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2022 Brazilian guidelines for hereditary angioedema – Part 1: definition, classification, and diagnosis

Diretrizes brasileiras do angioedema hereditário 2022 – Parte 1: definição, classificação e diagnóstico

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ABSTRACT

Hereditary angioedema is an autosomal dominant disease characterized by recurrent attacks of edema that affect the subcutaneous tissue and the submucosa, involving several organs. The main affected sites are the face, upper and lower limbs, gastrointestinal tract, and upper airways. Because health professionals lack knowledge about this condition, there is a significant delay in diagnosis, compromising the quality of life of affected individuals. Furthermore, delayed diagnosis may result in increased mortality from asphyxia due to laryngeal edema. The erratic nature of the attacks with variations in clinical course and severity of symptoms among different patients and in one patient throughout life constitutes a challenge in the care of patients with hereditary angioedema. The main type of hereditary angioedema results from more than 700 pathogenic variants of the *SERPING1* gene with functional or quantitative deficiency of the C1 inhibitor protein, but in recent years other mutations have been described in six other genes. Important advances have been made in the pathophysiology of the disease, and new drugs for the treatment of hereditary angioedema have been developed. In this context, the Brazilian Study Group on Hereditary Angioedema (GEBRAEH) in conjunction with the Brazilian Association of Allergy and Immunology (ASBAI)

RESUMO

O angioedema hereditário é uma doença autossômica dominante caracterizada por crises recorrentes de edema que acometem o tecido subcutâneo e o submucoso, com envolvimento de diversos órgãos. Os principais locais afetados são face, membros superiores e inferiores, as alças intestinais e as vias respiratórias superiores. Em decorrência da falta de conhecimento dessa condição por profissionais de saúde, ocorre atraso importante no seu diagnóstico, comprometendo a qualidade de vida dos indivíduos afetados. Além disso, o retardo no diagnóstico pode resultar em aumento da mortalidade por asfixia devido ao edema de laringe. A natureza errática das crises com variação do quadro clínico e gravidade dos sintomas entre diferentes pacientes, e no mesmo paciente ao longo da vida, se constitui em desafio no cuidado dos doentes que têm angioedema hereditário. O principal tipo de angioedema hereditário é resultante de mais de 700 variantes patogênicas do gene *SERPING1* com deficiência funcional ou quantitativa da proteína inibidor de C1, porém nos últimos anos outras mutações foram descritas em seis outros genes. Ocorreram avanços importantes na fisiopatologia da doença e novas drogas para o tratamento do angioedema hereditário foram desenvolvidas. Nesse contexto, o Grupo de Estudos Brasileiro em Angioedema

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updated the Brazilian guidelines on hereditary angioedema. Greater knowledge of different aspects resulted in the division of the guidelines into two parts, with definition, classification, and diagnosis being addressed in this first part.

Keywords: Angioedema, hereditary angioedema, diagnosis, classification, differential diagnosis

Hereditário (GEBRAEH) em conjunto com a Associação Brasileira de Alergia e Imunologia (ASBAI) atualizou as diretrizes brasileiras do angioedema hereditário. O maior conhecimento dos diversos aspectos resultou na divisão das diretrizes em duas partes, sendo nessa primeira parte abordados a definição, a classificação e o diagnóstico.

Descritores: Angioedema, angioedema hereditário, diagnóstico, classificação, diagnóstico diferencial.

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Hereditary angioedema: a look at the best care

In recent decades, there has been an important advance in knowledge about the pathophysiology and access to the molecular diagnosis of angioedema, which has allowed the identification of new forms associated with hereditary angioedema (HAE).[1] In addition, these advances have enabled the development of new, effective and safe drugs for the treatment of HAE. As a consequence, there was greater dissemination of the disease, which resulted in a greater number of patients identified, although national surveys still show a significant delay in the diagnosis of HAE, resulting in greater morbidity and mortality.[2]

The unpredictable and potentially fatal character of HAE negatively impacts the quality of life of affected individuals and their families.[2-4] Although this condition is characterized by the presence of symptoms only in periods of an angioedema crisis, other aspects influence the quality of life that are present in asymptomatic periods, emphasizing the need for continuous support for affected individuals.[3] Therefore, the support and guidance provided to patients and family members by the Brazilian Association of HAE Carriers (ABRANGHE) contribute to minimizing the burden and disseminating knowledge about the disease.

In this context, the first Brazilian guidelines for the diagnosis and treatment of hereditary angioedema were prepared by specialists from the Brazilian Association of Allergy and Immunology (ASBAI) in 2010 and updated in 2017, with the active presence of the Brazilian Study Group on Hereditary Angioedema (GEBRAEH).

Updating the Brazilian guidelines aims to disseminate knowledge about HAE, establish norms regarding its diagnosis and treatment in Brazil, following the best evidence and recommendations of international guidelines, with a view to better patient care. The most recent international guidelines indicate that the main goals of HAE treatment should be to achieve total control of the disease and provide a

normal life for the patient.[5] In addition, since the last update of the guidelines, in 2017, new treatments have been developed, as well as new forms of administration of existing drugs were approved by ANVISA, justifying the need for this update.

The 2022 Brazilian guidelines for the diagnosis and treatment of hereditary angioedema will be presented in two parts. In the first part, the definition, classification and diagnosis of HAE will be addressed and, in the second part, the therapeutic approach. A non-systematic literature review was performed with the selection of consensuses/guidelines and relevant articles from the MEDLINE database using PubMed. In addition, controversial points were debated among the participating authors.

What is hereditary angioedema?

Angioedema is a transient, circumscribed, asymmetrical, deforming, non-inflammatory, non-pruritic, sometimes painful, edema located in the subcutaneous layer of the skin and/or in the submucosa of some organs.[6,7]

HAE was first described in 1882 by Quincke, originally as "angioneurotic" edema, due to its association with psychological or psychiatric disorders.[8-10] In 1888, Osler established its hereditary nature, however, the first biochemical alteration associated with the disease, the deficiency of the C1 esterase inhibitor (C1-INH), was only identified 75 years later, when HAE was defined as a quantitative or qualitative deficiency of the C1 inhibitor (HAE-C1-INH).[11-13]

HAE is a rare, potentially fatal and underdiagnosed genetic disease, characterized by recurrent attacks of edema that can affect both the dermis and subcutaneous tissue as well as internal organs, predominantly the digestive system and upper respiratory tract.[14-15] It is characterized by angioedema without the presence of wheals, unlike histaminergic angioedema, where approximately 90% of patients have these skin lesions.[16] Approximately one third of patients with recurrent angioedema without wheals may be diagnosed with HAE.[17-18] Currently, two main groups of HAE are recognized: angioedema with C1-INH deficiency (HAE-C1-INH), and HAE with normal C1-INH (HAE-nC1-INH).The average worldwide prevalence of HAE-C1-INH has been estimated at approximately 1:67,000 (1.5 per 100,000 population), while HAE-nC1-INH is rarer, estimated to occur in 1:400,000 individuals.[19-20]

What are the causes of hereditary angioedema?

