
Hereditary angioedema: a current state-of-the-art review, II: historical perspective of non-histamine-induced angioedema

I. Leonard Bernstein, MD

Objective: To review the evolution of our understanding of hereditary angioedema (HAE) from the first historical reference to the present day.

Data Sources: MEDLINE and PubMed were searched using the following keywords: *history of HAE, C1 inhibitor, complements system, genetics of HAE, mechanisms of HAE, and treatment of HAE.*

Study Selection: Information was selected that outlines the advances made in complementology, the first report of HAE, and subsequent studies that elucidated the underlying mechanisms of this disease, leading to current therapy of this orphan disease.

Results: Generational research efforts in HAE have focused on the following: (1) several new clinical presentations, (2) acquired forms of non-histamine-induced angioedema, (3) the genetic basis for the inherited forms, (4) the effects of C1 inhibitor on contact phases of coagulation-fibrinolytic pathways, and (5) various therapies for short- and long-term control of the disease.

Conclusion: The progress made in understanding the pathogenesis and treatment of HAE is an excellent example of the “bench to the bedside” paradigm involving the collaboration between clinicians and researchers.

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INTRODUCTION

The symposium, “A Comprehensive Update on Angioedema,” was organized in part as a festschrift to Dr Virginia Donaldson, who first described the biochemical defect of the C1 esterase inhibitor (C1-INH) in 1963. Using that seminal report as a reference point, this historical perspective of angioedema will review significant milestones before and after that date.

The prebiochemical era was characterized by descriptive reports concerning angioedema without accompanying urticaria. The first account of angioedema without urticaria in a young count who was sensitive to eggs appeared in 1586 by Donati.¹ Arnoldsson et al² were able to trace generations of a family with angioedema back to the 17th century through the availability of an uninterrupted chronology of church records. Graves,³ whose name is now an eponym for thyrotoxicosis, also described the angioedema syndrome just before the midpoint of the 19th century. In 1882, a postdoctoral student of Heinrich Quincke, Eugen Dinkelacker,⁴ published a thesis on acute circumscribed edema of the skin with 12 references to previous reports. One year later, Quincke⁵ prepared a summary of this work with no references to the previous reports, although he was well aware of their existence. In subsequent confirmatory case reports, it was postulated that there was an association with “nervous influences” and the

term was transformed into *angioneurotic edema*.⁶ In 1888, it was Osler,⁷ however, who clearly defined the hereditary form of angioedema by collating 5 generations of 22 patients affected with this disorder. He was also the first to note the autosomal dominant inheritance pattern in these family trees. Apart from many other descriptive publications after Osler’s genealogical observations, there was little progress concerning the pathophysiologic features of this disease until the middle of the 19th century.^{8,9}

EARLY SCIENTIFIC ADVANCES

In the post-World War II scientific era, a unique confluence of immunologists, complementologists, and hematologists was already focused on elucidating enzymatic interactions among the complement cascade, the contact or fibrinolytic components of intrinsic coagulation, and non-histamine-induced serum permeability factors.^{10–17} In this decade, discoveries of diluted serum permeability factor (PF/Dil), the activation pathways of the Hageman factor (ie, factor XIa in the intrinsic coagulation cascade and prekallikrein in the contact system), and a specific esterolytic assay for complement serine protease and its inhibitor were all reported within a few years of each other.^{14,18–24} Taken together, this research background was a harbinger of delineating the role of permeability factors in hereditary angioneurotic edema, now referred to as hereditary angioedema (HAE), and culminated in 2 key landmark investigations in the late 1950s and early 1960s. Landerman et al^{25,26} observed increased cutaneous responses to the permeability factor, PF/Dil, in HAE, followed shortly thereafter by demonstrating deficiency in a serum inhibitor of both PF/Dil and kallikrein in patients with HAE. This was significant in that it was the first indication that a potent vascular

Affiliation: Allergy Section, Division of Immunology, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio.

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contact permeability factor (eg, kallikrein) derived from the contact system could be involved in HAE. Within a short time, a major function for an early complement enzyme, C1 esterase, as a significant mediator of vascular permeability in HAE was realized when Donaldson and Evans²⁷ discovered the biochemical absence of C1-INH in 3 patients with HAE. In addition, investigators demonstrated that the patient with HAE previously known to have an inhibitory deficit of serum kallikrein also lacked C1-INH.^{26,27} They, therefore, posited that there may be a close relationship between the effects of C1-INH and kallikrein inhibitor. A few years later, Donaldson et al²⁸ found that the permeability-increasing factor in plasma of patients during acute HAE also displayed kininlike activity. Although the properties of this kinin resembled kallidin and bradykinin, it differed from them in being subject to proteolysis by trypsin, which had no effect on these 2 synthetic polypeptide kinins. They postulated that an alternative vascular permeability candidate could be a polypeptide kinin released from C2 by C1s esterase (ie, a C2 kinin).²⁹ These initial experiments concerning the biochemistry of C1-INH, which presumably led to unrestrained kininlike activity, served as catalysts for remarkable research progress in defining the mechanisms of HAE. Future generational research efforts in HAE were focused on the following: (1) several new clinical presentations, (2) acquired forms of non-histamine-induced angioedema, (3) the genetic basis for the inherited forms, (4) the effects of C1-INH on contact phases of coagulation or fibrinolytic pathways, and (5) various therapies for short- and long-term control of the disease.

