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REVIEW ARTICLE

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Hereditary angioedema: Linking complement regulation to the coagulation system

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Abstract

Congenital deficiency of C1 inhibitor, the main inhibitor of the classic complement system pathway, leads to paroxysmal angioedema (hereditary angioedema) that can be debilitating or life-threatening for affected patients. In the past few years many new insights on the pathogenesis of angioedema formation in the presence of low levels of C1 inhibitor has been accumulated. There is a central role for bradykinin that is released upon activation of the kallikrein-kinin system that is insufficiently controlled by adequate levels of C1 inhibitor. As C1 inhibitor also possesses a central regulatory role of other plasma systems, including the contact activation system of coagulation and the plasminogen-plasmin system that governs endogenous fibrinolysis, it is interesting to observe the effects of C1 inhibitor deficiency on activation of these systems and relevance for hemostasis in vivo and thrombo-embolic disease. Interestingly, and despite significant activation of these pathways, C1 inhibitor deficiency is not at all associated with a hemorrhagic tendency or prothrombotic state. New therapeutic options for treatment of C1 inhibitor efficiency have become available in recent years, including various forms of C1 inhibitor concentrate. Restoration of C1 inhibitor levels in patients with hereditary angioedema has not resulted in thrombotic complications or any other relevant disorder associated with the hemostatic system.

KEYWORDS

bradykinin, C1 inhibitor, contact system, factor XII, hereditary angioedema, plasmin

Essentials

- Hereditary angioedema is caused by a deficiency in complement C1 inhibitor.
- C1 inhibitor is not only a regulator of complement activity but also has a major role in the kallikrein-kinin system, the contact system of coagulation, and fibrinolysis.
- Angioedema attacks are caused by release of bradykinin upon activation of the kallikrein-kinin system and mediated by contact system activation and plasmin formation.
- C1 inhibitor deficiency markedly affects both coagulation and fibrinolysis but new therapeutic interventions to manage hereditary angioedema have not been associated with clinically relevant disorders of hemostasis and thrombosis.

1 | INTRODUCTION

Hereditary angioedema (HAE) is a condition caused by deficiency of C1 inhibitor, in most cases as a dominant autosomal disorder although about one third of cases represent spontaneous genetic mutations in the *Serpin-1* gene. Affected patients present with paroxysmal localized swellings due to extravasation of fluid from the circulation into the extracellular space. In the past few decades it has become increasingly clear why deficiency of C1 inhibitor leads to angioedema with a central role of activation of the kallikrein-kinin system and related activity of the contact activation pathway of coagulation. Since C1 inhibitor occupies a central regulatory role in both systems, hereditary angioedema may provide useful insights in the physiological and pathophysiological roles the kallikrein-kinin and contact activation pathways play in hemostasis and thrombosis in vivo. This article reviews the current insights in the lessons we can learn from complement and related system activation regarding their relevance for hemostasis and thrombosis.

2 | CLINICAL MANIFESTATION OF HEREDITARY ANGIOEDEMA

Hereditary angioedema is manifested by recurrent and episodic swelling affecting any tissue in the human body, most frequently the facial area (including cheeks, eyelid, lips, or tongue), upper airways, upper or lower limbs, genital area, or intestinal and mesenterial structures. Attacks usually have a relatively slow onset (hours) and may be preceded by prodromal symptoms including erythema marginatum, muscle pain or itching.[1] Swelling located at the pharyngeal and laryngeal area is the most serious clinical manifestation as this may lead to airway obstruction and even asphyxia. Laryngeal complications have been reported in more than 20% of patients, sometimes leading to the requirement of tracheal intubation or even emergency tracheotomy.[1] In a retrospective study in the era before adequate treatment of the disease was universally introduced, 40% of patients with hereditary angioedema died from asphyxia.[2,3] Another dreaded manifestation of angioedema is swelling in the intestinal area leading to severe abdominal pain, nausea, vomiting, and diarrhea. Abdominal angioedema attacks may closely mimic acute abdominal diseases such as appendicitis and in the past patients often underwent unnecessary surgical intervention due to improper diagnosis. However, with modern imaging (eg, abdominal CT scan) distended intestinal bowel loops with extensive swelling in combination with free fluid in the abdomen and pelvis detected has greatly facilitated the diagnosis.[4]