C1-INH is a glycoprotein encoded by the *SERPING1* gene, located on chromosome 11, and which has more than 700 mutations already described in HAE-C1-INH1. C1-INH is a member of the serpin or serine protease inhibitor super family; it acts as a suicidal inhibitor that irreversibly imprisons the target protein in an inactive, highly efficient complex.[21,22] Pathogenic variants in the *SERPING1* gene result in a quantitative reduction in the production of C1-INH, mainly by the hepatocyte, and in a decrease in its functional activity, causing HAE-C1-INH type I, responsible for 85% of cases. In HAE-C1-INH type II, there is the production of a dysfunctional protein without alteration in the quantitative levels of C1-INH, identified in 15% of the remaining cases.[23-25]

The inheritance pattern in HAE-C1-INH is autosomal dominant. In 25% of patients, a *de novo* mutation occurs, without an evident family history of the disease.[26-28] In HAE-C1-INH, the mutation occurs in one of the two copies of the *SERPING1* gene, with rare published cases of homozygosity. Mutations resulting in HAE-C1-INH type I can occur anywhere in the *SERPING1* gene, while mutations responsible for HAE-C1-INH type II occur in exon 8, where the loop of the C1-INH reactive center is located, giving rise to a dysfunctional protein.[28] In HAE-C1-INH type I, plasma levels of C1-INH should be close to 50%, however, patients with this type of HAE have levels that vary between 5% and 30% of normal plasma levels. This discrepancy can be explained by the finding that the C1-INH product of the mutated *SERPING1* gene forms an aggregate with the normal C1-INH, and this aggregate is retained in the endoplasmic reticulum, configuring a dominant negative mechanism.[24,28] Biochemical penetrance, with laboratory alterations, approaches 100%, but the clinical expression and severity of the disease are highly variable.[28]

In 2000, patients and families with angioedema were first described who manifested symptoms similar to those of patients with HAE-C1-INH, however, with normal quantitative and functional levels of C1-INH. This type of HAE was initially described as HAE type III, however this nomenclature is no longer used, and this type of HAE is currently designated as HAE with normal C1-INH (HAE-nC1-INH).[29] The inheritance pattern in HAE-nC1-INH is also autosomal dominant.[28]

What is the mechanism involved in hereditary angioedema?

C1 is the first component of the classical complement pathway and forms a complex by binding to one molecule of C1q, two of C1r and two of C1s. This complex has slow auto activation, however, when binding to an immune complex, C1 acquires its full activity. C1-INH inhibits the activated form of C1, stabilizing it and decreasing its activation. Each activated molecule of C1r and C1s irreversibly binds to a molecule of C1-INH.[30,31]

Initially, C1-INH was recognized only for its activity in inhibiting the complement system, both in classical and lectin pathways, without which it would result in an overly activated system. Subsequently, C1-INH was also associated with the inhibition of several proteases, including plasma kallikrein, coagulation factors XII (FXII) and XI, and plasmin. Therefore, in addition to inhibiting the complement system, C1-INH participates in the regulation of the contact systems and kallikrein/kinin, coagulation, and fibrinolysis.[25,31-33] Further studies have revealed that C1-INH deficiency in HAE-C1-INH results in overproduction of bradykinin (BK) that binds to the B2 receptor (BDKRB2), playing an important role in angioedema.[34-36] The development of new treatments, such as the B2 receptor antagonist of BK and kallikrein inhibitors, reinforced the role of BK as the main mediator in HAE-C1-INH.[37,38]

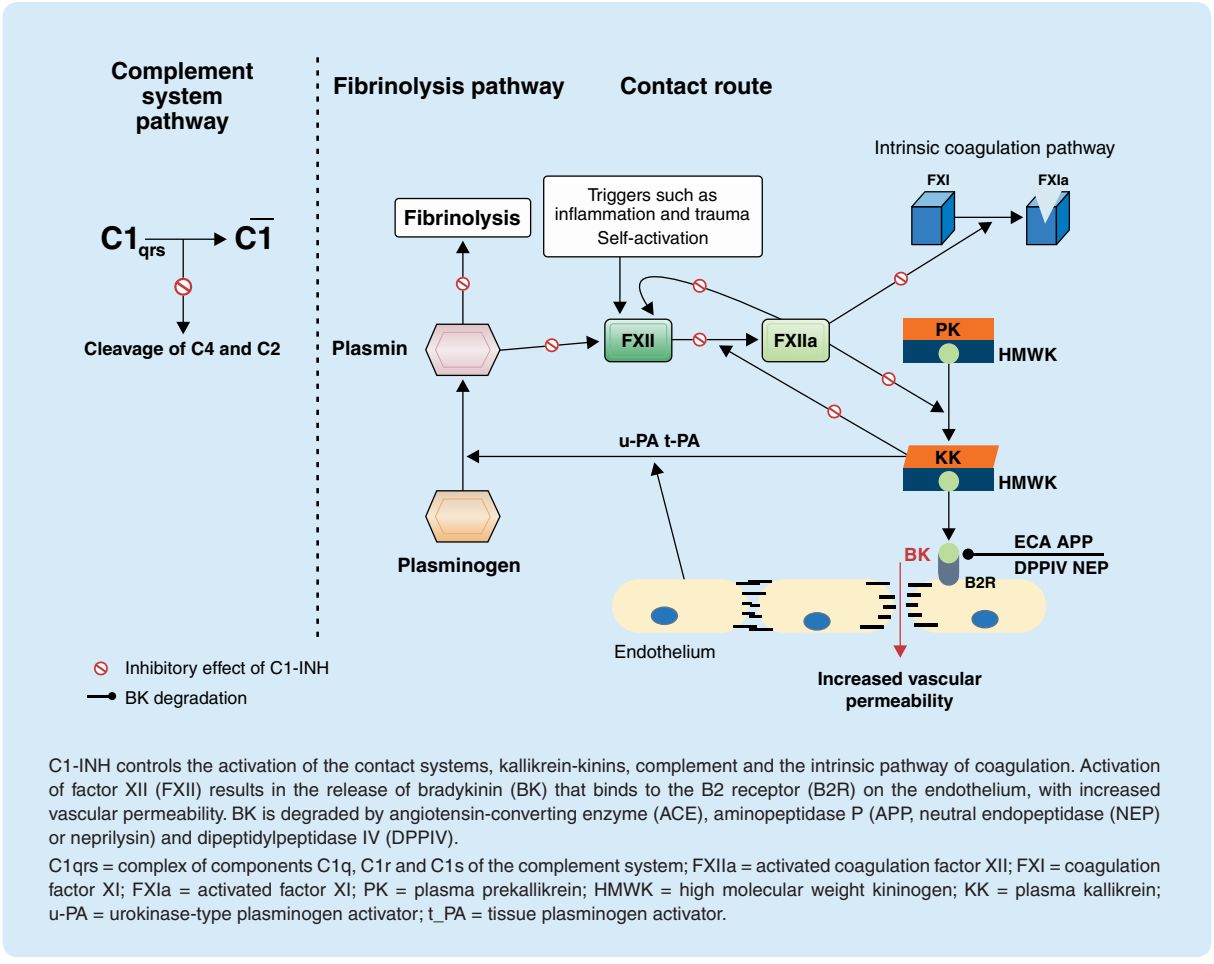
Commonly used synonymously, and despite exhibiting overlap and interactions, the terms plasma contact systems (SC) and kallikrein-kinin (SCC) are different. The SC refers to the proteolytic system initiated by the auto activation of factor XII (FXII), while the SCC consists of kallikrein that cleaves high molecular weight kininogen (HMWK) and thereby releases a vasoactive nonapeptide, BK.[39] Activation of FXII, with generation of FXIIa, is initiated by negatively charged surfaces, or macromolecules. Subsequently, FXIIa activates more FXII, in a process of self-activation. The next substrate in the cascade is prekallikrein, which will be converted to its active form, kallikrein, which in turn degrades HMWK, releasing BK. By binding to its B2 receptor, which is constitutively expressed on endothelial cells, BK interferes with endothelial junctions, increasing vascular permeability and inducing angioedema. BK also stimulates the production of nitric oxide by endothelial cells, which, consequently, triggers vasodilation by contracting the cytoskeleton. It is worth noting that the activation of FXII occurs close to the endothelial wall, determining the activation of the cascade that results in the production of BK that binds, in a paracrine way, to the B2 receptor on the endothelium. Additionally, kallikrein directly activates FXII and also acts on the fibrinolytic system, converting plasminogen into plasmin which, in turn, activates more FXII, forming a retroactivation cycle (Figure 1).[22,25,31,40-43]

