE                    | Acquired C1INH Deficiency | ACE Inhibitor Associated |
|------------------------------------------|----------------------|----------------------|---------------------------------|---------------------------|--------------------------|
| Age of onset                             | Childhood or teenage | Childhood or teenage | Teenage or young adult          | Middle age or older       | Adult                    |
| Family history                           | Usually +            | Usually +            | Essential                       | Negative                  | Negative                 |
| Predilection for specific swelling sites | None                 | None                 | Especially face and extremities | None                      | Especially face          |
| Prodrome                                 | Often                | Often                | Probably not                    | Probably not              | No                       |
| Predominantly affects women              | No                   | No                   | Yes                             | No                        | No                       |
| Associated with using an ACE inhibitor   | No*                  | No*                  | No*                             | No*                       | Yes                      |

\*May be made worse by an ACE inhibitor.

ACE = angiotensin-converting enzyme; C1INH = C1 inhibitor; HAE = hereditary angioedema.

Table 2 Distinguishing bradykinin-mediated angioedemas based on laboratory profile

| Test                   | Type I HAE | Type II HAE | Type III HAE | Acquired C1INH Deficiency | ACE Inhibitor Associated |
|------------------------|------------|-------------|--------------|---------------------------|--------------------------|
| C1INH antigenic level  | Low        | Normal      | Normal       | Low                       | Normal                   |
| C1INH functional level | Low        | Low         | Normal       | Low                       | Normal                   |
| C4                     | Low        | Low         | Normal       | Low                       | Normal                   |
| C1q                    | Normal     | Normal      | Normal       | Low                       | Normal                   |
| Factor XII mutation    | Absent     | Absent      | Occas found  | Absent                    | Absent                   |

ACE = angiotensin-converting enzyme; C1INH = C1 inhibitor; HAE = hereditary angioedema.

and II HAE have been described. Interestingly, mutations in the reactive mobile loop near or at the active site result in a dysfunctional protein that characterizes type II HAE. There is evidence that type I HAE often involves failure of the nascent protein to fold properly within the endoplasmic reticulum.

The mechanism by which a deficiency of C1INH causes increased vascular permeability and angioedema has been the subject of intense investigation over the past 30 years. Incubation of HAE plasma *ex vivo* at 37°C generates a factor that caused smooth muscle contraction and increased vascular permeability.<sup>30</sup> This “vascular permeability-enhancing factor” was correctly assumed to be the mediator of swelling in HAE; however, the final characterization of the factor remained elusive and controversial for many years.

C1INH is the principle inhibitor of several complement and contact system proteases as well as a minor inhibitor of coagulation factor XIa and plasmin.<sup>27</sup> During HAE attacks, each of these plasma proteolytic cascades is activated with the potential to generate several vasoactive compounds. Two potential mediators of swelling in HAE were identified as likely candidates to mediate enhanced vascular permeability in HAE: C2 kinin, generated through activation of the classic complement and fibrinolytic pathways,<sup>31</sup> and bradykinin, generated through activation of the contact system.<sup>32</sup> Despite initial suggestions that C2 kinin represented the vascular permeability-enhancing activity, compelling laboratory and clinical data have conclusively shown that bradykinin is the primary mediator of swelling in HAE.<sup>32–42</sup>

The nanopeptide bradykinin is generated when active plasma kallikrein cleaves high molecular weight kininogen.<sup>43</sup> Plasma kallikrein is activated from its inactive zymogen by the protease factor XII, and both plasma kallikrein and factor XII are normally inhibited by C1INH (Fig. 1). The released bradykinin moiety potently increases vascular permeability by binding to its cognate receptor (the bradykinin B2-receptor) on vascular endothelial cells. Given the plethora of evidence supporting bradykinin as the mediator of swelling in HAE, it was of little surprise that drugs targeting bradykinin generation or action have shown efficacy during angioedema attacks.<sup>44,45</sup>

## TYPE III HAE

In 2000, two separate groups described a familial form of angioedema in which the C1INH was absolutely normal.<sup>46,47</sup> Clinically, this new type of HAE (which is often called type III HAE) resembles types I and II HAE, although type III HAE presents at a somewhat older age and appears to have fewer abdominal and more facial attacks (Table 1).<sup>48</sup> Type III HAE was initially thought to occur exclusively in women, particularly during times of increased estrogen exposure. Subsequently, affected men have been found<sup>49,50</sup>; and the strength of the relationship between estrogen exposure and angioedema is shown to be modest.<sup>48</sup> At the current time, there are no firm criteria for making a diagnosis of type III HAE; however, it should be considered in patients with recurrent angioedema who have a strong family history of angioedema as well as normal C1INH antigenic and functional levels and a normal C4 level (Table 2).