In 15% to 30% of patients multiple localizations may occur simultaneously.[5] In a descriptive study of consecutive angioedema attacks in patients with hereditary angioedema 46%, 33%, and 6% of the attacks were related to the limbs, the intestinal tract, and upper airways, respectively.[6] In another series, 95% of hereditary angioedema patients suffered from skin manifestations, 60% from facial swelling, and 96% from abdominal attacks.[1] Symptomatic systemic hypotension most probably due to abdominal fluid displacement is another frequently reported symptom in 9% of patients. Although patterns of angioedema attacks can be quite consistent in a single patient, this may not predict the severity and location of a subsequent episode of swelling.[7,8]

Untreated angioedema attacks are self-limiting and usually last for 1-4 days. However, with modern treatment, relief of swelling and complete resolution may occur much more rapidly (see section 5). Nevertheless, recurrent angioedema attacks are associated with significant reduction in the quality of life and substantial physical and social disability. Although the attacks are reversible and treatable the recurrent character of the symptoms leads to a significant limitation of daily activities and to an increased rate of absence of work and school of both patients and their families.[9]

3 | MECHANISMS BY WHICH C1 INHIBITOR DEFICIENCY LEAD TO ANGIOEDEMA

C1 inhibitor is a single chain serine protease of 478 amino acid residues with a reported molecular weight of 76 kDa (105 kDa on SDS-polyacrylamide gel electrophoresis due to its abundant glycosylation).[10] Its normal plasma concentration is 240 mg/L with an estimated half-life of 67-72 hours. C1 inhibitor regulates many biochemical pathways in plasma, such as the classical pathway of complement, the contact phase system, the intrinsic coagulation system, and the plasminogen-plasmin system. C1 inhibitor has a central role in regulating the contact system since it is the principal inhibitor of factor XIIa and next to α_2-macroglobulin the most significant regulator of plasma kallikrein (Figure 1).[10] By binding and inhibiting factor XIIa and plasma kallikrein, C1 inhibitor effectively controls bradykinin generation.

The nonapeptide bradykinin and decapaptide Lys-bradykinin are liberated by proteolytic cleavage of high-molecular-weight kininogen or low-molecular-weight kininogen (LK), respectively. Bradykinin and Lys-bradykinin (kallidin) modulate smooth muscle cell relaxation thereby enhancing vasopermeability, causing the characteristic subcutaneous swelling as seen in hereditary angioedema. The importance of (Lys-) bradykinin in the development of angioedema can be inferred from several observations.[5,10] Patients with hereditary angioedema presenting with unilateral limb edema had significantly increased bradykinin concentrations in the affected extremity as compared to the non-affected extremity.[11,12] In general, in patients suffering from an angioedema attack enhanced plasma levels of (Lys-) bradykinin are detectable in comparison to levels in between attacks. Blocking the bradykinin receptor-2 abolishes the vaso-active effects of bradykinin and abrogates angioedema.[13] In addition, mice with C1-inhibitor deficiency suffer from increased vascular permeability which is not present if the bradykinin receptor-2 is knocked out as well.[14]

Kallikrein can also be generated as a result of prolylcarboxypeptidase (PRCP) activation of plasma prekallikrein (Figure 1).[15] The potential role of this pathway in angioedema is, however, unclear.