Plasma BK has an extremely short half-life as it is readily degraded by various peptidases (Figure 1). Angiotensin-converting enzyme (ACE) is the most important peptidase for BK degradation. Dipeptidyl peptidase IV (DPPIV, neutral endopeptidase (NEP) or neprilysin) and aminopeptidase P (APP) are other peptidases that act in the same process. BK is transformed by these enzymes into des-Arg-BK, which is its inactive form.[40,44]

Among the systems inhibited by C1-INH, SC and SCC have greater relevance for the genesis of HAE-C1-INH. C1-INH inhibits the auto activation of FXII to FXIIa, the conversion of prekallikrein to kallikrein, the activation of FXII by kallikrein, and the proteolytic cleavage of HMWK with the release of BK. With all these steps inefficiently inhibited in the HAE-C1-INH, there will be an exaggerated release of BK.[25,30]

In recent years, the role of the local endothelium has gained importance in the attempt to explain the local nature of angioedema. In response to various stimuli, such as infection, trauma, and stress, the endothelium releases vasoactive substances that modulate both vasodilation and vasoconstriction, as well as vascular permeability. Plasma prekallikrein circulates in complex with HMWK and this complex can be recruited to the surface of the endothelium. Thus, the endothelium plays a key role in inducing the angioedema crisis. The mechanism responsible for inducing this process in a certain part of the organism, and not in another, and the fact that the crisis is localized and not systemic is still unknown. In addition, C1-INH has already been shown to bind to adhesion molecules on the endothelium wall, in addition to the complement system, making its inhibitory action more efficient. In summary, the endothelium, through the action of some stimuli, can become locally activated, initiating the process that culminates in the release and compartmentalized action of BK.[25]

In HAE-nC1-INH, mutations in the gene *F12* coding for FXII were described in a number of patient families, and this type of HAE was designated as HAE-FXII.[45] Among the four mutations in the *F12* gene that cause HAE-FXII, all located in exon 9, the missense mutation c.983C>A, which leads to the substitution of the amino acid threonine for lysine at position 328 of the FXII



C1-INH controls the activation of the contact systems, kallikrein-kinins, complement and the intrinsic pathway of coagulation. Activation of factor XII (FXII) results in the release of bradykinin (BK) that binds to the B2 receptor (B2R) on the endothelium, with increased vascular permeability. BK is degraded by angiotensin-converting enzyme (ACE), aminopeptidase P (APP, neutral endopeptidase (NEP) or neprilysin) and dipeptidylpeptidase IV (DPPIV).

C1qrs = complex of components C1q, C1r and C1s of the complement system; FXIIa = activated coagulation factor XII; FXI = coagulation factor XI; FXIa = activated factor XI; PK = plasma prekallikrein; HMWK = high molecular weight kininogen; KK = plasma kallikrein; u-PA = urokinase-type plasminogen activator; t_PA = tissue plasminogen activator.

Figure 1
C1 inhibitor (C1-INH) sites of action in contact systems, kallikrein-kinins, complement and intrinsic coagulation pathway

protein (p.Thr328Lys), has been the most frequently found.[20] Pathogenic variants in the *F12* gene make FXII more susceptible to activation by plasmin and other proteases.[20,28,46] The thrombin that is generated after trauma can activate FXII and explain angioedema after this stimulus.[47] As already described, FXII plays a central role in the initial phases of SC and SCC activation, and in the increase of BK[25] release.