A mutation in the factor XII gene (Thr328Lys or Thr328Arg) that cosegregated with disease presence was described in some families with type III.<sup>51</sup> This mutation was reported to cause a gain-of-function in factor XII activity, an observation that was particularly exciting because a gain-of-function in factor XII would be expected to result in enhanced generation of bradykinin and thus explain the pathogenesis of this disorder (Fig. 1). Since then it has become clear that only a minority of families with type III HAE have a mutation in factor XII.<sup>48</sup> Furthermore, a recent study failed to confirm the gain-of-function in the mutant factor XII.<sup>52</sup>

The genetic heterogeneity of type III HAE suggests that this diagnosis may encompass a heterogeneous group of disorders. Because type III HAE can clearly cause severe laryngeal angioedema, the lack of clear diagnostic or pathophysiological understanding of this disease is of significant concern and requires additional research.

## ACQUIRED C1INH DEFICIENCY

In addition to its deficiency on a hereditary basis, C1INH deficiency also occurs in a sporadic acquired form (acquired C1INH deficiency).<sup>53</sup> These patients, who typically present in middle age or

older, experience recurrent angioedema that is similar if not identical to HAE attacks.<sup>54</sup> Patients with acquired C1INH deficiency are also at significant risk for laryngeal attacks. Hereditary and acquired C1INH deficiencies are, however, relatively simple to differentiate based on the lack of family history and much later age of onset in the acquired form (Table 1). Laboratory evaluation of acquired C1INH deficiency typically shows low C4 levels as well as low C1INH levels and activity similar to type I HAE; however, the C1q level is also frequently reduced in acquired C1INH deficiency but not in HAE (Table 2).<sup>55</sup>

The primary basis for the C1INH deficiency in acquired C1INH deficiency is increased catabolism of C1INH rather than decreased secretion of functional C1INH as found in HAE (Fig. 1).<sup>56,57</sup> The increased C1INH catabolism in acquired C1INH deficiency often related to underlying conditions. Many of these patients have tumors, particularly lymphoreticular malignancies, or other diseases that may consume C1INH.<sup>58,59</sup> Importantly, successful treatment of the underlying disease may resolve the acquired C1INH deficiency.<sup>60</sup> Patients with acquired C1INH deficiency also frequently have autoantibodies directed to C1INH, not infrequently associated with a monoclonal gammopathy of unknown significance.<sup>61,62</sup> The autoantibody has been shown to interfere with normal C1INH–protease interactions, favoring the degradation of C1INH into a smaller cleaved dysfunctional protein.<sup>39,63</sup>

## ACE INHIBITOR–ASSOCIATED ANGIOEDEMA

ACE inhibitors are a class of commonly used antihypertensive medications that are well recognized to be associated with angioedema in rare patients.<sup>64</sup> The angioedema associated with ACE inhibitor tends to show a predilection for involving the face, lips, tongue, and throat (Table 1).<sup>65</sup> The overall prevalence of ACE inhibitor–induced angioedema is estimated to range from 1 per 1000 patients using these drugs.<sup>66</sup> A recent large study among patients in the United States Veterans Affairs system revealed an overall incidence of 1.97 cases per 1000 patients initiating ACE inhibitor therapy (compared with 0.51 cases per 1000 in patients initiating therapy with an antihypertensive drug other than an ACE inhibitor).<sup>67</sup> Substantial variation in the risk of developing angioedema are seen among subsets of patients with black patients having a nearly fourfold increase in risk and women having a 1.5-fold increase in risk. The risk of developing angioedema while using an ACE inhibitor is highest during the 1st month of treatment but does not disappear even in patients who have been taking an ACE inhibitor for years.<sup>67,68</sup>