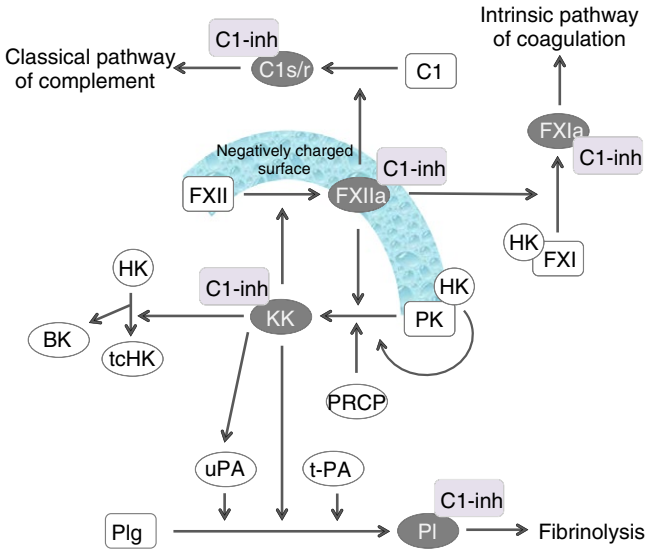

FIGURE 1 Schematic representation of the central role of C1 inhibitor in various plasma systems.[10,59] Upon contact with negatively charged surfaces factor XII (FXII) is (auto-) activated to activated factor XIIa (FXIIa). FXIIa activates the circulating complex of plasma prekallikrein (PK) with high-molecular-weight kininogen (HK). FXIIa activates PK to kallikrein (KK), which in turn can activate FXII to generate more FXIIa (positive feedback). Prolylcarboxypeptidase (PRCP) has also been shown to activate PK to KK. FXIIa can activate the classical pathway of complement as well as FXI from the intrinsic pathway of coagulation. KK is able to cleave single chain HK to two-chain HK (tc-HK) thereby releasing bradykinin (BK), which causes angioedema. In addition, KK can directly activate plasminogen (Plg) to plasmin (Pl) or indirectly by the activation of urokinase-type plasminogen activator (u-PA). C1-inhibitor (C1-Inh) occupies central regulatory roles in these processes as it inhibits FXIIa and KK, respectively. In addition it regulates the classical pathway of complement (via C1s/r), coagulation via FXIa and fibrinolysis via plasmin, respectively

4 | LINKING COMPLEMENT ACTIVATION TO ACTIVATION OF COAGULATION AND FIBRINOLYSIS

As C1 inhibitor is an important regulator of the contact phase system of coagulation and partly of the downstream intrinsic pathway, it may be that a deficiency of this protease inhibitor might affect the hemostatic system. A revised role of the contact system of coagulation has attracted a lot of attention in recent years. Briefly, contact-activated "intrinsic" coagulation appears not to be a physiologic generator of thrombin in vivo. Deficiencies of contact system proteases are not associated with an enhanced bleeding tendency.[16] However, in pathologic states (such as in sepsis) contact system activation may lead to factor XI activation and contribute to downstream thrombin generation, indicating that the contact system is a pathophysiologic generator of thrombin. In addition, contact protein deficiencies seem to protect from thrombosis risk and—inversely—activation of the contact system in experimental models can lead to pathologic thrombosis.[15,17,18]

During an angioedema attack in patients with hereditary angioedema there is abundant contact system activation detectable. Plasma levels of cleaved high molecular weight kininogen, and complexes between activated contact system components and C1 inhibitor are significantly higher in this situation as compared to normal.[19,20] Some studies showed increased factor XIIa levels during an angioedema attack, however, other observations demonstrated that factor XII levels did not change during this situation.[21–23] The activation of the contact system is associated with increased levels of prothrombin activation fragment F1+2, however, it is not clear whether that is a direct effect of intrinsic pathway activation.[21] Indeed, as factor VIIa levels are increased as well, it may well be that thrombin generation is a consequence of tissue factor-factor VIIa activation. The increase in factor VIIa activity may be a consequence of endothelial cell perturbation during an angioedema attack or as a result of the lack of inhibition of factor VII activating protease (FSAP) due to the C1 inhibitor deficiency.[24] An alternative explanation may be that there is some thrombin generation due to (secondary) factor XII activation in this situation. Recent studies on thrombin formation with thrombin generation assays demonstrate that the extent of thrombin generation during an angioedema attack is very mild and self-limiting.[25]

In addition, C1 inhibitor is an effective inhibitor of plasmin and it is estimated that during activation of fibrinolysis about 15% of plasmin is inhibited by C1-inhibitor in vivo.[26] Hence deficiency of C1 inhibitor can impair the ability to regulate plasmin activity. Also, C1 inhibitor deficiency leads to increased plasma kallikrein activity, which may directly activate plasminogen into plasmin or indirectly mediate plasminogen activation by activating urokinase-type plasminogen activator or via factor XIIa generation. An additional mechanism may be that insufficiently inhibited FSAP (see above) can also cause urokinase-mediated plasminogen activation.[27] Plasmin itself may generate further factor XII activation and can thereby cause a potentiation of bradykinin generation and angioedema. Indeed, factor XII deficient patients showed a reduced contact activation-dependent activation of endogenous fibrinolysis in vivo.[28]

