

Hereditary angioedema with normal C1 inhibitor: Four types and counting



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The pathogenesis of hereditary angioedema (HAE) was elucidated in an elegant series of studies conducted during the 1980s and 1990s. Type I and II HAE were shown to result from mutations in *SERPING1* that lead to decreased plasma levels of functional C1 inhibitor (C1INH).¹ The diagnosis of HAE was further categorized by the demonstration in plasma of either low C1INH protein levels (type I HAE) or normal levels with dysfunctional protein (type II HAE). In the absence of adequate functional C1INH, the plasma contact system is insufficiently regulated with consequent generation of bradykinin, a vasoactive peptide that causes increased vascular permeability by binding to the bradykinin B2 receptor.² A number of new medications targeting the plasma contact system or the bradykinin B2 receptor were developed in the first 2 decades of the 21st century and have transformed the treatment of HAE.

In 2000, 2 groups independently described families with HAE in which the affected subjects had entirely normal C1INH levels and function.^{3,4} The pathophysiologic mechanism of this type of HAE was unknown, and there were no diagnostic tests or biomarkers available to establish the diagnosis.⁵ From its original description, HAE with normal C1INH levels was understood to be unresponsive to treatment with antihistamines, corticosteroids, and epinephrine. Furthermore, a number of anecdotal or small uncontrolled studies reported that bradykinin pathway-targeted medications appeared to work in these patients, suggesting that this might also be a bradykinin-mediated disease. Despite these reports, the lack of pivotal clinical studies and the inability to definitively establish the diagnosis have made treating these patients highly fraught.

A major breakthrough in our understanding of HAE with normal C1INH levels came with the discovery in 2006 that some families with HAE with normal C1INH levels had mutations in exon 9 of the *F12* gene (which codes for FXII) that cosorted with disease activity.⁶ This led to the convention of naming HAE with normal C1INH as either HAE-FXII in patients with a causal *F12* mutation or HAE-unknown in patients without a *F12* mutation. Over the past several years, the relevance of these *F12* mutations

for contact system activation and bradykinin generation has been substantially advanced. One of the *F12* mutations, p.Thr309Lys, was shown to cause enhanced susceptibility of the contact system to become activated both *ex vivo* and *in vivo*.⁷ The *F12* mutations were also shown to enhance susceptibility of FXII to activation by plasmin,⁸ providing a potential explanation for the efficacy of antifibrinolytic medications in the treatment of HAE with normal C1INH levels, including HAE-FXII. Unfortunately, only 20% to 25% of patients with HAE with normal C1INH levels in Europe have a *F12* mutation.^{5,6} Although HAE-FXII has been found in other regions in addition to central Europe, it is notable that HAE-FXII appears to be very rare in the United States.

In this issue of the *Journal*, Bafunno et al⁹ used whole-exome sequencing to identify a novel mutation in the angiotensin 1 gene (*ANGPT1*), which cosorted with angioedema symptoms in an Italian family with HAE-unknown. This article makes 3 important contributions to our understanding of HAE with normal C1INH levels. First, it identifies a new diagnostic marker that can be used to establish a diagnosis in patients with recurrent angioedema without urticaria. Second, it confirms that HAE with normal C1INH levels encompasses a diverse group of individual diseases. Third, it broadens our concept of the underlying pathophysiology of HAE from an exclusive focus on the contact system to now including the vasculature itself.

Without a diagnostic biomarker, HAE with normal C1INH levels is difficult to diagnose accurately. Genotyping exon 9 has become a routine part of the evaluation of patients suspected of having HAE with normal C1INH levels in many centers, and when results are positive, it confirms the diagnosis. Although this report identified the *ANGPT1* mutation in only a single Italian family, affected members of a second Brazilian family of non-Italian extraction with HAE with normal C1INH levels were independently discovered to have an *ANGPT1* mutation (A. Grumach, personal communication). Therefore genotyping *ANGPT1* should become part of the complete workup for patients suspected of having HAE with normal C1INH levels.