However, not all patients with HAE-nC1-INH had mutated here that of the *F12*, that is, most remained with the HAE of *unknown cause* (HAE-U).[48] With the advent of new full-exome sequencing technologies, mutations in five genes other than *F12* have been described in families of HAE-nC1-INH1 patients (Table 1). A mutation in heterozygous and autosomal dominant transmission in the plasminogen gene (*PLG*) has been described and, to date, the mechanism of angioedema is still unclear.[49] In the same year, a mutation in the angiopoietin 1 gene (*ANGPT1*) he was identified. This mutation broadens the pathophysiological spectrum of angioedema, as it involves a gene unrelated to SC and SCC. Mutation of *ANGPT1* results in the synthesis of decreased amounts of *ANGPT1* in plasma and a decreased binding to its Tie2 receptor (*tunica interna* endothelial cell kinase 2). The binding of *ANGPT1* to Tie2 is important for the stabilization and reduction of vascular permeability.[50] Another mutation in the kininogen 1 gene (*KNG1*) was described in 2019 and the mechanism of angioedema is still unknown, but it may be related to the process of BK[51] formation. Subsequently, a mutation with possible gain of function in the myoferlin gene (*MYOF*) was associated with a new subtype of HAE-nC1-INH. Myoferlin is an endothelial cell membrane protein and modulates signal transduction via vascular endothelial growth factor (VEGF). The interaction of myoferlin

Table 1
Types of hereditary angioedema with normal C1-INH with identified pathogenic variants[1,20,53]

Type of HAE-nC1-INH	Gene	cDNA change	Change in protein	Chromosome	First description
HAE-FXII	*F12*	c.983C>A[a]	p.Thr328Lys	5	Dewald & Bork (2006)
HAE-FXII	*F12*	c.983C>G	p.Thr328Arg	5	Dewald & Bork (2006)
HAE-FXII	*F12*	c.971_1018+24del72	indel	5	Bork et al. (2011)
HAE-FXII	*F12*	c.892_909dup	p.Pro298_Pro33dup	5	Kiss et al. (2013)
HAE-PLG	*PLG*	c.988A>G	p.Lys330Glu	6	Bork et al. (2018)
HAE-ANGPT1	*ANGPT1*	c.807G>T[b]	p.Ala119Ser	8	Bafunno et al. (2018)
HAE-KNG1	*KNG1*	c.1136T>A[b]	p.Met379Lys	3	Bork et al. (2019)
HAE-Myoferlin	*MYOF*	c.651G>T[b]	p.Arg217Ser	10	Arian et al. (2020)
HAE-HS3OST6	*HS3ST6*	c.430A>T[b]	p.Thr144Ser	16	Bork et al. (2021)

[a] Mutation found in more than 90% of patients with HAE-FXII.
[b] Mutations described in only a single family.

with VEGF signaling pathways may be related to the release of nitric oxide which, in turn, is an important mediator of vascular permeability.[52] The most recently described mutation was that of the heparan sulfate-glucosamine 3-O-sulfotransferase 6 (*HS3ST6*) gene. It is suspected that this mutation leads to incomplete synthesis of heparan sulfate, affecting the structure of proteoglycans, and the consequent change in the interaction of HMWK with endothelial cells.[53]

Understanding the influence of estrogen, endogenous and/or exogenous on HAE-C1-INH, both in types I and II and in HAE-FXII, is still incomplete. The HAE-C1-INH is negatively impacted by estrogen, and the HAE-FXII was once considered estrogen-dependent, since some patients with an *F12* mutation have clinical manifestations only after pregnancy or with the use of contraceptives containing this hormone.[54-56] Estrogen stimulates the release of some cytokines and the heat shock protein called Hsp90, which in endothelial cells can convert prekallikrein into kallikrein, which cleaves HMWK, releasing BK. Additionally, kallikrein activates FXII either directly or by inducing the degradation of plasminogen to plasmin, which in turn activates FXII. Therefore, estrogen, by stimulating the release of Hsp90, induces the activation of FXII, mainly in HAE-FXII.[57] The promoter region of *F12* contains an estrogen-response element and has been shown to increase transcription of FXII mRNA in response to the hormone. It is likely that estrogen also contributes to increased BK B2 receptor expression. The action of BK is mediated by nitric oxide, and estrogen is a regulator of the release of this substance, contributing to BK-mediated angioedema. Finally, estrogen can decrease the degradation of BK by interfering with the activity of the angiotensin-converting enzyme.[33,58,59]

Therefore, so far, mutations in seven different genes have been described in patients with HAE, the most frequent being in the *SERPING1* gene followed by mutations in the *F12* gene related to HAE-C1-INH and HAE-FXII, respectively.[20] Other mutations identified in HAE patients and families involve genes encoding proteins that participate in BK production pathways, such as *SERPING1*, *F12*, *KNG1* and possibly *PLG* (fibrinolytic system).[20] Mutations in genes involved in the regulation of vascular permeability at the endothelium level, such as *ANGPT1* and *MYOF*, or in the endothelial regulation of the kinin system, such

as *HS3ST6*, have also been described in patients with HAE-nC1-INH, revealing new pathogenic pathways that may become therapeutic targets.[1,20,53] Thus, hereditary angioedema can also be classified based on the new mechanisms described:

– Bradykinin angioedema: HAE-C1-INH (types I and II), HAE-FXII, HAE-PLG, HAE-KNG;
– Angioedema due to vascular endothelium dysfunction: HAE-ANGPT1, HAE-MYOF and HAE-HS3ST6.

What are the typical clinical manifestations of hereditary angioedema?

General features

HAE symptoms can start at any age, however, in most patients they start in the first or second decade of life. Studies show the onset of symptoms in 75% of patients with HAE-C1-INH up to 15 years of age.[2,26,60-64] In general, in 50% of HAE-C1-INH cases, the onset of symptoms occurs around 10 years of age, with an increase in the frequency and severity of crises at puberty.[65] In the HAE-nC1-INH, most cases are triggered in adolescence, as reported in a Brazilian cohort, in which 72% of patients (n = 197) had their first crisis between the second and third decades of life.[66,67]

HAE is manifested by recurrent and unpredictable episodes of angioedema, in any part of the body.[68-70] The frequency and severity of HAE crises varies between patients and throughout the life of the same patient.[5,68,69,71,72] It is described that 5% of individuals with HAE are asymptomatic, and 25% develop sporadic symptoms.[69,73-75] The frequency of attacks is individual and varies from sporadic episodes to more than one attack per week. This wide variation in phenotypic expression is not correlated with plasma concentrations of C1-INH, and it is likely that other genetic and/or environmental factors may influence seizure frequency.[76]

A peak of symptoms is observed between 12 and 24 hours, spontaneously regressing in two to five days. THE Edema onset is usually slow and gradual, and usually occurs around eight hours. However, in places such as the abdomen and larynx, angioedema can develop more quickly.[68-70] In hereditary angioedema wheals do not occur and there is no response to treatment with antihistamines, corticosteroids and adrenaline.[6,7]

HAE-C1-INH types I and II do not differ in terms of clinical symptoms. Although the HAE attacks both sexes, tends to be more severe and frequent in women, due to the role of estrogen in the pathogenesis of the disease. The clinical presentation of HAE-nC1-INH is similar to HAE-C1-INH, but the symptoms are less frequent, and other differences are also described.[66,72]

The course of the disease tends to be more severe the earlier the onset of symptoms.[69,77] Likewise, a worsening in the frequency and severity of seizures is observed after puberty, both in women and in men.[65] In some older patients, the symptoms become milder, however, the angioedema attacks rarely stop completely.[65,68]

