Consensus Statement on the Diagnosis, Management, and Treatment of Angioedema Mediated by Bradykinin. Part I. Classification, Epidemiology, Pathophysiology, Genetics, Clinical Symptoms, and Diagnosis

Spanish Study Group on Bradykinin-Induced Angioedema (SGBA) (Grupo Español de Estudio del Angioedema mediado por Bradicinina: GEAB)

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Abstract

Background: There are no Spanish guidelines or consensus statement on bradykinin-induced angioedema.
Aim: To review the pathophysiology, genetics, and clinical symptoms of the different types of bradykinin-induced angioedema and to draft a consensus statement in light of currently available scientific evidence and the experience of experts. This statement will serve as a guideline to health professionals.
Methods: The consensus was led by the Spanish Study Group on Bradykinin-Induced Angioedema (SGBA), a working group of the Spanish Society of Allergology and Clinical Immunology. A review was conducted of scientific papers on different types of bradykinin-induced angioedema (hereditary and acquired angioedema due to C1 inhibitor deficiency, hereditary angioedema related to estrogens, angioedema induced by angiotensin-converting enzyme inhibitors). Several discussion meetings of the SGBA were held in Madrid to reach the consensus.
Results: The pathophysiology, genetics, and clinical symptoms of the different types of angioedema are reviewed. Diagnostic approaches are discussed and the consensus reached is described.
Conclusions: A review of bradykinin-induced angioedema and a consensus on diagnosis are presented.

Key words: Angioedema. C1-inhibitor. Bradykinin. Estrogens. ACE inhibitors.

Resumen

Introducción: No existen guías previas españolas sobre el manejo del angioedema mediado por bradicinina.
Objetivos: Revisar la fisiopatología, genética y clínica y alcanzar un consenso sobre el diagnóstico de los diferentes tipos de angioedema mediado por bradicinina a la luz de la evidencia científica disponible y la experiencia de los expertos, que sirva como guía para profesionales de la salud.
Métodos: SGBA/GEAB, un grupo de trabajo de la SEAIC dirigió el consenso. Se realizó una revisión de los documentos científicos publicados sobre los diferentes tipos de angioedema mediado por bradicinina [angioedema hereditario o adquirido por deficiencia de inhibidor de la C1 esterasa, angioedema hereditario relacionado con estrógenos (AEH tipo III, AEH-FXII), angioedema inducido por IECA (inhibidores del enzima convertidor de angiotensina]. Hubo varias reuniones del SGBA/GEAB para alcanzar el consenso.
Resultados: Se revisan la fisiopatología, genética y clínica de los diferentes tipos de angioedema por bradicinina. Por otro lado, se discuten los procedimientos diagnósticos y se describe el consenso alcanzado sobre el diagnóstico.
Conclusiones: Se presenta una revisión del angioedema mediado por bradicinina y un consenso sobre el diagnóstico del angioedema mediado por bradicina.

Palabras clave: Angioedema. C1 inhibidor. Bradicinina. Estrógenos. Inhibidores de la ECA.

Introduction

This paper is a consensus statement on the diagnosis, management, and treatment of angioedema (AE) mediated by bradykinin (BK). It was drafted in light of current available scientific evidence and the experience of experts. It is intended to serve as a guideline for health professionals. We also performed a thorough review of published literature on BK-induced AE so that it could serve as a basis for consultation.

The first part of the consensus addresses the epidemiology, classification, genetics, pathophysiology, clinical symptoms, and diagnosis of BK-induced AE. Treatment, follow-up, and special situations (eg, contraception, pregnancy, blood donation, organ transplant) will be addressed in the second part [1].

BK-induced AE can be divided into 2 main groups: *a)* AE with a deficiency in the C1-esterase inhibitor (C1-INH), which may be hereditary (HAE-C1-INH) or acquired (AAE-C1-INH); and *b)* AE without C1-INH deficiency. AE without C1-INH deficiency comprises 2 subgroups: estrogen-related HAE and AE induced by angiotensin-converting enzyme inhibitors (AE-ACEi) (Table 1).

a) Deficiency of functionally active C1-INH may be hereditary or acquired. The hereditary form (HAE-C1-INH) is a primary immunodeficiency and is the most common genetic defect of the complement system. Two phenotypic variants have been described [2-3]. Type I is the most common (85%) and is characterized by a quantitative decrease in C1-INH, which results in diminished functional activity (HAE-C1-INH type I). Type II (15%) is characterized by normal or high levels of C1-INH, which is dysfunctional (HAE-C1-INH type II). The acquired form (AAE-C1-INH) is biochemically characterized by low yC1-INH concentrations and/or diminished C1-INH function and no family history. It is mainly associated with B-cell lymphoproliferative diseases and occasionally with autoimmune, neoplastic, and infectious diseases. In some cases, autoantibodies to C1-INH interfere with its functional activity. The production of C1-INH is normal or slightly increased.

b) Recently, a hereditary variant of AE related to estrogens was described and was initially called hereditary angioedema type III (HAE type III) [4-5]. In this type, both C1-INH levels and function are normal or slightly decreased. HAE type III is heterogeneous, and, in some cases, a mutation has been detected in the *F12* gene (HAE-FXII) [6].

The remaining hereditary AE forms with normal C1-INH function and in which no mutations of the *C1NH* gene or the *F12* gene have been named HAE-unknown [6].

The prevalence of the different types of BK-induced AE is not known. It is estimated that HAE-C1-INH (types I and II) affects between 1 in 10,000 and 1 in 50,000 inhabitants, with no differences in prevalence in relation to gender and race. A national registry of patients with HAE-C1-INH types I and II has been published in Spain and reports a minimum national prevalence of 1.09/100 000 inhabitants [7].