The angioedema resulting from use of an ACE inhibitor occurs on a class-specific rather than a drug-specific basis. All patients who develop angioedema without urticaria while taking an ACE inhibitor should be suspected of potentially having ACE inhibitor-associated angioedema. Because this angioedema tends to be recurrent and potentially life-threatening when involving the larynx,<sup>69,70</sup> patients who develop ACE inhibitor-associated angioedema must discontinue the use of all ACE-I drugs. Although there has been concern about switching patients who experience angioedema on an ACE inhibitor to an angiotensin receptor blocker, several studies have shown that there is no evidence of increased risk when such a patient is switched to an angiotensin receptor blocker.<sup>71–73</sup>

The pathophysiology of ACE inhibitor–associated angioedema is thought to relate to decreased catabolism of bradykinin. ACE, also known as kininase 2, is an endopeptidase that degrades a variety of peptides including bradykinin (Fig. 1). A drug (omapatrilat) that inhibited both ACE and neutral endopeptidase (which is also involved in the degradation of bradykinin) had a substantially increased risk of angioedema.<sup>74</sup> Furthermore, patients with a history of ACE inhibitor–associated angioedema were more likely than patients who tolerated ACE inhibitors without angioedema to have decreased plasma aminopeptidase P (another endopeptidase involved in the degradation of bradykinin) activity.<sup>75</sup> Other studies suggest that in addition to bradykinin, substance P (a peptide also degraded by ACE) may be involved in ACE inhibitor–associated angioedema.<sup>76</sup>

## CONCLUSIONS

Bradykinin is a pluripotent peptide mediator, exerting different effects depending on the tissue in which it is generated. When generated in the vascular space, bradykinin can mediate enhanced vascular permeability—leading to movement of fluid from the vascular space into the interstitial fluid (angioedema). Mechanistic studies have suggested (and in some cases proven) that increased levels of bradykinin are responsible for the angioedema associated with HAE, acquired C1INH deficiency, and ACE inhibitor–associated angioedema. Recognition of this fact is critically important because bradykinin-mediated angioedema is different in many key respects than the more common histamine-mediated angioedema. Severe laryngeal swelling is not infrequently encountered in bradykinin-mediated angioedema, and bradykinin-mediated angioedema does not respond to the drugs typically used to treat histamine-mediated angioedema. Furthermore, novel therapies are becoming available that for the first time provide effective treatment for bradykinin-mediated angioedema. Because the characteristics and treatment of these angioedemas are quite distinct from each other and histamine-mediated angioedema, it is crucial that the physician be able to recognize and distinguish these swelling disorders.

## REFERENCES

- Osler W. Hereditary angio-neurotic oedema. *Am J Med Sci* 95:362–367, 1888.
- Zilberberg M, Jacobsen T, and Tillotson G. The burden of hospitalizations and emergency department visits with hereditary angioedema and angioedema in the United States, 2007. *Allergy Asthma Proc* 31:511–519, 2010.
- Lumry WR, Castaldo AJ, Vernon MK, et al. The humanistic burden of hereditary angioedema: Impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc* 31:407–414, 2010.
- Asero R, Riboldi P, Tedeschi A, et al. Chronic urticaria: A disease at a crossroad between autoimmunity and coagulation. *Autoimmun Rev* 7:71–76, 2007.
- Davis AE III. The pathogenesis of hereditary angioedema. *Transfus Apher Sci* 29:195–203, 2003.
- Agostoni A, Cicardi M, and Porreca W. Peripheral edema due to increased vascular permeability: A clinical appraisal. *Int J Clin Lab Res* 21:241–246, 1992.
- Donaldson VH, Ratnoff OD, Dias Da Silva W, and Rosen FS. Permeability-increasing activity in hereditary angioneurotic edema plasma. II. Mechanism of formation and partial characterization. *J Clin Invest* 48:642–653, 1969. (PMCID: 322269.)
- Christiansen SC and Zuraw BL. Hereditary angioedema: Management of laryngeal attacks. *Am J Rhinology & Allergy* 25:379–382, 2011.
- 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* 106:1147–1154, 2000.
- Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy Asthma Clin Immunol* 6:24, 2010. (PMCID: 2921362.)
- Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med* 359:1027–1036, 2008.
- Bygum A. Hereditary angio-oedema in Denmark: A nationwide survey. *Br J Dermatol* 161:1153–1158, 2009.
- Frank MM, Gelfand JA, and Atkinson JP. Hereditary angioedema: The clinical syndrome and its management. *Ann Intern Med* 84:586–593, 1976.
- Agostoni A, and Cicardi M. Hereditary and acquired C1-inhibitor deficiency: Biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 71:206–215, 1992.
- Bork K, Meng G, Staubach P, and Hardt J. Hereditary angioedema: New findings concerning symptoms, affected organs, and course. *Am J Med* 119:267–274, 2006.
- Prematta MJ, Kemp JG, Gibbs JG, et al. Frequency, timing, and type of prodromal symptoms associated with hereditary angioedema attacks. *Allergy Asthma Proc* 30:506–511, 2009.