Triggering factors

Angioedema episodes can occur spontaneously, but in up to 91% of cases they are induced by physical, psychological, infectious, drug or hormonal factors.[5,78-80] Emotional stress is reported by HAE-C1-INH patients as the most frequent triggering factor for crises.[80,81] Mechanical trauma, even if mild, is the second most frequent trigger in the HAE-C1-INH, and angioedema characteristically begins in the traumatized area.[82] Angioedema can be triggered by dental, surgical or diagnostic procedures, usually occurring around 4 to 36 hours after the intervention.[83,84] Infections in general, especially viral infections, are considered a relevant trigger of HAE crises, especially in children.[82,85] Situations in which there is an increase in estrogen levels, such as the use of oral contraceptives, hormone replacement therapy during menopause, pregnancy and menstruation, are of potential risk for triggering crises in the HAE-C1-INH.[86]

Several drugs that interfere with BK metabolism have been described as associated with an increased risk of angioedema attacks. In the vast majority of cases, the mechanism involves inhibition of BK degradation, resulting in an elevation of its serum level and, consequently, angioedema.[40] Drugs used in the treatment of arterial hypertension with action on the renin-angiotensin-aldosterone system (RAAS), such as angiotensin-converting enzyme (ACE) inhibitors and, with lower risk, angiotensin II receptor blockers (ARBs), were associated with acquired angioedema, however, can also trigger HAE.[40,87]

Likewise, gliptins that inhibit the DPPIV enzyme, used as oral hypoglycemic agents, reduce BK

catabolism and are potential triggers for the development of crises.[40,87] Neprilysin inhibitors, another class of drugs used in the treatment of arterial hypertension and heart failure, such as sacubitril, can cause angioedema, especially when used in combination with RAAS inhibitors.[40,87,88] Inhibitors of the intracellular protein mTOR, immunosuppressants used in the treatment of cancer, represent an additional risk for patients with HAE-C1-INH.[89]

Other less frequent triggers of angioedema attacks are described by patients, such as exposure to extreme temperatures, alcohol consumption, ingestion of some foods, and fatigue.[80,90,91]

Prodromes

Prodromes are reported in several patients with HAE-C1-INH, preceding the crisis by one to 24 hours.[81,92,93] One third of patients present with macular, erythematous-serpiginous, fleeting and non-pruritic skin lesions, usually on the trunk and limbs, known as erythema marginatum, or also serpiginous erythema.[94] In children, erythema marginatum is described as an independent phenomenon, without subsequent angioedema, and often as the initial manifestation of HAE-C1-INH.[95] Non-specific symptoms such as asthenia, thirst, hunger, nausea, mental fatigue, mood swings, depression, anxiety, irritability, aggression, muscle aches, tingling or tightness in the affected area, as well as flu-like symptoms as well have been reported as prodromal symptoms.[81,93,94]

Erythema marginatum has not been reported as a prodrome in patients with HAE-nC1-INH, however other nonspecific symptoms such as fatigue, chest pain and palpitations have been observed in some cases.[20] Some patients with HAE-nC1-INH have skin lesions that resemble ecchymosis, however, there are few cases described.[96-99]

The prodromal manifestations allow the early initiation of treatment in case of crisis and, thus, reduce the morbidity and mortality associated with HAE-C1-INH. However, complaints are very variable and, to date, there is no scientific evidence of their predictive value.[92,93] The presence of erythema marginatum, the most characteristic prodrome of HAE-C1-INH, has been associated with a delay in the diagnosis of the disease, as it is often confused with urticaria.[100]

Location

The three most characteristic sites of involvement of HAE are: subcutaneous, abdomen and larynx.[2,68-70] Subcutaneous involvement is the most frequent, affecting 95% of patients with HAE-C1-INH, highlighting the extremities, genitalia and face as the most common sites involved. The abdomen is the second most common site of involvement, occurring in up to 93% of cases. In crises, several sites can be affected simultaneously, a characteristic that distinguishes HAE from other causes of angioedema without urticaria.[2,6,68-70]

Abdominal pain due to intestinal loop edema can be intense and spasmodic, lasting from many hours to several days. Often, these symptoms can be confused with an acute surgical abdomen, resulting in unnecessary appendectomies and exploratory laparotomies in up to one third of patients, both in the HAE-C1-INH and in the HAE-nC1-INH.[101,102] Edema of the mucosa of the gastrointestinal tract can cause compression of the lumen and a clinical picture of temporary paralytic ileus, causing nausea and vomiting. Watery diarrhea due to accumulation of fluid in the lumen of the edematous bowel is also common. Leakage of fluid into the peritoneal cavity can result in ascites with increased volume of the abdomen, often identified by ultrasound as fluid in the abdominal cavity.[103] Hemoconcentration, arterial hypotension and even hypovolemic shock can occurin these patients secondary to substantial fluid loss to the interstitium or cavity.[69]

The involvement of the larynx, more precisely in the supraglottic region, occurs in 50% of patients, and at least one episode occurs during the patient's lifetime.[2,68-70] Laryngeal edema is more frequent between 11 and 45 years of age, and rare before the third year of life.[104,105] Although less frequent that skin and abdominal symptoms, laryngeal edema is potentially fatal, particularly in untreated patients. Another important aspect is that there may be edema of regions above the larynx, such as the base of the tongue and oropharynx, which may also impede the passage of air and result in asphyxia and hence the term upper airway edema, rather of laryngeal edema, has been used.[73,78,106] Has been described high frequency of tongue edema in patients with mutation in the gene encoding plasminogen (HAE-PLG).[20] The most frequent onset of laryngeal angioedema is approximately eight hours, nonetheless, may have a sudden onset and cause acute airway obstruction.[104,105] It is worth noting that patients with

facial edema are considered at risk for upper airway edema. Although less frequent than cutaneous and abdominal symptoms, lethal laryngeal edema may be the first presentation of HAE-C1-INH.[104,105]

Unusual clinical manifestations of HAE-C1-INH, such as linear blisters, severe headache, dysuria, and acute pancreatitis have also been described in the medical literature.[107-109]

What tests confirm the diagnosis?