Table 1. Classification of Bradykinin-Induced Angioedema

Bradykinin-induced AE	With C1-INH deficiency	Hereditary (HAE-C1-INH)	Type I (HAE-C1-INH Type I)
			Type II (HAE-C1-INH type II)
		Acquired (AAE-C1-INH)	
	With normal CI-INH	Hereditary (estrogen-related) (HAE type III)	With FXII mutation (HAE-FXII)
			Without FXII mutation (HAE-unknown)
		Associated with ACEi (AE-ACEi)	

Abbreviations: AE, angioedema; ACEi, angiotensin-converting enzyme inhibitors; C1-INH, C1 esterase inhibitor

Although there are no prevalence and incidence studies on HAE-FXII and AAE-C1-INH, the prevalence of both conditions seems to be low. In contrast, the published prevalence of AE-ACEi is much higher, ranging from 0.1%-2.2% [8,9] to as high as 2.8%-6% in a prospective assessment of some clinical trials [10].

HAE-C1-INH, AAE-C1-INH, and HAE-FXII are rare diseases (prevalence of less than 1 in 2000 inhabitants) and are registered as such in the Orphanet database (http://www.orpha.net/). Since 1999, the European Union (EU) has had specific legislation on orphan drugs and rare diseases, which has helped the development of drugs for these types of diseases [11].

According to the experience of the Spanish Study Group on Bradykinin-Induced Angioedema (SGBA) (Grupo Español de Estudio del Angioedema mediado por Bradicinina; GEAB), these illnesses are not well known by primary care physicians and other specialists, leading to problems in diagnosis and clinical management, especially in emergency treatment.

Although there are international guidelines on the management and treatment of AE due to C1-INH deficiency, application of these guidelines in Spain has proven difficult, due to regulatory and structural differences, uneven knowledge of the disease among health professionals (eg, physicians, chemists, nurses, and dentists), and differences in health care management. Therefore, we need to create diagnostic and treatment guidelines for BK-induced AE. This is the first consensus document to address BK-induced AE as a whole and not just as that caused by C1-INH deficiency.

Methods

SGBA/GEAB, a working group of the Sociedad Española de Alergia e Inmunología Clínica (SEAIC; *Spanish Society of Allergy and Clinical Immunology*), led the consensus.

Bibliographic Search

Data sources: A comprehensive search of the English-language scientific literature on different types of BK-induced AE was carried out on PubMed using the following key words: *angioedema, bradykinin, hereditary angioedema, acquired angioedema, C1 inhibitor deficiency, C1 inhibitor, estrogens, HAE type III, HAE-FXII*, and *angiotensin I-converting enzyme inhibitors*. Additional references were identified from the reference list of published articles. Searches were last updated on September 30, 2010.

Discussion

Several discussion meetings were held in Madrid to reach the consensus.

Document

Each author was responsible for a specific part of the manuscript and carried out the relevant search. The final document was elaborated by the coordinator (T Caballero) and reviewed by all the co-authors in successive rounds according to a modification of the Delphi method.

Genetics

Genetic disorders differ according to the type of HAE.

Hereditary AE Due to C1-INH Deficiency or Dysfunction (HAE-C1-INH Types I and II)

The C1-INH protein is encoded by the *C1NH* gene (GenBank X54486; Swiss-Prot PO5155), also known as *SERPING1*, which is located on chromosome 11 sub-region q11-q13.1. This gene is characterized by the presence of frequent Alu repeats in the introns. Alu repeats are the largest multigene family in the human genome and may also act as nucleation points for homologous recombination between dispersed Alu elements. This could result in different genetic exchanges, including duplications, deletions, translocations, and insertions, and thereby favor genetic instability [12,13].

HAE-C1-INH is transmitted in an autosomal dominant manner, and patients are heterozygous, except in specific cases of patients with consanguineous parents [14,15]. The fact that heterozygous individuals have C1-INH levels between 5% and 30% of the normal range (far from the expected 50% for an autosomal dominant defect) seems to be due not only to a defect in the synthesis of C1-INH, but also to excessive catabolism of this protein in patients with HAE-C1-INH type I [16] or to a decrease in expression of mRNA of the normal *C1NH* allele [17].

Structural abnormalities of the *C1NH* gene in patients with HAE-C1-INH are very heterogeneous, with more than 200 mutations registered and only a few mutations encountered more than once [18-24]. A high prevalence of de novo mutations has been described in approximately 25% of cases of HAE-C1-INH [18,25]. The mutations are different in the 2 types of HAE due to C1-INH deficiency. In type I, they are very heterogeneous, are distributed throughout the *C1NH* gene, and consist of large rearrangements, including partial deletions and, less frequently, partial duplications [26-29]. In contrast, the mutations involved in HAE-C1-INH type II are located in the same position in exon 8 of the *C1NH* gene, which encodes the active center or hinge region, generating inactive C1-INH [30].

The genetic disorders described in HAE due to C1-INH deficiency are collected in large universal genetic databases (OMIM ID 106100, Human Gene Mutation Database 119041) and in a database specific to this disease (http://hae.enzim.hu), which includes genetic studies performed in Spain [23].

Hereditary AE Related to Estrogens (HAE Type III), Including Hereditary AE Associated With a Mutation in FXII (HAE-FXII)

HAE type III is a highly heterogeneous entity that includes 2 or more conditions with different genetic causes. The existence of 2 different substitutions of one base for another in the DNA (missense mutation) has been demonstrated. These substitutions, p.Thr309Lys and p.Thr309Arg, are located at the same position in exon 9 of the gene that encodes FXII, which is located on chromosome 5 (OMIM 610618) [31-35]. To date, all patients whose cases have been published have been heterozygous for the 2 described mutations. The subgroup of HAE type III with the described mutations in *F12* is known as HAE-FXII [6].

Pathogenesis

This group of diseases shares a common element, namely, the presence of locally high transient and episodic levels of BK [8,10,32,36-43]. There is no inflammatory component or allergy, so treatment is very different from that of AE with an allergic or histaminergic origin [44-46].

BK is a nonapeptide from the kinin family that splits off from the high-molecular-weight kininogen as a consequence of the plasma kallikrein action resulting from activation of the contact system (Figure 1) [47]. It is involved in tissue permeability, vascular dilation, and vascular smooth muscle relaxation processes; therefore, elevation increases vascular permeability, and plasma extravasation into the interstitial space of subcutaneous or submucosal tissue, thus leading to onset of AE [37,46]. Its biological effect is exerted through activation of the bradykinin B2 receptor (B2R), which is constitutively expressed in the membranes of endothelial and smooth muscle cells [48,49].