Within several years after the original biochemical deficit was reported, Rosen et al³⁰ reported another affected HAE kindred with normal serum concentrations of C1-INH but dysfunctional inhibitory properties with respect to the cleavage functions of C1 esterase. Since then, similar reports of patients with functionally inactive variants have appeared worldwide. It was, therefore, evident that 2 unique populations of HAE existed: (1) HAE type 1, with low or absent antigen content and markedly reduced or absent esterolytic activity; and (2) HAE type 2, with normal antigen content but marked reduction in functional activity. A less frequent form of familial recurrent angioedema occurs in women and is estrogen induced.³¹ Two separate kindreds were described with a unique clinical constellation consisting of normal C1-INH content and function, exacerbation by estrogens, and autosomal dominant inheritance.^{32,33} Recently, missense mutations in the Hageman coagulation factor XII gene were reported in 5 families of German kindred for this familial form of HAE.³⁴

The first report of acquired angioedema with C1-INH deficiency appeared in 1972.³⁵ This occurred in a woman who later developed histologically proven lymphosarcoma. Since then, multiple instances have been associated with B-cell lymphoproliferative or other malignant diseases.^{36–40} Such entities have been designated as acquired angioedema type 1. The B-cell lymphoproliferative group is often associated with anti-idiotypic antibodies that rapidly consume C1-INH.⁴⁰ An-

other specific type of acquired C1-INH deficiency reported in 1986 occurred in autoimmune diseases, such as lupus erythematosus, and was associated with autoantibodies to C1-INH (acquired angioedema type 2).^{41,42} It was occasionally diagnosed in the absence of other diseases.⁴³ Some of these patients also exhibited low C1q plasma levels.

GENETIC BASIS OF HAE

The next achievement in HAE research was a more detailed exploration of its genetic basis by determination of its primary structure, complementary DNA cloning, and chromosomal localization. After C1-INH was first purified in 1961, the primary structure of C1-INH was determined by peptide and DNA sequencing, and it was also heavily glycosylated.⁴⁴ Comparison of its amino acid and complementary DNA sequences revealed it to be a member of the large serine protease inhibitor (serpin) family. It was homologous to many serpins at a domain of 120–amino acid residues within the C terminus of the molecule. The C1 inhibitor gene was mapped to chromosome 11 (p11.2–q13). After these genetic accomplishments, more than 150 mutations have been reported in patients with HAE, with both type 1 and 2 phenotypes.^{45–49} Thus far, in-depth analysis of these extensive genetic databases does not suggest that variability of disease expression or severity can be attributed to specific mutant proteins.

Elaboration of the pathophysiologic features of HAE has been a continuum because the unique enzymatic function of C1-INH was discovered in 1962. Stepwise research in this area included the following: (1) identification of C1-INH as a serine protease by specific esterolytic assays, (2) determination of its reactive site and function as a suicide serpin, and (3) examination of how C1-INH regulates several pathways of complement (ie, classic and mannose-binding lectin), the intravascular coagulation and contact systems via its activation effects on factor XII (factor XIIa), factor XI (factor XIa), and kallikrein. In addition, it is thought to regulate fibrinolysis to some extent by activating tissue plasminogen activating factor and plasmin.

The trail of research leading to the final identification of C1-INH as a member of the serpin family of serine esterases can be traced to the early investigations of the first 4 components of complement by Lepow et al.¹¹ During these early studies, Ratnoff and Lepow⁵⁰ demonstrated that C1 was a serine esterase because of its ability to hydrolyze several synthetic ester substrates (*p*-toluene sulfonyl-L[*r*]-arginine methyl ester and *N*-acetyl-L[*r*]-tyrosine ethyl ester). At about the same time, Becker¹⁵ demonstrated that diisopropyl fluorophosphate, a potent sulfhydryl-containing reducing agent of reactive serine esterase sites, was equally effective in neutralizing the functionality of serine esterases, such as C1 and the PF/Dil skin permeability factor.¹⁴ During his research, Lepow also described the presence of a serum inhibitor of C1 enzymatic activity, which at that time was incompletely characterized. As previously discussed, the functional and biochemical nature of a similar inhibitor of PF/Dil and kallikrein

was subsequently noted by Landerman et al²⁶ and was further characterized by Donaldson and Evans²⁷ in patients with HAE. The inhibitory effect of C1-INH on C1 esterase function in these experiments was assayed by synthetic ester hydrolytic assays previously used by Ratnoff and Lepow.⁵⁰ Subsequent cloning and DNA assembly of C1-INH not only proved that it was a serpin but also located its corresponding central enzyme-substrate combining site.⁴⁴ After binding occurs, the serpins and their corresponding proteases lose activity, thereby providing the basis for designating serpins as suicide substrates.