Every individual with clinical suspicion of HAE or who has a family history of similar symptoms, should undergo laboratory tests to confirm HAE-C1-INH. The measurement of the serum level of C4 can be used to screen for HAE (Figure 2). In quantitative deficiency or dysfunction of C1-INH, stabilization of the C1 complex is low, becoming partially activated and C4, its preferred substrate, depleted. In most patients with HAE-C1-INH types I and II, C4 is continuously decreased in plasma, but there is the possibility of normal C4 levels.[79] In these situations, C4 measurement is recommended in the crisis period, if the clinical history is suggestive and the analysis of C1-INH levels is not available.[5,110] Quantitative (by radial immunodiffusion or turbidimetry/nephelometry) and functional (by chromogenic assay) assessment of C1-INH are recommended for definitive diagnosis. Most patients (85%) have quantitative C1-INH below 50% of the normal range, establishing the diagnosis of HAE-C1-INH type I.[79] When the C1-INH concentration is normal (or even high, in some cases), the C1-INH functional test is essential. The diagnosis of HAE-C1-INH type II is characterized by normal or elevated quantitative C1-INH and reduced functional activity of C1-INH, corresponding to approximately 15% of patients with HAE-C1-INH.[111] In Brazil, the C4 test is widely available in clinical analysis laboratories, while the other tests are performed only in more specialized laboratories. It is important to emphasize that the collection and manipulation of samples can be limiting factors for the broad access to the evaluation of C1-INH, as degradation and consumption of complement components can occur very easily.[112] Thus, the biochemical measurements necessary for the diagnosis of HAE-C1-INH, especially the functional assessment of C1-INH, can generate false-positive results, and it is advisable to carry out at least two measurements collected on different days.[5,111,113]

In acquired angioedema due to C1-INH deficiency (AEA-C1-INH), C4 and C1-INH concentrations, as well as functional assessment, may be reduced. In this case, the C1q dosage must be performed and is reduced in approximately 70% of the cases. Clinical features such as symptoms of later onset in adulthood and absence of a family history of recurrent angioedema suggest the diagnosis.[114,115.] Also, considering that a percentage of patients with AEA-C1-INH may have normal plasma levels of C1q, genetic evaluation of the *SERPING1* gene is recommended for the differential diagnosis. In cases with de novo mutations or questionable clinical history, genetic evaluation may also be necessary.[116]

In children under one year of age, plasma levels of C1-INH may be below the values considered normal due to immunological immaturity, recommending the genetic analysis of *SERPING1* to aid in the diagnosis of HAE-C1-INH.[77,117]

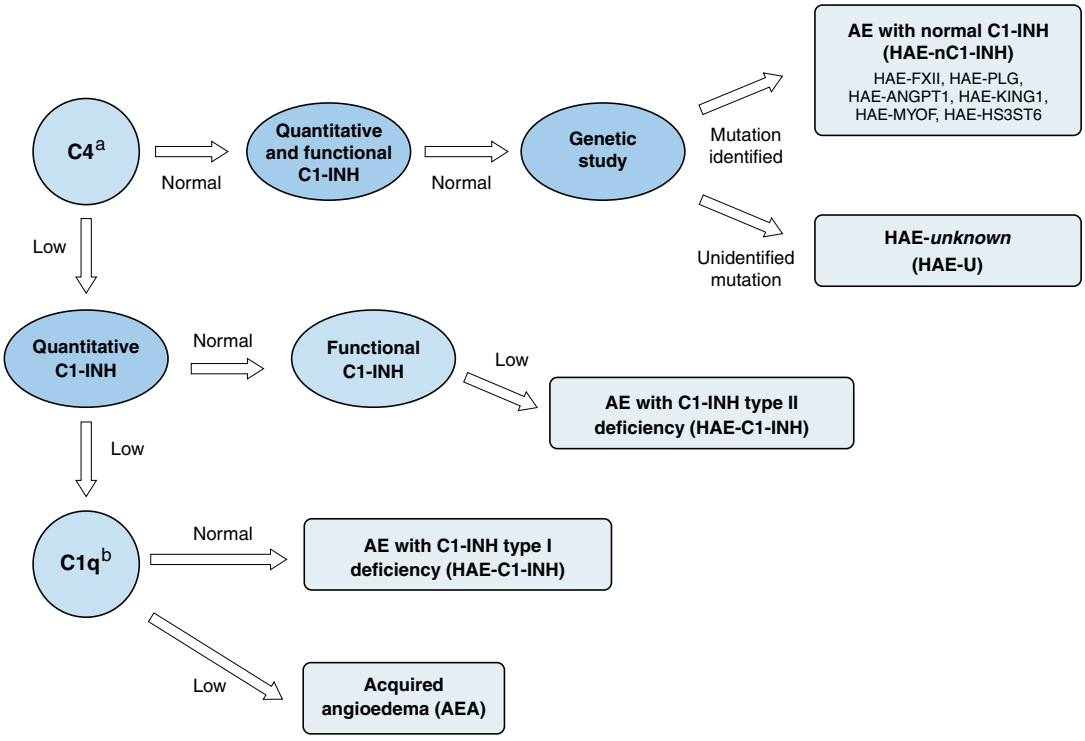
SERPING1 genotyping can be performed by Sanger sequencing or next-generation sequencing, and must cover the eight exons of the gene, including its splicing sites. In the absence of pathogenic variants, the presence of large deletions and insertions should be evaluated using techniques such as multiplex ligation-dependent probe amplification (MLPA) or long-range PCR, although these tests are not widely available.[28] The pathogenicity assessment of new variants identified in *SERPING1* should follow the international guidelines established by the American College of Medical Genetics and Genomics (ACMG) for HAE.[20,118] Although not essential for the diagnosis of symptomatic patients, the determination of the mutations that cause HAE-C1-INH helps in family screening and early prevention, even in asymptomatic carriers.

For cases of suspected HAE and consistent and normal results of C4 and C1-INH, the HAE-nC1-INH should be investigated, for which there are no biochemical markers available, and the only alternative is genetic diagnosis.[1,20]

In patients with HAE, it is estimated that the delay in diagnosis is still high, and national studies document that this delay in diagnosis varies between 14 and 18 years.[2,26,60-64]

What are the diagnostic criteria for HAE?

Some criteria to standardize the diagnosis of HAE have been proposed (Table 2).[72] Among them, some are required for the diagnosis, while others constitute a strong indication, but are not necessary,



[a] If C4 normal, repeat during the angioedema crisis.

[b] Request depending on clinical history.

AE = angioedema, HAE = hereditary angioedema, AEA = acquired angioedema, HAE-U = hereditary angioedema of unknown cause, HAE-FXII = hereditary angioedema due to Factor XII gene mutation, HAE-PLG = hereditary angioedema due to plasminogen gene mutation , HAE-ANGPT1 = hereditary angioedema due to an angiopoietin 1 gene mutation, HAE-KNG1 = hereditary angioedema due to a kininogen 1 gene mutation, HAE-MYOF = hereditary angioedema due to a myoferlin gene mutation, HAE-HS3ST6 = hereditary angioedema due to the mutation in the 3OST6 heparan sulfate gene.