Other kinins are kallidin (Lys-bradykinin), a decapeptide obtained by the action of tissue kallikrein on low-molecular-weight kininogen (LW) [47] and the metabolites des-Arg-bradykinin and des-Arg-kallidin [50].

Plasma BK is quickly transformed into peptides by the action of 2 metallopeptidases, kininase I (carboxypeptidase N [CPN] and kininase II (angiotensin converting enzyme: [ACE] [51-53] (Figure 1). Other enzymes that may contribute to the degradation of BK are aminopeptidase P (APP), neutral endopeptidase (enkephalinase or neprilysin), dipeptidyl peptidase IV, and aminopeptidase N [50].

CPN is responsible for the transformation of BK into its active metabolite des-arginine^9-bradykinin (des-Arg^9-BK) or bradykinin-(1-8), which has low affinity for B2R but interacts with bradykinin type 1 receptor (B1R) [45]. ACE and neutral endopeptidase degrade BK into bradykinin-(1-7). Both bradykinin-(1-8) and bradykinin-(1-7) are degraded to bradykinin-(1-5) by ACE. For its part, APP inactivates BK by splitting the Arg residue [45].

The role of BK and B2R in the generation of AE is well understood [54] and has been the basis for the development of new treatments for HAE-C1-INH, such as icatibant acetate, a selective blocker of B2R [55]. B1R is closely related to

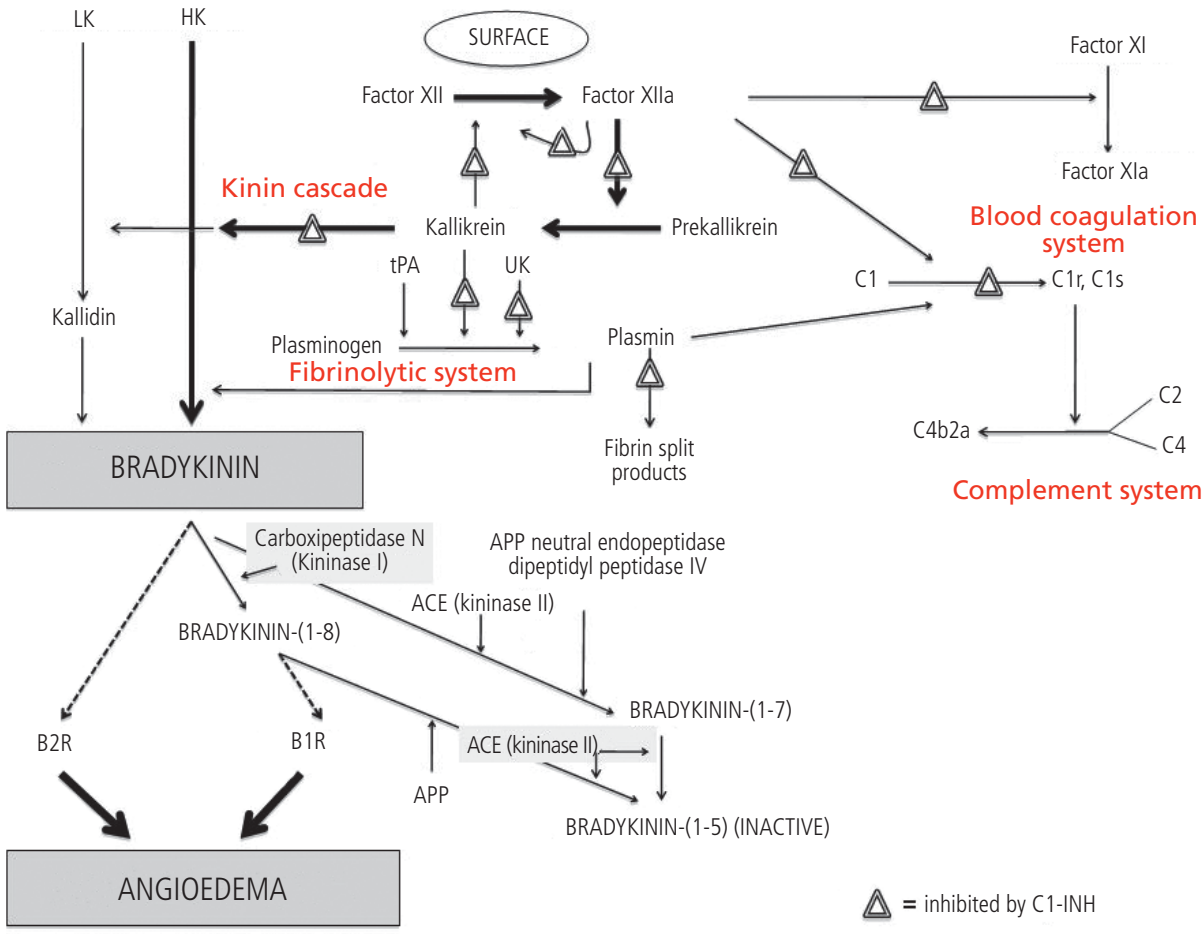

Figure 1. The contact system is formed by a substrate, HK and 2 zymogens (prekallikrein and FXII), which reciprocally activate each other to form the enzymes kallikrein and activated FXII (XIIa). BK is released from HK as a result of the enzymatic excision by kallikrein. BK indicates bradykinin; B2R, bradykinin B2 receptor; BIR, bradykinin B1 receptor; LK, low-molecular-weight kininogen; HK, high-molecular-weight kininogen; ACE, angiotensin-converting enzyme; C1-INH, C1 esterase inhibitor; APP, aminopeptidase P; UK, urokinase; tPA, tissue plasminogen activator.

