Laboratory Approaches for Assessing Contact System Activation

Sandra C. Christiansen, MD[a], Bruce L. Zuraw, MD[a,b,*]

KEYWORDS

• Contact system • Hereditary angioedema • C1 inhibitor • Bradykinin • C4
• C1 inhibitor complexes • Vascular permeability

KEY POINTS

- Activation of the plasma contact system generates bradykinin and causes swelling in hereditary angioedema (HAE) due to C1 inhibitor (C1INH) deficiency (HAE-C1INH), HAE associated with factor XII (FXII) mutations, and acquired C1INH deficiency (AC1D).
- Bradykinin is suspected to be the mediator of swelling in several other forms of angioedema, such as HAE of unknown type, idiopathic nonhistaminergic angioedema, and angioedema associated with inhibitors of kininases.
- Laboratory tests to detect activation of the contact system and generation of bradykinin remain limited to research settings at the current time.

INTRODUCTION

Angioedema is a common clinical finding that can reflect multiple underlying pathophysiologic mechanisms. It is the physical manifestation of fluid movement from the blood vessel into the interstitial fluid that occurs as a consequence of transiently increased vascular permeability. Unlike hydrostatic or oncotic causes of edema, angioedema results from the action of mediators on endothelial cells that disrupt the adherens junction, resulting in vascular leak.[1] Histamine, cysteinyl leukotrienes, and bradykinin are recognized as the principal biologic mediators of swelling.[2] A majority of angioedema cases are thought to involve mast cell activation, triggering the release of histamine and other mediators, such as leukotrienes.[3] Less frequently, angioedema is linked to the generation of bradykinin. Because the prognosis and treatment of bradykinin-mediated angioedema are markedly different from those of histamine-mediated or leukotriene-mediated angioedema, it is of considerable clinical

[a] Department of Medicine, University of California, 9500 Gilman Drive, Mailcode 0732, La Jolla, CA 92093, USA; [b] San Diego Veterans Administration Healthcare System, Medicine Service, 3350 La Jolla Village Drive, San Diego, CA 92161, USA
* Corresponding author. Department of Medicine, University of California, 9500 Gilman Drive, Mailcode 0732, La Jolla, CA 92093, USA.
E-mail address: bzuraw@ucsd.edu

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importance to identify whether angioedema is mast cell mediated (often called histaminergic) or bradykinin mediated. This article reviews the forms of angioedema that are likely bradykinin mediated and discusses the laboratory approaches for establishing a diagnosis.

BRADYKININ-MEDIATED ANGIOEDEMA

The kallikrein-kinin system consists of proteases (kallikreins) that cleave their substrate (kininogens) to release bioactive kinin. There are 2 primary kallikreins, tissue kallikrein and plasma kallikrein (PK), which are immunologically and functionally distinct. Tissue kallikrein is widely distributed in mammalian tissues and releases Lys-bradykinin (BK) from low-molecular-weight kininogen. To date, there is no evidence that tissue kallikrein participates in angioedema. On the other hand, there is substantial evidence showing that PK is involved in bradykinin-mediated angioedema (See Allen P. Kaplan and Kusumam Joseph's article, "Pathogenesis of Hereditary Angioedema: the Role of the Bradykinin Forming Cascade," in this issue).

Activation of the contact system results in the generation of bradykinin, a biologic mediator of enhanced endothelial permeability. Bradykinin-mediated vascular leakage in susceptible individuals can trigger attacks of angioedema typified by nonpitting asymmetric tissue swelling. There is strong evidence that implicates activation of the contact system and generation of bradykinin in the pathogenesis of swelling in HAE-C1INH. The evidence for a role of contact system activation and bradykinin in HAE with normal C1INH (HAE-nl-C1INH) is highly suggestive but currently less clearly delineated. The evidence for both forms of HAE is summarized.

Role of Bradykinin in Hereditary Angioedema due to C1 Inhibitor Deficiency

Landerman and colleagues[4] reported in 1962 that plasma from patients with HAE failed to inhibit PK and plasma dilution factor—now known to be FXII. One year later, Donaldson and Evans[5] established that C1INH activity was absent in patients with HAE, thus providing the definitive biochemical explanation for the cause of type I HAE. Soon thereafter, Rosen and colleagues[6] described a group of HAE patients who had normal plasma C1INH protein levels but lacked C1INH functional activity, thereby defining type II HAE.

C1INH is the major inhibitor of both active PK and active FXII of the contact system cascade.[7] The genesis of swelling in HAE types I and II has been established to evolve from the generation of bradykinin, engagement with the constitutively expressed B2-receptor on endothelial cells, and resultant vascular leak. Acceptance of the central role of the contact system in HAE was founded on series of observations recently reviewed.[8] In 1980 Curd and colleagues[9] detected active PK in the interstitial fluid from patients with HAE followed in 1982 by sequencing bradykinin as the permeability inducing factor.[10] This observation was extended by Fields and colleagues,[11] demonstrating that bradykinin, not C2 kinin, was responsible for vascular permeability. Further proof of the central role of contact system activation in HAE included the consumption of high-molecular-weight kininogen (HMWK) and cleavage of PK during attacks[12] as well as evidence that HMWK was cleaved during HAE attacks.[13–15]

Subsequently, plasma BK levels in HAE-C1INH subjects were shown significantly increased during attacks and normal or slightly increased during remission.[16,17] Most recently, well-controlled clinical trials have shown that the PK inhibitor ecallantide as well as the bradykinin B2-receptor antagonist icatibant are effective in the treatment of HAE-C1INH.[18,19] The increased circulating BK levels during attacks have been claimed to originate from the site of angioedema.[17] Based on the