Figure 2
Algorithm for the diagnosis of hereditary angioedema[1,5,14,72]

being, therefore, supporting criteria. For example, the detection of a mutation in the *SERPING1* gene in HAE-C1-INH is not necessary for the diagnosis and is therefore a supporting criterion. The characteristic of non-inflammatory subcutaneous angioedema lasting more than 12 hours and the presence of abdominal pain of undefined organic etiology, lasting more than six hours, in addition to laryngeal edema, are important characteristics in HAE.[14]

These criteria are not absolute and clinical history is predominant, especially in locations where laboratory tests are not available. In HAE-nC1-INH, a therapeutic test can help to establish the diagnosis.[72]

In Figure 3, we suggest a list of warning signs and an acronym to encourage diagnostic suspicion and promote awareness of HAE-C1-INH.

What is not hereditary angioedema?

Two main pathophysiological mechanisms of angioedema are described: by activation of mast cells and/or basophils, resulting in the release of histamine and other mediators (histaminergic angioedema); and by excess BK (bradykinin-mediated or non-histaminergic angioedema), as seen in HAE-C1-INH, AEA-C1-INH, and angioedema induced by ACE

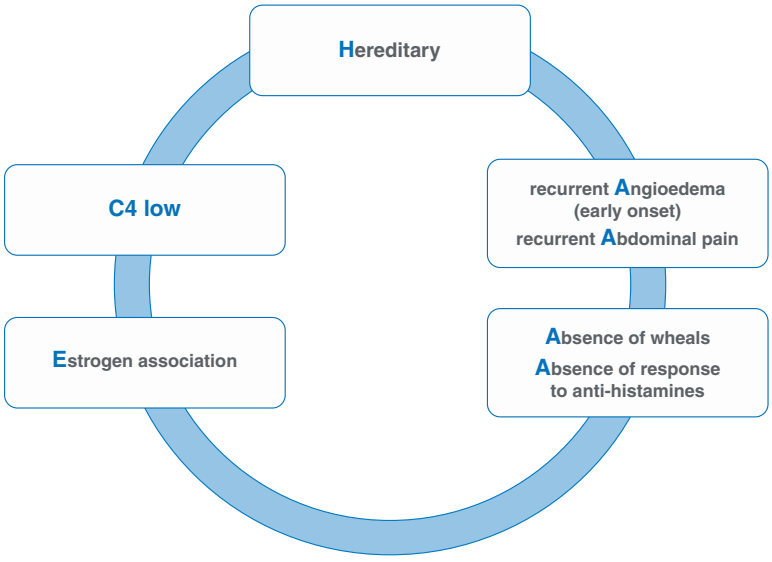
inhibitors or gliptins, drugs involved in BK metabolism (Figure 4).[8,17,119] Therefore, the main differential diagnoses of HAE are the other types of angioedema, especially those with chronic or recurrent presentation. Knowledge about the pathophysiological mechanisms, clinical characteristics and response to drugs used during the crisis contribute to the suspicion of other causes of angioedema. In addition to clinical aspects, laboratory evaluation helps in the discrimination between histamine-mediated and bradykinin-mediated angioedema (Table 3).

The most frequent type of recurrent angioedema is histaminergic, which has some characteristics that differentiate it from HAE, including the presence of wheals, improvement with antihistamines, and triggering of symptoms by the use of nonsteroidal anti-inflammatory drugs (NSAIDs). However, histaminergic angioedema can present without urticaria, and NSAIDs are among the main causes of angioedema, even in those patients who do not have urticaria.[9] Current guidelines for the treatment of chronic spontaneous angioedema/urticaria highlight the fact that some patients will not respond to conventional doses of antihistamines and may need to be increased in dose, reaching up to four times the daily recommended doses to control symptoms. Therefore, to confirm or rule out the histaminergic nature of angioedema, a therapeutic trial of antihistamines using four times the recommended dose for a period of time of

Table 2
Criteria for the diagnosis of hereditary angioedema

Weight	Criterion
HAE-C1-INH	
Required	History of recurrent angioedema in the absence of wheals, without the use of medications that may trigger angioedema
Required	Decreased antigenic or functional C1-INH (< 50% of normal)
Required	Decreased C4 levels (baseline or measured in crisis)
Support	Detection of a pathogenic variant in the *SERPING1* gene (not required for diagnosis) Family history of recurrent angioedema Age of onset < 40 years
HAE-nC1-INH	
Required	History of recurrent angioedema, in the absence of wheals, without the use of medications that may trigger angioedema
Required	Antigenic and functional C4, C1-INH levels unchanged or close to normal values
Required (one of 2)	1) Demonstration of a mutation associated with the disease OR 2) Family history of recurrent angioedema and lack of efficacy of high-dose second-generation antihistamine therapy for at least a month or an expected interval of three or more attacks of angioedema, whichever is longer
Support	1) History of rapid and lasting response to a drug that inhibits bradykinin AND 2) documented visible angioedema; or in patients with abdominal symptoms, evidence of intestinal wall edema documented by CT or MRI

HAE-C1-INH = hereditary angioedema with C1 esterase inhibitor deficiency, HAE-nC1-INH = hereditary angioedema with normal C1 esterase inhibitor, MRI = MRI, CT = CT scan.
Adapted from Busse PJ et al.[2].