B2R and is activated by Lys-des-Arg^9-BK and des-Arg^9-BK, metabolites of kallidin and BK, respectively [45]. B1R is not expressed in a constitutional manner, but is induced in the cell membrane by inflammation, as occurs during the response to tissue damage, bacterial endotoxins (eg, lipopolysaccharides), and proinflammatory cytokines interleukin 1ß (IL-1ß) or tumor necrosis factor α [48,56-59]. The involvement of B1R in the generation of AE is uncertain, although recent in vivo and in vitro studies in experimental animal models and with human cells suggest a possible contribution of B1R to the development and maintenance of AE, especially in the presence of proinflammatory cytokines [56].

All those factors that activate the contact system can produce an increase in the formation of BK and thereby increase the frequency and severity of AE attacks [40]. Similarly, inhibition or activation of enzymes involved in the metabolism of BK, as well as polymorphisms that affect their concentration or activity, can influence the generation of AE and, therefore, the severity of the clinical expression of this pathology.

Elevated levels of endogenous and exogenous estrogens can lead to worsening of AE episodes through various mechanisms [60,61]. Exogenous administration of estrogens may increase levels of FXII, kallikrein, and kinins [62-69] and inhibit ACE [70-72]. In addition, estrogens enhance the genetic expression and function of B2R [73].

ACEi produce a decrease in the catabolism of BK and thus an increase in BK plasma levels, resulting in worsening of the different types of BK-induced AE [6,74].

Trauma may trigger episodes of AE through contact system activation by the release of phospholipid microparticles from damaged cells and from activated platelets [74,75].

Angioedema With C1-INH Deficiency

In this group, AE is caused by a decrease in C1-INH or a deficit in the functioning of C1-INH, which in turn leads to an excessive increase in the production of BK [44].

The C1 fraction of complement (C1 esterase) is the first protein of the complement system. It circulates in an inactive form and is activated during immunological processes. Its function is to initiate the complement cascade, splitting off proteins from the classical pathway (C4 and C2) [76].

C1-INH, also called SERPING1, belongs to the serpin superfamily (serine protease inhibitors) [76] and is synthesized primarily in hepatocytes [77]. It acts both as an inhibitor of the first step in the activation of the classical complement pathway and as the main inhibitor of the contact system (through inhibition of activated FXII and of the conversion of prekallikrein into kallikrein) and hence as an inhibitor of the formation of BK [45].

C1-INH is the primary regulator of the activity of the complement C1r and C1s fractions, controlling both the rate of activation and inactivation of C1q [76]. In patients with excess functioning of C1 esterase due to a lack of C1-INH, levels of C2 and C4, the natural substrates of the complement C1s fraction, decrease much more pronouncedly during AE attacks [74,78]. The protein that follows C2 in the classical complement cascade is C3, and its level is usually normal in patients with HAE-C1-INH, since it is controlled independently of C1-INH [79].

C1-INH also inactivates other proteases in the complement system (mannose-binding lectin–associated serine proteases [MASP-1 and MASP-2]) and in other plasma cascades, namely, the contact system (FXII and kallikrein), the coagulation system (factor XI and thrombin), and the fibrinolytic system (tissue plasminogen and plasmin) (Figure 1) [76].

C1-INH is the most potent inhibitor of the contact system; therefore, low concentrations can activate the system [45]. Its lack produces uncontrolled activation of FXII, leading to formation of kallikrein. The lack of C1-INH also produces activation of the fibrinolytic system with an increase in plasmin [80-81]. Kallikrein produces an increase in BK through its split from high-molecular-weight kininogen [41]. This step is facilitated by the presence of plasmin [82] (Figure 1).

HAE-C1-INH: The C1-INH deficiency is hereditary, producing either low levels of C1-INH (HAE-C1-INH type I) or normal levels of C1-INH with altered function (HAE-C1-INH type II). In both cases, there is uncontrolled activation of the complement system.

AAE-C1-INH: C1-INH deficiency is acquired. It is characterized by massive activation of the classical complement pathway and accelerated catabolism of C1-INH [83]. Initially, neoplastic lymphatic tissues were observed to consume C1-INH and components of the classical complement pathway [84,85]. The associated disease led to C1-INH consumption either by triggering massive activation of the classical complement pathway or by acting directly on C1-INH. Anti-idiotype antibodies can react with M-components to form idiotype–anti-idiotype complexes that bind C1q [86]. In addition, catabolism of C1-INH can increase through excessive activation of C1 esterase by abnormal proteins (globulins or immune complexes), which increases C1_C1-INH binding and depletion of both C1 and C1-INH [87]. Finally, a high percentage of patients have IgG, IgA, or IgM autoantibodies to C1-INH, which block C1-INH activity [88-90].

Regardless of the mechanism of C1-INH consumption, low levels of C1-INH are associated with an increase in activity of the complement and contact systems. This results in low levels of the complement C4 fraction in plasma and normal levels of C3 in plasma. C1q levels are frequently very low in the acquired form [91].

Angioedema Without C1-INH Deficiency

Hereditary angioedema related to estrogens (HAE type III), including hereditary angioedema associated with a mutation in F12 (HAE-FXII): In HAE type III, an increase in BK is produced through the activation of FXII. A highly conserved mutation has been detected in the *F12* gene (AE linked to FXII) (HAE-FXII) in a subgroup of patients (20%) [6,31,32,35]. Some studies have shown an increase in the amidolytic enzyme activity of FXII, but not in its plasma levels, in patients with HAE-FXII who are carriers of the p.Thr309Lys mutation [6,32]. Modification of FXII may activate the kinin system and cause excessive formation of BK and generation of AE [32]. The role of the *F12* gene mutation in the generation of AE remains unclear, and BK has not been confirmed as the final

mediator in HAE type III. However, the clinical similarities with HAE-C1INH [6,92,93], the marked worsening with estrogens [6,92,93] and ACEi [6,90,91], the lack of response to treatment with antihistamines and corticosteroids [6,92,93], and the response to treatment with tranexamic acid [55,92,94], pdhC1INH [6,92], and icatibant acetate [95] support the assertion that contact system activation is involved in its pathogenesis and that BK is the primary mediator [96].

The expression and plasma levels of FXII are regulated by estrogens [69], since there is an estrogen response element in the promoter region of the *F12* gene that contributes to an increase in its genetic expression during pregnancy [69,97]. This would explain the prevalence of the disease in females and the triggering of AE episodes by relatively high levels of estrogens.