IDENTIFICATION OF RELEVANT MEDIATORS

Once the enzymatic nature of C1-INH was verified, a contemporary pathophysiologic investigation was directed at its substrate's cleavage end products, which were thought to be the ultimate causes of the severe vascular permeability associated with HAE. As previously discussed, the first to be studied was the C2 complement component, the cleavage of which resulted in a kinin-enhancing permeability factor termed *C2 kinin*.²⁸ Because the permeability-enhancing activity of this kinin was relatively low, research emphasis shifted to more potent permeability-increasing factors (or their precursors) associated with the contact, coagulation, and/or fibrinolytic systems of the intrinsic coagulation pathway. These included factors XIIa and XIa, kallikrein, tissue plasminogen activator, and plasmin. Of these components, the ability of kallikrein to cleave high-molecular-weight kininogen into bradykinin seemed to be the most likely candidate for the profound edema effects noted in HAE.⁵¹ This was suggested by several independent investigations.^{51–53} One of these studies⁵³ isolated an HAE plasma peptide that was inactivated by carboxypeptidase *N* but not by trypsin, a profile more characteristic of bradykinin than the previously described C2 kinin. Finally, a series of elegant experiments clearly identified bradykinin as the major vascular permeability factor of HAE.⁵⁴ Bradykinin has also been demonstrated in the plasma of patients with HAE during attacks of angioedema.⁵⁵

MURINE MODEL OF HAE

A murine model of HAE developed by targeted disruption of the C1-INH gene in murine embryonic stem cells proved to be a useful experimental corollary with respect to vascular permeability phenomena and possible therapeutic approaches.⁵⁶ It was possible to produce C1-INH-deficient homozygous and heterozygous mice, all of which exhibited increased vascular permeability after intravenous administration of Evans blue. Vascular permeability was significantly decreased in animals pretreated with C1-INH, a kallikrein inhibitor, and a synthetic bradykinin receptor 2 antagonist. This model provided proof of concept for current therapeutic modalities to be discussed later in this monograph.⁵⁷ Similar evidence that the fibrinolytic system may be involved is not yet available, but it is postulated that any protease substrate (ie, plasmin or tissue plasminogen activator) requiring inac-

tivation by C1-INH leads to further consumption of the inhibitor.^{58–60}

EVOLUTION OF THERAPY FOR HAE

Before 1960, there was no effective treatment of acute HAE attacks or prophylactic measures for control of recurrent episodes. In 1960, Spaulding⁶¹ reported the empirical use of methyltestosterone in daily doses ranging from 5 to 30 mg. Interestingly, Landerman et al²⁶ had treated their index case of HAE with 5 mg of testosterone. This anecdotal experience went unnoticed until 1976, when it was demonstrated that one of the methylated testosterone derivatives (danazol) was not only an effective prophylactic therapy but also led to increased levels of C1-INH and almost normal return of C2 and C4 complement levels.⁶² Since that initial observation, danazol and an analogue, stanazolol, have become standard prophylactic treatments for short- and long-term prophylaxis of HAE. Masculinity effects, however, are obvious complications for women with HAE, and treatment of children is problematic because of the possibility of premature epiphyseal long bone closings. Hepatocellular adenomata have also been reported.⁶³ The evolution of treatment for acute HAE attacks has proceeded more rapidly outside the United States. Fresh frozen plasma was first suggested for the treatment of acute HAE attacks in 1969, but there have been reports that this treatment can worsen acute swelling because of the presence of plasma proteases and substrates that produce bradykinin, which generates and mediates angioedema. In 1972, Frank et al⁶⁴ reported that the antifibrinolytic agent, ϵ -aminocaproic acid, was an effective therapy for acute HAE attacks. However, most observers believe that the effects of this treatment are modest at best. Tranexamic acid, another antifibrinolytic agent, is used for acute HAE attacks in Europe and reportedly is more successful. Unfortunately, it has prominent adverse effects. It is not available in the United States.

The most promising agents for the treatment of acute HAE attacks are not available in the United States but have been used successfully in Europe for at least 2 decades. Despite a controlled study of vapor-heated C1-INH concentrate showing statistically effective results, there is as yet no Food and Drug Administration–approved similar agent available in the United States.⁶⁵ Several plasma-derived and purified recombinant forms of C1-INH are undergoing clinical trials in the United States. A plasma kallikrein inhibitory agent, DX-88, has completed US phase 3 trials and is in phase 4 open-label investigations. Results of these trials indicated that it was effective in the short-term treatment of HAE attacks. In addition, a bradykinin β_2 -receptor antagonist, icatibant, is in phase 2 and phase 3 clinical trials in the United States. Even assuming optimal efficacy for these therapies, subsidence of the edema may take several hours after these agents are administered, so it is imperative that patients with HAE who have laryngeal edema be monitored closely for possible intubation as a life-saving intervention.

The following sections of this monograph will review current concepts concerning pathophysiologic features and the most pragmatic evidence-based approaches to the management of HAE and associated diseases.

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- Requests for reprints should be addressed to:*
I. Leonard Bernstein, MD
University of Cincinnati College of Medicine
231 Albert Sabin Way, Mailing Location 563
Cincinnati, OH 45267-0563
E-mail: i.leonard.bernstein@uc.edu
-