Med Clin (Barc). 2015;145(8):356–365

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Diagnosis and treatment

Hereditary angioedema☆

Angioedema hereditario

Teresa Caballero Molina[a,b,c,*], María Pedrosa Delgado[a,c], Carmen Gómez Traseira[a,c]

[a] Instituto de Investigación del Hospital Universitario La Paz (IdiPaz), Madrid, Spain
[b] Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER, U754), Madrid, Spain
[c] Grupo Español de estudio del Angioedema mediado por Bradicinina (GEAB), Madrid, Spain

ARTICLE INFO

Article history:
Received 15 September 2014
Accepted 11 December 2014
Available online 10 March 2016

Introduction

Angioedema (AE) is the swelling (oedema) of the subcutaneous and/or submucosal tissue due to a transient increase in vascular permeability by the release of vasoactive mediators, which produces a swelling of the affected area.

AE can be associated or not to urticaria. A consensus classification of AE without wheals has recently been published, which essentially divides Hereditary AE (HAE) and Acquired AE (AAE) (Table 1).[1]

Hereditary forms are divided into those occurring with deficiency of the C1 esterase inhibitor (C1-INH) and *C1NH* gene mutation (C1-INH-HAE) and those without C1-INH deficiency (nC1-INH-HAE).

Hereditary angioedema with C1 esterase inhibitor deficiency

2 phenotypic variants have been described as antigenic concentrations of C1-INH.[2] Type I (85%) is characterized by a quantitative decrease of C1-INH and, therefore, a decrease in its functional activity; in type II (15%) normal or elevated concentrations of dysfunctional C1-INH, with a low functional activity.

Hereditary angioedema without C1 esterase inhibitor deficiency

In 2000 a variant of HAE was described in which both, concentrations and function of C1-INH were normal.[3,4] It was proposed to call it type III HAE or HAE with normal C1 inhibitor (nC1-INH-HAE).[3] This HAE type has also been termed oestrogen dependent HAE[4] or HAE associated with oestrogen.[2] The molecular basis for some families with this type of HAE is a mutation in the gene *F12* encoding coagulation factor XII (FXII),[5,6] so it was proposed to call it HAE-FXII.[7] To refer to cases of HAE without C1-INH deficiency and without mutation in the *F12* gene, the term HAE without C1-INH deficiency of unknown cause[7] was proposed. It is proposed to stop using the term HAE typeIII.[8]

The prevalence of the various types of HAE is unknown. It is estimated that C1-INH-HAE affects 1:10,000 and 1:100,000[9] (about 1:50,000). In Spain the minimum prevalence is 1.09/100,000.[10] On the other hand, there are no prevalence studies of nC1-INH-HAE, although it seems very low.

Pathophysiology

Both C1-INH-HAE as well as nC1-INH-HAE are characterized by increased production of bradykinin (BK),[1,2,6,9] that binds to type 2 BK receptor (BR2) and produces a localized increase in vascular permeability and AE[9] (Fig. 1). The BK is rapidly metabolized by endogenous kininases[9] (Fig. 2).

High concentrations of endogenous or exogenous oestrogens may lead to a worsening of AE[11,12] by several mechanisms.[9] Taking drugs that inhibit angiotensin converting enzyme (ACE) inhibitors can also cause a worsening of AE by inhibition of the primary BK inactivator.[9]

Genetics

Both C1-INH-HAE as well as HAE-FXII are autosomal dominant hereditary diseases.[9]

☆ Please cite this article as: Caballero Molina T, Pedrosa Delgado M, Gómez Traseira C. Angioedema hereditario. Med Clin (Barc). 2015;145:356–365.

* Corresponding author.
E-mail addresses: mteresa.caballero@idipaz.es, mteresa.caballero@salud.madrid.org (T. Caballero Molina).

Table 1
Classification of angioedema without wheals.

Acquired	No identified cause	Response to H1 antihistamines	Idiopathic histaminergic acquired angioedema (IH-AAE)
		Non-response to H1 antihistamines	Idiopathic non-histaminergic acquired angioedema (InH-AAE)
	ACEI treatment (enalapril, etc.)	No other cause of AE	Acquired angioedema associated with ACEI (ACEI-AAE)
	C1-INH deficiency	No family history. Start > 40 years	Acquired angioedema with C1-INH deficiency (C1-INH-AAE)
Hereditary	C1-INH deficiency	C1-INH genetic deficiency	Hereditary angioedema with C1-INH deficiency (C1-INH-HAE)
	Normal C1-INH (nC1-INH-HAE)	Gene mutation *F12*	Hereditary angioedema with FXII mutation (HAE-FXII)
		Unknown cause	Unknown cause hereditary angioedema (U-HAE)

nC1-INH-HAE, hereditary angioedema with normal C1 esterase inhibitor; C1-INH, C1 esterase inhibitor; FXII, coagulation factor XII; H1, histamine receptor type 1; ACEI, angiotensin-converting enzyme inhibitors.
Modified from Cicardi et al.[1]