In some patients, *ACE* and *APP* gene polymorphisms have been associated with lower circulating levels of these enzymes, which are responsible for the degradation of BK and its active metabolite [98].

AE-ACEi: BK and substance P have been implicated in the pathogenesis of AE induced by ACEi [41,99,100]. An increase in local BK is produced as a result of inhibition of its catabolism by the blocking of ACE [8,37,39,41,101] (Figure 1). ACEi slow the processing of C-terminal arginine residues of vasoactive peptides such as BK, thus prolonging their biological activity [102]. In some patients, there has been a decrease in the activity of dipeptidyl peptidase IV, which may contribute to an increase in BK by slowing down its metabolism [99,100].

CPN is responsible for the transformation of BK into its active metabolite, des-arg-BK, which is elevated in patients with AE-ACEi [102].

With the exogenous administration of ACEi, APP remains primarily responsible for the inactivation of BK and des-Arg-BK. Therefore, individuals with low plasma concentrations of aminopeptidase are more likely to develop AE at the onset of treatment with ACEi [101]. CPN or APP plasma activity and levels are reduced in some patients with AE-ACEi [50,103,104].

Insertion/deletion polymorphisms have been described in the *ACE* gene and are responsible for 50% of the variability in ACE serum levels [105]: insertion of the allele (I) is associated with reduced expression of ACE mRNA and a decrease in the degradation of BK [106]. Genetic variants of the gene that encodes APP (*XPNPEP2*) lead to reduced APP activity and higher levels of BK and des-Arg9-BK, which have been associated with a higher prevalence of AE-ACEi [104].

Clinical Features

Angioedema With C1-INH Deficiency

Hereditary Angioedema With C1-INH Deficiency or Dysfunction (HAE-C1-INH Types I and II)

HAE-C1-INH is characterized by recurrent episodes of submucosal or subcutaneous edema at various locations (face, extremities, buttocks, genitals, gastrointestinal tract, larynx, other) [91,107], which usually revert within 48 to 72 hours, although they can persist for up to 5 days on rare occasions. Attacks that affect the extremities are the most common.

Clinical expression is extremely variable—some patients remain asymptomatic all their life—and has no significant correlation with C1-INH plasma concentrations [72]. According to the Spanish national registry, 13.7% of patients were asymptomatic [7]. Although symptoms can start at any stage of life, they most commonly appear at school age. Half of all patients present symptoms in the first decade of life and a third during the second. The condition tends to worsen after puberty [74].

Some patients experience symptoms that help to predict the attack (prodrome). These symptoms include sudden mood swings, anxiety, notable asthenia, itching, or skin paresthesia, the sensation of skin thickening, and erythema marginatum–like exanthema [74,108,109].

A precipitating factor can be identified in 50% of attacks (Table 2)[61,91,107,108,110,111].

Depending on the location of the edema, we can observe the following (Table 3):

Cutaneous or peripheral involvement: This is the most common manifestation and can affect the face, extremities, genitals, buttocks, and trunk. It is episodic, recurrent, circumscribed with poorly defined borders and without erythema, pruritus, or increased temperature. It is not associated with urticaria [74,91,112]. The extremities are the most commonly involved location.

Gastrointestinal involvement: Between 70% and 80% of patients present recurrent abdominal pain caused by edema in the stomach or intestinal wall [74,107,113] and free fluid in the peritoneal cavity. Gastrointestinal involvement is the only manifestation of the disease in up to 21% of cases, thereby delaying diagnosis [114]. Episodes can range from slight discomfort to intense abdominal pain and cramping that is refractory to analgesic treatment and progresses to abdominal distension, nausea, vomiting, and constipation (due to obstruction of the gastrointestinal tract). Sometimes, after the attack has resolved, passage of edema fluid from the wall to the intestinal lumen can lead to diarrhea [115,116].

Table 2. Precipitating Factors of Acute Angioedema Attacks in Patients With HAE-C1-INH

Psychological	Emotional stress, anxiety
Trauma (even minimal)	Particularly important are those affecting the oral cavity (dental manipulations, gastroscopy, bronchoscopy, orotracheal intubation)
Hormones	Menses, pregnancy, and puberty
Drugs	Estrogen-containing drugs (oral contraceptives, hormonal replacement therapy) and ACEi
Infections	Upper respiratory tract infections, *Helicobacter pylori* infection

Abbreviation: ACEi, angiotensin-converting enzyme inhibitors; HAE-C1-INH, hereditary angioedema due to C1 inhibitor deficiency.

Table 3. Typical Symptoms of Bradykinin-Induced Angioedema

Location	Clinical Characteristics	Therapeutic Response
Skin	Recurrent nonerythematous, nonpruriginous, circumscribed angioedema, with no temperature increase. Not associated with urticaria	No response to conventional treatment with corticosteroids, antihistamines, and adrenaline. Good response to treatment with pdhC1INH, rhC1INH, icatibant acetate, and ecallantide
Gastrointestinal tract	Recurrent colicky abdominal pain (sometimes severe), abdominal distension, nausea, vomiting, constipation or diarrhea, orthostatic hypotension, dehydration, and hypovolemic shock. Differential diagnosis should be made with acute abdomen	No response to conventional treatment with analgesics. Good response to pdhC1INH, rhC1INH, icatibant acetate, and ecallantide
Larynx	Pharyngolaryngeal edema, upper airway collapse, asphyxia, and death	No response to conventional treatment with corticosteroids, antihistamines, and adrenaline. Good response to pdhC1INH, rhC1INH, icatibant acetate, and ecallantide

Hypovolemia, resulting from the loss of fluid, plasma expulsion, and vasodilation, can occur in some cases and may produce orthostatic hypotension, dehydration, and hypovolemic shock [117,118].

Differential diagnosis with acute surgical abdomen is often made in the emergency room, since there may be abdominal defense, as well as an elevation of the hematocrit to 65% and leukocytosis due to hemoconcentration [107,119]. Approximately one-third of patients with undiagnosed HAE are operated on unnecessarily during an abdominal attack [91].