17. Papadopoulou-Alataki E. Upper airway considerations in hereditary angioedema. *Curr Opin Allergy Clin Immunol* 10:20–25, 2010.
18. Bork K, Hardt J, Schicketanz KH, and Ressel N. Clinical studies of sudden upper airway obstruction in patients with hereditary angioedema due to C1 esterase inhibitor deficiency. *Arch Intern Med* 163:1229–1235, 2003.
19. Bork K, and Ressel N. Sudden upper airway obstruction in patients with hereditary angioedema. *Transfus Apher Sci* 29:235–238, 2003.
20. Bork K, and Barnstedt SE. Laryngeal edema and death from asphyxiation after tooth extraction in four patients with hereditary angioedema. *J Am Dent Assoc* 134:1088–1094, 2003.
21. Bork K, Siedlecki K, Bosch S, et al. Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clin Proc* 75:349–354, 2000.
22. Agostoni A, Cicardi M, Cugno M, and Storti E. Clinical problems in the C1-inhibitor deficient patient. *Behring Inst Mitt* 93:306–312, 1993.
23. Roche O, Blanch A, Caballero T, et al. Hereditary angioedema due to C1 inhibitor deficiency: Patient registry and approach to the prevalence in Spain. *Ann Allergy Asthma Immunol* 94:498–503, 2005.
24. Gompels MM, Lock RJ, Abinun M, et al. C1 inhibitor deficiency: Consensus document. *Clin Exp Immunol* 139:379–394, 2005.
25. Donaldson VH, and Evans RR. A biochemical abnormality in hereditary angioneurotic edema: Absence of serum inhibitor of C'1-esterase. *Am J Med* 35:37–44, 1963.
26. Rosen FS, Pensky J, Donaldson V, and Charache P. Hereditary angioneurotic edema: Two genetic variants. *Science* 148:957–958, 1965.
27. Davis AE III. C1 inhibitor and hereditary angioneurotic edema. *Annu Rev Immunol* 6:595–628, 1988.
28. Lomas DA, Belorgey D, Mallya M, et al. Molecular mousetraps and the serpinopathies. *Biochem Soc Trans* 33:321–330, 2005.
29. Patston PA, Gettins P, Beechem J, and Schapira M. Mechanism of serpin action: Evidence that C1 inhibitor functions as a suicide substrate. *Biochemistry* 30:8876–8882, 1991.
30. Donaldson VH, Ratnoff OD, Da Silva WD, and Rosen FS. Permeability-increasing activity in hereditary angioneurotic edema plasma. II. Mechanism of formation and partial characterization. *J Clin Invest* 48:642–653, 1969.
31. Donaldson VH, Rosen FS, and 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* 40:174–183, 1977.
32. Curd JG, Prograis L Jr, and Cochrane CG. Detection of active kallikrein in induced blister fluids of hereditary angioedema patients. *J Exp Med* 152:742–747, 1980.
33. Curd JG, Yelvington M, Burrige N, et al. Generation of bradykinin during incubation of hereditary angioedema plasma. *Mol Immunol* 19:1365, 1982.
34. Fields T, Ghebrehiwet B, and 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* 72:54–60, 1983.
35. Lammle B, Zuraw BL, Heeb MJ, 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* 59:151–161, 1988.
36. Berrettini M, Lammle B, White T, et al. Detection of in vitro and in vivo cleavage of high molecular weight kininogen in human plasma by immunoblotting with monoclonal antibodies. *Blood* 68:455–462, 1986.
37. Schapira M, Silver LD, Scott CF, et al. Prekallikrein activation and high-molecular-weight kininogen consumption in hereditary angioedema. *N Engl J Med* 308:1050–1054, 1983.
38. Nussberger J, Cugno M, Amstutz C, et al. Plasma bradykinin in angio-oedema. *Lancet* 351:1693–1697, 1998.
39. Zuraw BL, and Curd JG. Demonstration of modified inactive first component of complement (C1) inhibitor in the plasmas of C1 inhibitor-deficient patients. *J Clin Invest* 78:567–575, 1986.
40. Zuraw BL, Lammle B, Sugimoto S, et al. Cleavage of high molecular weight kininogen in plasma during attacks of angioedema in hereditary angioedema. *J Allergy Clin Immunol* 79:177, 1987.
41. Shoemaker LR, Schurman SJ, Donaldson VH, and Davis AE. Hereditary angioneurotic oedema: Characterization of plasma kinin and vascular permeability-enhancing activities. *Clin Exp Immunol* 95:22–28, 1994.
42. Han ED, MacFarlane RC, Mulligan AN, et al. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest* 109:1057–1063, 2002.