Hereditary angioedema types I and II with C1 esterase inhibitor deficiency

The C1-INH protein is encoded by the gene *C1NH* or *SERPING1*, located on chromosome 11, subregion q11–q13.1.[2] Patients suffering from C1-INH-HAE are mostly heterozygous, although homozygous cases have been described in patients with consanguineous parents.[9]

Mutations in the *C1NH* gene are very heterogeneous. More than 300 different ones have been published.[9] Mutations in C1-INH-HAE type I are distributed throughout the gene and are very diverse.[9] By contrast, in the C1-INH-HAE type II mutations are of the single base modification type (point mutations), located in the exon 8, in the region encoding the active centre or hinge region of the protein, generating a non-functional C1-INH.[9] There is a high prevalence of de novo mutations (around 25% of C1-INH-HAE cases).[9]

Hereditary angioedema with normal C1 esterase inhibitor

nC1-INH-HAE is very heterogeneous and includes HAE-FXII. The *F12* gene encoding the FXII is located on chromosome 5. The 2 mutations described initially consist of substitutions in the DNA of one base for another (*missense mutations*) (p.Thr 309Lys, p.Thr 309Arg) and are located in exon 9 of gene *F12*.[5,6,11,13,14] Sporadic cases have been described of other mutations that affect the same region of gene *F12*.[11]

Clinical signs and symptoms

HAE is characterized by recurrent episodes of transient, limited, cold, white, hard and non-pruritic swelling of the dermis or subcutaneous or submucosal tissue, without accompanying urticaria.[2,9] It can affect different areas of the subcutaneous tissue in the submucosa of the gastrointestinal tract and upper respiratory tract.[2,7,9] Table 2 summarizes the typical symptoms depending on the affected area. The most frequent episodes in C1-INH-HAE are peripheral cutaneous and abdominal,[15] and peripheral in nC1-INH-HAE.[11] Combined and migratory attacks are frequent.[2,15] In nC1-INH-HAE there is a higher incidence of facial involvement (labial and lingual) and a lower percentage of abdominal and laryngeal attacks.[11] Characteristically, haemorrhages have been observed in oedematous areas of the skin.[11]

The episodes are self-limited. Typically, the attack intensity increases during the first 12–24 h, and then begins to subside spontaneously during the following 48–72 h, although they can last up to 5 days.[2,11]

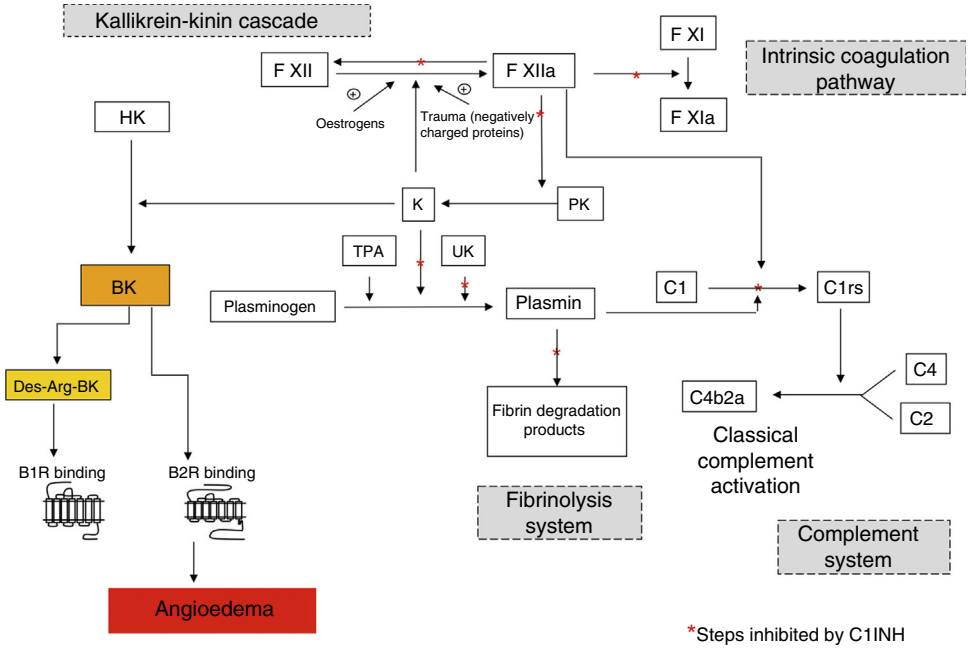

Fig. 1. Pathophysiology of hereditary angioedema.
TPA, tissue plasminogen activator; BK, bradykinin; B1R, bradykinin B1 receptor; B2R, bradykinin B2 receptor; C1, fraction 1 of complement; C1rs, components C1r and C1s of the complement; C1-INH, C1 esterase inhibitor; C2, fraction 2 of complement; C4, fraction 4 of complement; C4b2a, C3 convertase; FXI, coagulation factor XI; FXIa, activated coagulation factor XI; FXII, coagulation factor XII; FXIIa, activated coagulation factor XII; HK, high molecular weight kininogen; K, kallikrein; PK, prekallikrein; UK, urokinase.
Modified from Guilarte.[60]