Hereditary Angioedema with Normal C1 Inhibitor

Update on Evaluation and Treatment

Markus Magerl, MD[a,*], Anastasios E. Germenis, MD, PhD[b], Coen Maas, PhD[c], Marcus Maurer, MD[a]

KEYWORDS

• Hereditary angioedema • Factor XII • Plasmin • Mutation • Bradykinin • C1-inhibitor

KEY POINTS

- Clinically, hereditary angioedema with normal C1 inhibitor (HAE-nC1) is similar to hereditary angioedema caused by C1 inhibitor (C1-INH) deficiency, but not identical. About a quarter of HAE-nC1 cases are attributed to mutations in the F12 gene; in three-quarters of the cases the pathomechanism is still widely unknown.
- Swelling attacks in patients with HAE-nC1 are thought to be caused by bradykinin.
- As of now, there are no routine laboratory tests to confirm the diagnosis of HAE-nC1, so the diagnosis is based on history and clinical criteria.

INTRODUCTION

Hereditary angioedema (HAE) was first described by Dinkelacker[1] and Quincke[2] in 1882 and a few years later by Osler[3] as recurrent angioedema with a positive family history. In 1963, Donaldson[4] identified the "absence of serum inhibitor of C′ 1-esterase" (C1-INH) as the underlying disorder of type 1 HAE caused by C1-INH deficiency (HAE-C1-INH). Not long after, Rosen and colleagues[5] described a second genetic variant of HAE-C1-INH, which is caused by deficient functional activity of

Conflicts of interest: M. Magerl has received consultancy/honorarium fees from Shire, Viropharma, CSL Behring, and Sobi. A.E. Germenis has received research support from Shire (grant no: IIR-GRC-000905), Amgen, and Novartis; has received consultancy fees from Shire; has received lecture fees from Novartis and Amgen; and has received travel support from Shire. C. Maas is consultant to Shire, Pharming. M. Maurer has received research support, consultancy/lecture fees, and/or travel support from Biocryst, CSL Behring, and Shire/Dyax/Viropharma.

[a] Department of Dermatology and Allergy, Allergie-Centrum-Charité/ECARF, Charité - Universitätsmedizin Berlin, Charitéplatz 1, Berlin 10117, Germany; [b] Department of Immunology and Histocompatibility, Faculty of Medicine, School of Health Sciences, University of Thessaly, Panepistimiou 3, GR-41500 Biopolis, Larissa, Greece; [c] Department of Clinical Chemistry and Haematology, University Medical Center Utrecht, Heidelberglaan 100, Utrecht 3584CX, The Netherlands

* Corresponding author.

E-mail address: markus.magerl@charite.de

Immunol Allergy Clin N Am 37 (2017) 571–584

http://dx.doi.org/10.1016/j.iac.2017.04.004

immunology.theclinics.com

C1-INH. Bradykinin, which results from activation of the contact system, was first suspected in the 1960s to be the mediator responsible for the signs and symptoms of both types of HAE-C1-INH,[6,7] and this was proved in the 1990s.[8] In 2000, a new form of HAE with normal C1-INH was first described, independently from each other, by Binkley and colleagues[9] and Bork and colleagues.[10] Initially, this new type of HAE was called HAE type 3. Its current designation is HAE with normal C1-INH (HAE-nC1). Four mutations in the FXII gene have been described to be linked to HAEnC1,[11–13] all of which affect the proline-rich region (PRR) of the FXII protein. HAE-nC1 in patients with a mutation in the FXII gene is designated as HAE with F12 gene mutation (HAE-FXII). However, in most patients with HAE-nC1, no mutation in the FXII gene can be found, and the pathogenesis remains unclear (HAE unknown [HAE-UNK]).

THE PATHOPHYSIOLOGY OF HEREDITARY ANGIOEDEMA WITH NORMAL C1 INHIBITOR

Swelling attacks in patients with HAE-C1-INH are brought about by activation of the contact system and the subsequent generation of bradykinin, which causes extravasation by activating the bradykinin 2 receptor. This pathomechanism is thought to also be involved in HAE-nC1. The contact system, a side-branch enzyme system of the coagulation system, consists of factor XII (FXII), plasma prekallikrein (PPK), and high-molecular-weight kininogen (HK). These factors generate spontaneous enzymatic activity when they assemble on surface materials (**Fig. 1**). The contact system is linked to the coagulation system by factor XI (FXI): both PPK and FXI are complexed with HK in the systemic circulation. Surfaces that activate the contact system can be non-natural, such as the inner surfaces of extracorporeal membrane oxygenation devices,[14] or the mineral particulate kaolin, which is commonly used in coagulation diagnostics.[15] However, several endogenously occurring triggering materials for contact system activation have been identified. These materials include extracellular nucleic acids,[16] platelet polyphosphate,[17] mast cell–derived heparin,[18] and aggregated proteins,[19] including toxic aggregates that are formed by amyloid-β peptide.[20] During contact activation, FXII lands on the activating surface and becomes spontaneously active. Both PPK and FXI are presented for activation by activated FXII (FXIIa). Several reciprocal cleavage steps between FXIIa and plasma kallikrein (PK) are needed to generate a burst of enzyme activity. HK is needed to concentrate these factors on

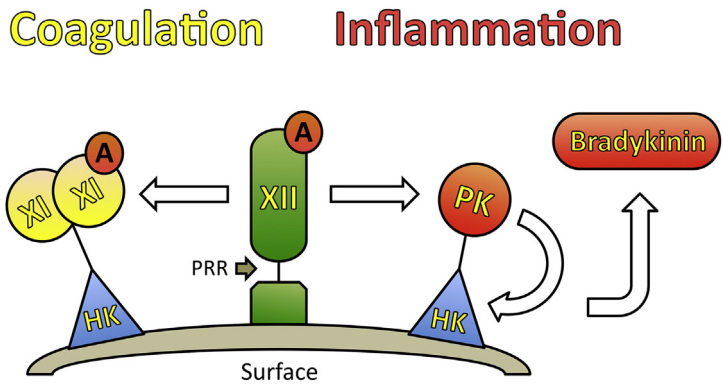

Fig. 1. Assembly and crosstalk of the factors of the contact system. Factor XII (XII) attaches to the surface and becomes active (FXIIa). Next, it can activate PPK to active plasma kallikrein (PK). Simultaneously, FXIIa activates factor XI (FXIa). HK mediates assembly of PK and FXI on the contact surface. Ultimately, bradykinin is liberated by PK from HK.