Laryngeal involvement: This is the most serious clinical manifestation, as it can progress to collapse of the airways and death by asphyxiation. Some series describe laryngeal episodes that occur at least once in the patient's lifetime in 50% of cases [120] and as a first attack in some cases [121].

Presentation at other sites: Isolated cases have been reported of transient pleuritic symptoms due to pleural effusion [107], pancreatitis, nonviral hepatitis, hemiparesis, seizures due to local transient cerebral edema, and urinary symptoms [122,123].

Clinical Peculiarities in Children and Adolescents

Attacks that affect the extremities are the most common. Abdominal episodes are more frequent than laryngeal episodes [91,107,124], appearing as the initial symptom in 40%-80% of children [125-127].

Among the noteworthy precipitating factors in this age group are dentition, minimal mechanical trauma, upper respiratory infections, menstruation, and estrogen hormone contraception [61,91,107,124,128-132]. Restriction of physical activities is not recommended, but should be decided on an individual basis.

Angioedema With Acquired C1-INH Deficiency (AAE-C1-INH)

The clinical characteristics of AAE-C1-INH are indistinguishable from those of HAE-C1-INH. The distinctive features are as follows: *1)* older age of onset (fourth and fifth decade of life or later) [133-134]; *2)* no family history of AE (although with HAE-C1-INH approximately 25% may have a de novo mutation [25]); *3)* poorer response to pdhC1INH replacement therapy in acute attacks; *4)* improved response to maintenance antifibrinolytic therapy; and *5)* clinical manifestations of the associated disease that may appear years after onset of AE [74,135-137].

Angioedema Without C1-INH Deficiency

Hereditary Angioedema Related to Estrogens (HAE Type III), Including Hereditary Angioedema Associated With a Mutation in F12 (HAE-FXII)

AE episodes in women are clinically identical to HAE-C1-INH, although facial locations seem to be more frequent in some series [6]. Clinical symptoms generally start or are exacerbated in the presence of high levels of endogenous (pregnancy) or exogenous estrogens (oral contraceptives, hormone replacement therapy), ACEi, or ARB [4-6,138,139].

Angioedema Induced by Angiotensin-Converting Enzyme Inhibitors (AE-ACEi)

AE may develop in a minority of patients during treatment with ACEi. It is not dose-related, usually occurs after years of treatment, and can occur with any ACEi [39]. Sporadic episodes may occur during treatment with these drugs. It is clinically similar to those described above, primarily affects the orofacial region (tongue, lips), and could potentially be life-threatening, due to the development of laryngeal edema [140-143]. There have also been reports of abdominal AE, sometimes as the only location [101,144]. Episodes may persist for months, after medication has been withdrawn.

Diagnosis

The rarity and broad clinical heterogeneity of this disease

means it is often underdiagnosed, and there are significant diagnostic delays after the onset of symptoms. While declining, diagnostic delay is still around 13.1 years [7].

Laboratory Diagnosis

Angioedema With C1-INH Deficiency (HAE-C1INH Type I/II and AAE-C1-INH)

Confirmation of clinical suspicion requires a reduction in C1-INH functional activity, which must be lower than 50% (see attached algorithm in Figure 2) [125].

Screening is conducted by determining C4, which is decreased not only during AE attacks, although some cases have reported normal C4 [145,146]. Therefore, when clinical suspicion is high, quantitative and functional values of C1-INH should be determined at the same time. Additionally, in those cases in which C4 is normal, it should be determined during an attack [123,147].

Quantitative and functional measurements of C1-INH rule out or confirm the disease and distinguish between HAE-C1-INH type I and II (Table 4). Thus in type II, unlike type I, quantitative levels may be normal or even increased.

Diagnosis should be based on 2 quantitatively and/or functionally reduced readings of C4 and C1-INH, separated by 1 to 3 months.

On finding low levels of C4 and a reduction in C1-INH functional activity, C1-INH deficiency can be diagnosed with a specificity of 98%-100% [145] and with a negative predictive value of 96% [148]. As C4 deficiency is relatively common [7], determination of both parameters is necessary in order to establish a diagnosis. Moreover, C1-INH and C4 values do not correlate with clinical severity [74].

In the initial diagnosis, if the patient is being treated with attenuated androgens, C4 should be determined 2 weeks after the patient has stopped taking those drugs. If pdhC1INH or fresh frozen plasma (FFP) has been administered, the laboratory determination can be made on the third day after administration.

Antigenic levels of C1q are extremely useful for the diagnosis of AAE-C1-INH, in which they are typically diminished, and allow us to differentiate the acquired form