C1 inhibitor–deficient patients showed abundantly elevated plasmin-α2 antiplasmin complex and D-dimer levels during an angioedema attack.[29] More needs to be known as to the role of plasmin in initiating acute attacks of hereditary angioedema. The relevance of fibrinolytic activation as a consequence of C1 inhibitor deficiency and the pathogenesis of angioedema is illustrated by the efficacy of lysine analogues, such as tranexamic acid, in the prevention and treatment of angioedema attacks.[30,31] Lysine analogues inhibit the conversion of plasminogen to plasmin by competitively blocking lysine binding sites of plasminogen and may thereby limit the amount of plasmin generated and downstream effects of plasmin formation.[32]

Interestingly, and despite significant activation of the contact activation/intrinsic pathway of coagulation as well as the endogenous fibrinolytic system, C1 inhibitor deficiency is not associated with a hemorrhagic tendency or prothrombotic state.

5 | TREATMENT OF C1 INHIBITOR DEFICIENCY AND CONSEQUENCES FOR HEMOSTASIS AND THROMBOSIS

Management of hereditary angioedema is aimed at reducing the severity and duration of an angioedema attack. In addition, strategies to prevent angioedema attacks (either in high risk situations for angioedema formation, such as intra-oral surgery or endotracheal intubation) or in a long-term setting are available as well.[7,31]

Attenuated androgens, such as danazol and stanozol, can be used for prophylaxis of angioedema attacks. Androgens have been demonstrated to increase mRNA expression of C1 inhibitor and since hereditary angioedema is a heterozygous disease, upregulation of the healthy gene may result in higher levels of C1 inhibitor.[33] Besides, attenuated androgens promote bradykinin degradation through an increase in aminopeptidase P.[34] The ability of attenuated androgens to reduce the frequency and severity of angioedema attacks was shown in randomized controlled studies decades ago.[35,36] Attenuated androgens may cause changes in lipid profiles but have not been associated with atherosclerosis or thrombotic complications.[37]

Tranexamic acid (see above) has been shown to be effective in the prevention and treatment of angioedema attacks, although not in all cases. It can often be used for long-term prophylaxis in children, in whom androgens are contraindicated.[7,8] Although tranexamic acid is an inhibitor of fibrinolysis, its chronic use in patients with hereditary angioedema is not known to cause thrombotic complications.[38]

The current most rational approach for prevention and treatment is the administration of C1 inhibitor concentrate. Plasma-derived C1 inhibitor concentrate is available in many countries since the 1970s and was shown to be effective in raising C1 inhibitor plasma levels and reducing angioedema attacks.[39–42] To achieve licensing in the US, recently two placebo-controlled randomized controlled trials confirmed the efficacy of this therapy. Nanofiltered plasma-derived C1 inhibitor concentrate decreased the time to the onset of relief from an angioedema attack from more than 4 hours in the placebo group to 2 hours in the treatment group.[43] Likewise, the International Multicenter Prospective Angioedema C1-Inhibitor Trial (IMPACT) showed that another plasma-derived C1 inhibitor concentrate significantly reduced the time to the onset of symptom relief dose-dependently from 90 minutes to 30 minutes in the C1 inhibitor concentrate group at a dose of 20 U/kg C1-inhibitor concentrate and from 90 minutes to 72 minutes at a dose of 10 U/kg, respectively.[44] Prophylactic administration of C1-inhibitor was demonstrated to be effective in a placebo-controlled cross-over study in which the frequency of angioedema attacks was significantly reduced from 12.7 in the placebo group to 6.3 over 12 weeks in the group treated with 1000 U C1 inhibitor concentrate twice a week.[43] Intravenous self-administration of C1 inhibitor concentrate was shown to be effective in markedly reducing time to initiation of treatment and a significantly reduced time to relief and total resolution of angioedema symptoms.[45,46] A recent trial demonstrated the feasibility of subcutaneous administration of C1 inhibitor concentrate, thereby further facilitating its use for patients.[47]