43. Cochrane CG, and Griffin JH. The biochemistry and pathophysiology of the contact system of plasma. *Adv Immunol* 33:241–306, 1982.
44. Zuraw BL, and Christiansen SC. New promise and hope for treating hereditary angioedema. *Expert Opin Investig Drugs* 17:697–706, 2008.
45. Bork K, Frank J, Grundt B, et al. Treatment of acute edema attacks in hereditary angioedema with a bradykinin receptor-2 antagonist (Icatibant). *J Allergy Clin Immunol* 119:1497–1503, 2007.
46. Binkley KE, and Davis A III. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol* 106:546–550, 2000.
47. Bork K, Barnstedt SE, Koch P, and Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 356:213–217, 2000.
48. Bork K, Wulff K, Hardt J, et al. Hereditary angioedema caused by missense mutations in the factor XII gene: Clinical features, trigger factors, and therapy. *J Allergy Clin Immunol* 124:129–134, 2009.
49. Bork K, Gul D, and Dewald G. Hereditary angio-oedema with normal C1 inhibitor in a family with affected women and men. *Br J Dermatol* 154:542–545, 2006.
50. Martin L, Raison-Peyron N, Nothen MM, et al. Hereditary angioedema with normal C1 inhibitor gene in a family with affected women and men is associated with the p.Thr328Lys mutation in the F12 gene. *J Allergy Clin Immunol* 120:975–977, 2007.
51. Cichon S, Martin L, Hennies HC, et al. Increased activity of coagulation factor XII (Hageman factor) causes hereditary angioedema type III. *Am J Hum Genet* 79:1098–1104, 2006.
52. Bork K, Kleist R, Hardt J, and Witzke G. Kallikrein-kinin system and fibrinolysis in hereditary angioedema due to factor XII gene mutation Thr309Lys. *Blood Coagul Fibrinolysis* 20:325–332, 2009.
53. Caldwell JR, Ruddy S, Schur PH, and Austen KF. Acquired C1 inhibitor deficiency in lymphosarcoma. *Clin Immunol Immunopathol* 1:39–52, 1972.
54. Zingale LC, Castelli R, Zanichelli A, and Cicardi M. Acquired deficiency of the inhibitor of the first complement component: Presentation, diagnosis, course, and conventional management. *Immunol Allergy Clin North Am* 26:669–690, 2006.
55. Breitbart SI, and Bielory L. Acquired angioedema: Autoantibody associations and C1q utility as a diagnostic tool. *Allergy Asthma Proc* 31:428–434, 2010.
56. Melamed J, Alper CA, Cicardi M, and Rosen FS. The metabolism of C1 inhibitor and C1q in patients with acquired C1-inhibitor deficiency. *J Allergy Clin Immunol* 77:322–326, 1986.
57. Zuraw BL, and Altman LC. Acute consumption of C1 inhibitor in a patient with acquired C1-inhibitor deficiency syndrome. *J Allergy Clin Immunol* 88:908–918, 1991.
58. Schreiber AD, Zweiman B, Atkins P, et al. Acquired angioedema with lymphoproliferative disorder: Association of C1 inhibitor deficiency with cellular abnormality. *Blood* 48:567–580, 1976.
59. Cicardi M, Beretta A, Colombo M, et al. Relevance of lymphoproliferative disorders and of anti-C1 inhibitor autoantibodies in acquired angio-oedema. *Clin Exp Immunol* 106:475–480, 1996.
60. Gelfand JA, Boss GR, Conley CL, et al. Acquired C1 esterase inhibitor deficiency and angioedema: A review. *Medicine* 58:321–328, 1979.
61. Jackson J, and Feighery C. Autoantibody-mediated acquired deficiency of C1 inhibitor. *N Engl J Med* 318:122–123, 1988.
62. Jackson J, Sim RB, Whelan A, and Feighery C. An IgG autoantibody which inactivates C1-inhibitor. *Nature* 323:722–724, 1986.
63. Malbran A, Hammer CH, Frank MM, and Fries LF. Acquired angioedema: Observations on the mechanism of action of autoantibodies directed against C1 esterase inhibitor. *J Allergy Clin Immunol* 81:1199–1204, 1988.
64. Brown NJ, and Vaughan DE. Angiotensin-converting enzyme inhibitors. *Circulation* 97:1411–1420, 1998.
65. Byrd JB, Adam A, and Brown NJ. Angiotensin-converting enzyme inhibitor-associated angioedema. *Immunol Allergy Clin North Am* 26:725–737, 2006.
66. Slater EE, Merrill DD, Guess HA, et al. Clinical profile of angioedema associated with angiotensin converting-enzyme inhibition. *JAMA* 260:967–970, 1988.