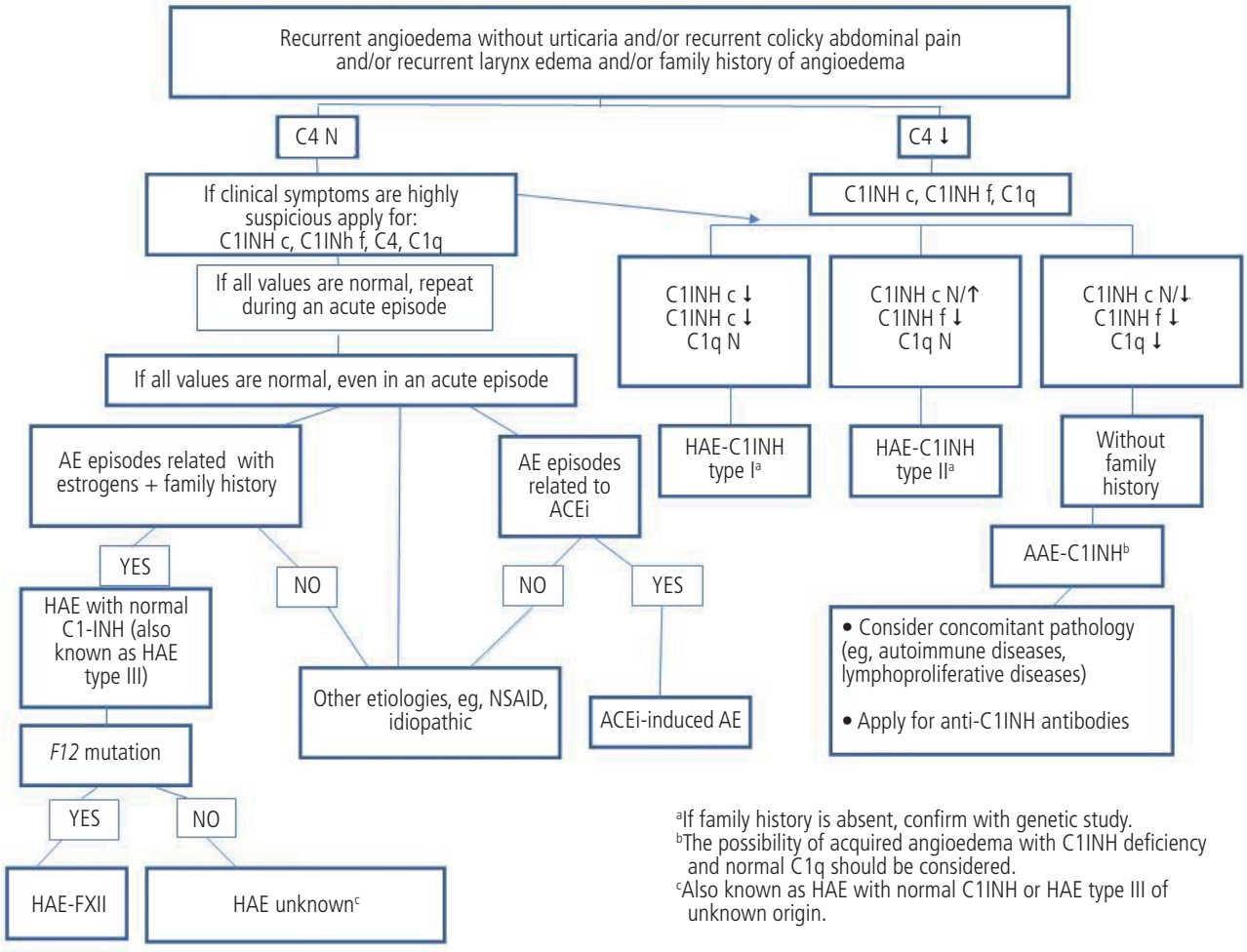

Figure 2. Diagnostic algorithm. AAE indicates acquired angioedema; ACEi, angiotensin-converting enzyme inhibitor; C1-INH, C1 esterase inhibitor; HAE, hereditary angioedema; C1-INHc, C1-INH concentration; C1-INHf, C1-INH function; NSAID, nonsteroidal anti-inflammatory drug.

Table 4. Complement Values in the Different Types of Angioedema

Type	Antigenic C1-INH	Functional C1-INH	C4	C1q
HAE-C1-INH type I	↓	<50%	↓[a]	N
HAE-C1-INH type II	N/↑	<50%	↓	N
AAE-C1-INH	↓/N	↓	↓	↓
HAE with normal C1-INH	N	N/↓[b]	N	N
AE-ACEi	N	N	N	N

Abbreviations: AE-ACEi, angioedema induced by angiotensin-converting enzime inhibitors; AAE-C1-INH, acquired angioedema due to C1 inhibitor deficiency; HAE-C1-INH, hereditary angioedema due to C1 inhibitor deficiency; N, normal.
[a]Can be normal in some cases.
[b]Can be mildly decreased in some patients [6].

of AE (AAE-C1-INH) from the hereditary form (HAE-C1-INH) [91]. However, C1q can also be diminished in some cases of HAE-C1-INH, such as homozygous individuals, and sometimes in cases temporarily due to other causes, such as the presence of autoantibodies and viral infections [149-151].

As for other complement parameters, CH50 may be diminished or normal. Serum C2 levels are diminished during AE attacks, but are seldom normal between attacks in some patients. However, CH50 and C2 determinations are complex and not indicated in the study of HAE-C1-INH [152]. The levels of the other complement factors are normal in this type of AE.

Laboratory Techniques

The methods for determining the various parameters are specified in Table 5.

The functional activity of C1-INH should be determined by a chromogenic method rather than by enzyme-linked immunosorbent assay (ELISA), due to its high discriminatory power (positive predictive value of 98%) [153]. As a reference standard, an established mixture of more than 50 plasma samples should be used [74,147], and this must be preserved in optimum conditions. The determination should be made in plasma, and the samples preserved below ±20ºC [153]. Consequently, determinations should be conducted in experienced laboratories.

A false-positive diagnosis can be ruled out with the determination of functional activity of C1-INH along with the determination of C4, provided that storage conditions and the technique used are correct.

Angioedema Without C1-INH Deficiency (HAE Type III and AE-ACEi)

In HAE without C1-INH deficiency, both for cases when the *F12* mutation is present and for cases when the cause of AE is not known, C4 and quantitative and functional values for C1-INH are normal. There are cases, however, in which C1-INH function is slightly diminished [6]. It has been hypothesized that the decrease may be due to uncontrolled proteolysis of C1-INH by contact system proteases, such as *F12*, whose expression is regulated by estrogens [33]. Therefore, this form of AE should be suspected in cases with a positive family history and when the angioedema is associated with exogenous estrogens or with hyperestrogenic states such as pregnancy. Confirmation of the diagnosis should be established through genetic testing, although, as already explained, the *F12* gene mutation is not present in all patients.

In AE-ACEi, the values of complement factors are also normal. It should be suspected in all patients with AE (especially if located on the head and neck) who are receiving ACEi and do not respond to treatment with antihistamines, corticosteroids, or adrenaline. Normal results in the study of complement factors help to reinforce clinical suspicion and to rule out the possibility of AE with C1-INH deficiency.