An alternative to plasma-derived C1 inhibitor concentrate is a recombinant concentrate, purified from milk of transgenic rabbits expressing the human C1 inhibitor gene. The major difference between this agent and the plasma-derived product is the much shorter half-life of about 2 hours (probably due to differences in glycosylation).[48] Nevertheless, recombinant C1 inhibitor was effective in both treating acute angioedema attacks and (more surprisingly) in a prophylactic setting to a similar extent as the plasma-derived agent.[49,50]

In view of the central role of C1 inhibitor on the contact activation system and endogenous fibrinolytic system restoration of C1 inhibitor levels may hypothetically have consequences for hemostasis or development of thrombosis. Indeed, there have been some reports in the US Food and Drug Administration (FDA) Adverse Event Reporting System database regarding thromboembolic events associated with the use of human plasma-derived C1 esterase inhibitor concentrate in patients with hereditary angioedema. Preclinical studies showed a potential prothrombotic effect of extremely high doses of C1 inhibitor concentrate (25 times higher than the dose used in patients with hereditary angioedema). However, the randomized controlled trials mentioned above and large registries of long-term treatment of patients with hereditary receiving C1 inhibitor concentrate angioedema have not shown any indication of a significantly enhanced thromboembolic risk or any other clinically relevant abnormality in hemostasis.[51–53] One of the largest registries (Berinert Registry Data) including more than 15,000 infusions in 343 patients recorded 1 thromboembolic event (0.3% per patient). In the randomized controlled trials thromboembolic events were very rare and only occurred in patients with underlying pathology predisposing for thrombosis. A recent comprehensive review of all available data confirmed the safety regarding thromboembolic events with the use of C1 inhibitor concentrate.[54]

A novel form of treatment for hereditary angioedema is represented by icatibant, a selective bradykinin-2 receptor antagonist. Subcutaneous administration of icatibant was shown to be superior to placebo in initiating symptom relief (2.5 hours compared to 4.5 hours in the control group) and was demonstrated to have some modest benefit compared to tranexamic acid in a subsequent randomized controlled trial.[55,56] It should be mentioned that the comparison between icatibant and tranexamic acid is slightly difficult as tranexamic acid can be used both as an agent that is used in case of an angioedema attack as well as a prophylactic agent whereas icatibant is used for acute angioedema attacks only. The most important side-effect of icatibant is local skin irritation but this compound has not been associated with thrombotic complications.

Very recently, inhibition of other components of the contact activation system (such as plasma kallikrein and factor XIIa) has been focus of new drug development. Lanadelumab is a humanized monoclonal antibody that inhibits plasma kallikrein.[57] In a recent phase III trial subcutaneous administration of lanadelumab significantly reduced HAE attacks in comparison with placebo. Based on these results, lanadelumab is now (pre-) approved in

the US, EU, Canada, Australia, and Switzerland for prevention of HAE attacks in patients aged ≥12 years. In addition, BCX7353, an oral small-molecule inhibitor of plasma kallikrein was evaluated in a phase II dose-escalation trial in 77 patients.[58] The rate of angioedema attacks was significantly lower among patients who received BCX7353 at daily doses of 125 mg or more than among those who received placebo. The most important reported adverse events were mild gastrointestinal complaints. Although no relevant increases risks of bleeding or thrombosis have been reported in the available preclinical and clinical studies with kallikrein inhibitors,[57,58] the net effect on hemostasis in vivo and thrombosis remains to be elucidated.

6 | CONCLUSION

Hereditary angioedema is a disease characterized by deficiency of C1 inhibitor, whereby uncontrolled activation of the kallikrein-kinin system leads to excessive bradykinin formation and subsequent angioedema attacks. The relevance of C1 inhibitor as a principal regulator of various plasma protease systems, including the contact phase system, intrinsic coagulation, and endogenous fibrinolysis, is illustrated by the activation of these systems during angioedema attacks. Fortunately, various therapeutic and preventive interventions have been developed and evaluated in recent decades to better manage angioedema attacks in affected patients. Despite the central role of C1 inhibitor in coagulation and fibrinolysis, restoration of deficient C1 inhibitor levels has not been associated with clinically relevant disorders of hemostasis and thrombosis.

RELATIONSHIP DISCLOSURE

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