When initially described, HAE with normal C1INH levels was called type III HAE. It has become increasingly clear that HAE with normal C1INH levels does not represent a single type of HAE (Fig 1). Until recently, HAE with normal C1INH levels was divided into patients with a known *F12* mutation (HAE-FXII) and those without a *F12* mutation (HAE-unknown). This article marks the third discrete form of HAE with normal C1INH levels (HAE-ANGPT1). Another group has recently discovered a mutation in the plasminogen gene that cosorted with disease activity, identifying a fourth type of HAE with normal C1INH levels (HAE-PLG).¹⁰ We do not yet know how many of the patients with HAE with normal C1INH levels will fall into one of the 3 known gene mutation subtypes. In all likelihood, a large group of patients will still be classified as HAE-unknown, and other mutations remain to be discovered in the future.

Perhaps the most important implication of the identification of *ANGPT1* mutations causing HAE with normal C1INH levels is that we now must expand our understanding of the

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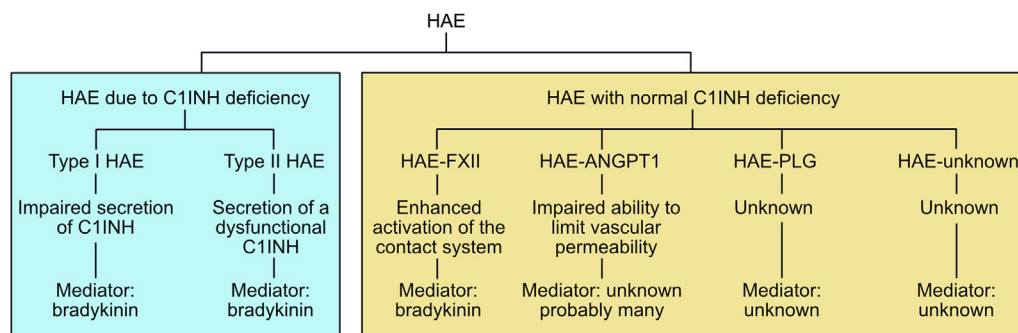


FIG 1. Current understanding of the types of HAE and the mechanism of swelling. HAE can be divided into 2 broad groups: (1) C1INH deficiency or (2) normal C1INH levels. Each broad group has several subtypes. HAE types are shown, as well as the most likely mechanism leading to angioedema and the mediator of swelling.

pathophysiology of HAE beyond the contact system to the vasculature. This mutation was unexpected because it identified a gene that is not directly related to either the contact system or bradykinin receptors. The authors show that the p.Ala119Ser mutation decreases the amount of ANGPT1 in plasma and also impairs the ability of ANGPT1 to form multimers, leading to a reduction in the ability of the mutant protein to bind to its cognate receptor, tunica interna endothelial cell kinase 2 (Tie2). ANGPT1-Tie2 signaling is known to stabilize the vasculature and diminish vascular permeability. In contrast, angiopoietin 2 (ANGPT2) often antagonizes ANGPT1, thereby enhancing vascular permeability. The authors found a decreased ANGPT1/ANGPT2 ratio in patients carrying the p.Ala119Ser mutation compared with healthy control subjects. These results provide a plausible mechanism by which the vasculature in patients with p.Ala119Ser becomes susceptible to enhanced vascular permeability mediated by a variety of mediators, rather than just bradykinin. Knockout of *ANGPT1* or the gene for Tie2 is embryonically lethal because of vascular defects; however, the p.Ala119Ser mutation causes only a partial deficiency of ANGPT1. Using nailfold capillaroscopy, the authors found that the patients carrying this mutation showed evidence of microvascular abnormalities. Whether these patients might manifest other vascular abnormalities in addition to the angioedema needs to be followed. It is also interesting to note that several different therapeutic approaches have been developed to restore normal ANGPT1-Tie2 signaling and reduce vascular permeability and inflammation, potentially offering a novel approach to HAE treatment.

HAE has been described as an experiment in nature that has taught us much of what we know about the plasma contact system. The clear phenotype of HAE, as well as the easily measurable

response to treatment, make HAE an excellent model to test experimental hypotheses. Nature's experiments continue to teach us, and we might now see HAE contribute to our understanding of vascular biology.

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