67. Miller DR, Oliveria SA, Berlowitz DR, et al. Angioedema incidence in US veterans initiating angiotensin-converting enzyme inhibitors. *Hypertension* 51:1624–1630, 2008.
68. Agostoni A, Cicardi M, Cugno M, et al. Angioedema due to angiotensin-converting enzyme inhibitors. *Immunopharmacology* 44:21–25, 1999.
69. Brown NJ, Snowden M, and Griffin MR. Recurrent angiotensin-converting enzyme inhibitor-associated angioedema. *JAMA* 278:232–233, 1997.
70. Roberts DS, Mahoney EJ, Hutchinson CT, et al. Analysis of recurrent angiotensin converting enzyme inhibitor-induced angioedema. *Laryngoscope* 118:2115–2120, 2008.
71. Cicardi M, Zingale LC, Bergamaschini L, and Agostoni A. Angioedema associated with angiotensin-converting enzyme inhibitor use: Outcome after switching to a different treatment. *Arch Intern Med* 164:910–913, 2004.
72. Yusuf S, Teo K, Anderson C, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: A randomised controlled trial. *Lancet* 372:1174–1183, 2008.
73. Johnsen SP, Jacobsen J, Monster TB, et al. Risk of first-time hospitalization for angioedema among users of ACE inhibitors and angiotensin receptor antagonists. *Am J Med* 118:1428–1429, 2005.
74. Kostis JB, Packer M, Black HR, et al. Omapatrilat and enalapril in patients with hypertension: The Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. *Am J Hypertens* 17:103–111, 2004.
75. Adam A, Cugno M, Molinaro G, et al. Aminopeptidase P in individuals with a history of angio-oedema on ACE inhibitors. *Lancet* 359: 2088–2089, 2002.
76. Byrd JB, Touzin K, Sile S, et al. Dipeptidyl peptidase IV in angiotensin-converting enzyme inhibitor associated angioedema. *Hypertension* 51:141–147, 2008. (PMCID: 2749928.) □

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