Table 5. Laboratory Techniques for Measurement of Complement Values. Adapted from [148,153]

Measurement	Technique	Substrate	Comments
C4	Radial immunodiffusion or nephelometry	Sera or plasma (sodium citrate or EDTA)	
Quantitative C1-INH	Radial immunodiffusion or nephelometry or ELISA	Sera or plasma (sodium citrate or EDTA)	
Functional C1-INH[a]	Chromogenic assay	Plasma (sodium citrate or EDTA)	Freeze below ±20ºC
C1q	Radial immunodiffusion	Sera or plasma	

Abbreviations: AE, angioedema; ACEi, angiotensin-converting enzyme inhibitors; C1-INH, C1 esterase inhibitor.

Genetic Study

Although the genetic study will confirm the diagnosis, it is especially useful in the following situations [154]:

- Early diagnosis of offspring (before 1 year of age).
- Case studies with high clinical suspicion where the complement study is inconclusive.
- Cases with no family history, in order to characterize a possible de novo mutation.
- Doubtful cases, in order to differentiate the hereditary form from the acquired form.
- Pre-implantation genetic diagnosis.
- Diagnosis of HAE type III (HAE with no C1-INH deficiency): detection of the FXII mutation is the only test to date that confirms the diagnosis of HAE-FXII.

Diagnosis in Offspring

Children of parents with HAE-C1-INH types I and II have a 50% risk of inheriting the disease. Some authors propose searching for the genetic mutation, if it is known, in cord blood [155]. Determination of antigenic and functional C1-INH levels in cord blood is not very useful, since data indicate that they are reduced in the cord blood of 30%-50% of normal infants [155,156].

In the absence of a genetic diagnosis, it is advisable to wait until the infant is at least 1 year old before making a determination of C1-INH, since false positives and false negatives are often reported in determinations in infants younger than a year.

Clinically Suspected Diagnosis in the Emergency Department

We must consider a diagnosis of BK-induced AE in the following cases:

• Peripheral AE with no urticaria and/or pharyngo-laryngeal edema that does not respond to treatment with optimal doses of adrenaline, antihistamines, and/or corticosteroids.

• Recurrent abdominal cramps within the differential diagnosis of acute abdomen. Ultrasound has proven exceptionally useful in the diagnosis [157,158]. Findings may be variable and include ascites, thickening of the abdominal wall, and intestinal hypermotility or hypomotility. These findings have also been reported after computed tomography scan [159]; however, exploration by ultrasound is preferable for reasons of safety.

• In patients treated with ACEi who do not respond to conventional treatment.

In cases that are refractory to conventional treatment, pdhC1INH or icatibant acetate can be considered (see Treatment). The therapeutic response will be useful for diagnosis. In these cases, although determination of complement factor levels is not considered urgent, it is advisable to take samples of plasma in EDTA or citrate before administering pdhC1INH or FFP for further diagnosis.

The final version has been read and approved by all the authors.

Financial Support

Dr. Teresa Caballero is a researcher with the Hospital La Paz Health Research Institute (IdiPaz) program for promoting research activities (2009).

Publication of this manuscript is sponsored by the Spanish Society of Allergy and Clinical Immunology (SEAIC) and IdiPaz.

Acknowledgments

We would like to thank SEAIC for support with the preparation of this consensus.

Conflict of interest/Disclosures

Dr María Luisa Baeza has not received sponsorship for educational purposes and has not been paid for providing consultancy services. She has taken part in a clinical trial sponsored by Jerini AG/Shire.

Dr Teresa Caballero has received sponsorship for educational purposes, has been paid for providing consultancy services, and has taken part in clinical trials sponsored by Jerini AG/Shire, CSL-Behring, Dyax Corp, Pharming NV, and Viropharma Pharmaceutical.

Dr Rosario Cabañas has received sponsorship for educational purposes and has taken part in clinical trials sponsored by CSL-Behring, Dyax Corp, and Pharming NV.

Dr Angel Campos has received sponsorship for educational purposes and for providing consultancy services and has taken part in clinical trials sponsored by Jerini AG/Shire and Pharming NV.

Dr Stefan Cimbollek has received sponsorship for educational purposes and has taken part in clinical trials sponsored by Jerini AG/Shire, CSL-Behring, and Pharming NV.

Dr Carmen Gómez-Traseira has received sponsorship for educational purposes sponsored by Jerini AG/Shire.

Dr Teresa Gonzalez-Quevedo has received sponsorship for educational purposes, has been paid as lecturer by Jerini AG/Shire, and has taken part in clinical trials sponsored by CSL-Behring, Dyax Corp, and Pharming NV.

Dr Mar Guilarte has received sponsorship for educational purposes and has participated in clinical trials sponsored by Jerini AG/Shire and Pharming NV.

Dr Jesús Jurado-Palomo has taken part in clinical trials sponsored by CSL-Behring and Pharming NV.

Dr José Ignacio Larco has taken part in a clinical trial sponsored by CSL-Behring.

Dr María Concepción López-Serrano has received sponsorship for educational purposes, has been paid for providing consultancy services, and has taken part in clinical trials sponsored by Jerini AG/Shire, CSL-Behring, Dyax Corp, and Pharming NV.

Dr Margarita López Trascasa has received sponsorship for educational purposes sponsored by Jerini AG/Shire.

Dr Carmen Marcos has been paid for providing consultancy services sponsored by Jerini AG/Shire.

Dr Jesús Muñoz has not received sponsorship for educational purposes, has not been paid for providing consultancy services, and has not taken part in any clinical trials sponsored by Jerini AG/Shire, CSL-Behring, Dyax Corp, Pharming NV, and Viropharma Pharmaceutical.

Dr María Pedrosa has received sponsorship for educational purposes and has taken part in clinical trials sponsored by Jerini AG/Shire, CSL-Behring, and Pharming NV.

Dr Nieves Prior has received sponsorship for educational purposes and has taken part in clinical trials sponsored by Jerini AG/Shire, CSL-Behring, Dyax Corp, and Pharming NV.

Dr María Rubio has received sponsorship for educational purposes, has been paid for providing consultancy services, and has taken part in clinical trials sponsored by Jerini AG/Shire.

Dr Anna Sala has received sponsorship for educational purposes, has been paid for providing consultancy services, and has taken part in clinical trials sponsored by Jerini AG/Shire and Pharming NV.

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Manuscript received February 7, 2011; accepted for publication April 11, 2011.

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