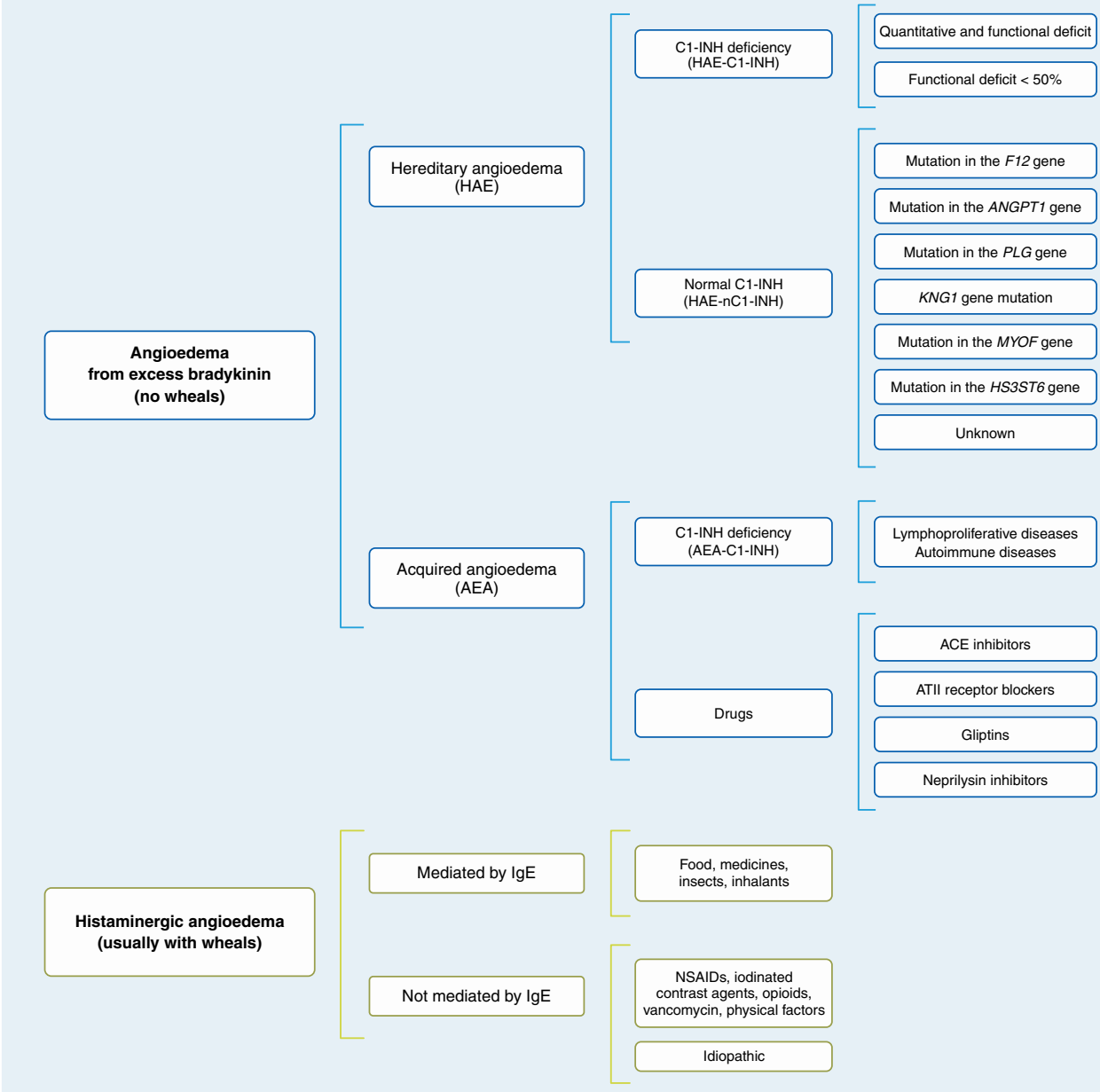
HAAAAE = Heridarity, recurrent Angioedema, recurrent Abdominal pain, Absence of wheals, Absence of response to antihistamines, association with Estrogen.
Adapted from: Giavina-Bianchi P et al.[14].

Figure 3
Warning signs for the diagnosis of HAE-C1-INH[14]

approximately six weeks is sufficient to assess your response to treatment. The safety of increasing the dose of antihistamines, including bilastine, cetirizine, levocetirizine, desloratadine, ebastine, fexofenadine and rupatadine, has been demonstrated.[16,120] Although BK-mediated angioedema is less frequent, the risk of mortality in this type of angioedema is 45 times greater than that of histaminergic angioedema.[121]

Regarding the acquired forms of BK-mediated angioedema, it is very important to ask the patient about the use of ACE inhibitors. As ACE is the main enzyme involved in BK degradation, its inhibition leads to increased serum concentrations of this mediator, and can cause angioedema. Up to 0.7% of individuals using ACE inhibitors have recurrent angioedema, with an increased risk among Afro-descendants, smokers, the elderly and females.[17,44] ACE-induced angioedema most often involves the face, tongue, oropharynx and larynx, however sporadic cases of abdominal episodes have been reported. The mean time for the onset of symptoms of angioedema is 1.8 years, however symptoms occur in 25% of cases within the first month of using the medication. They can also occur up to 10 years after the introduction of treatment.[122] ACE inhibitors should be discontinued in all patients with recurrent angioedema, even if the angioedema has been triggered after several years of drug use. Although ACEI-induced angioedema attacks may resemble those of HAE, patients will have normal levels of C4 and C1q, in addition to normal quantitative and/or functional levels of C1-INH (Table 4). More rarely, angiotensin II receptor blockers (ARB) and gliptins can induce angioedema.[123]

AEA-C1-INH is an even rarer type of angioedema than HAE, with an estimated prevalence of 1.5:1,000,000 individuals, without genetic inheritance.[114,115] In this type of angioedema, the onset of symptoms occurs later, there is no family history of angioedema, and the disease is due to the consumption of C1-INH or the production of C1-INH neutralizing autoantibodies,



HAE = hereditary angioedema, C1-INH = C1 inhibitor, *F12* = coagulation factor XII, *ANGPT1* = angiopoietin-1, *PLG* = plasminogen, *KNG1* = kininogen 1, *MYOF* = myoferlin, *HS3ST6* = heparan sulfate 3ST6, ACE = angioetensin, ATII = angiotensin II, IgE = immunoglobulin E, NSAIDs = non-steroidal anti-inflammatory drugs.

Figure 4
Classification of angioedema[1,7,8, 17,119]

associated with lymphoproliferative or autoimmune diseases, respectively. As a consequence, C1-INH activity is low, the complement system is activated, and C1q is generally reduced, a particular feature that may help in the differential diagnosis. In addition to C1-INH function below 50% of normal, C1-INH antigen levels are often reduced, although the presence of cleaved C1-INH can result in normal C1-INH antigenic levels

Table 3
Characteristics of recurrent angioedema regarding the mediator, clinical and laboratory aspects[1,7,20,119]

	HAE-C1-INH (types I and II)	HAE-nC1-INH	HAE-C1-INH	Histaminergic AE
Mediator	Bradykinin	Bradykinin	Bradykinin	Histamine
Clinical condition	Family history Trauma Early start Serpiginous erythema may be a prodrome	Family history Trauma Later Women Language (HAE-PLG) Hematoma can occur	Underlying disease Later	No family history Spontaneous Any age Urtica in 90% of cases Preferred location on face/lips
Laboratory tests	C4 low C1-INHq low/normal or increased C1-INHf low	C4 normal C1-INHq normal C1-INHf normal Molecular test for variant search	C4 low C1-INHq low C1q low	C4 normal C1-INHq normal C1-INHf normal

AE = angioedema, HAE-C1-INH = hereditary angioedema with C1 Inhibitor deficiency, HAE-nC1-INH = hereditary angioedema with normal C1 Inhibitor, HAE-PLG = hereditary angioedema due to plasminogen gene mutation, C1-INHq = quantitative C1-INH, C1-INHf = functional C1-INH.

in about 20% of patients. As there is a great overlap of AEA-C1-INH associated with autoantibodies and lymphoproliferative diseases, its classification as the same disease is suggested.[124,125]

Idiopathic non-histaminergic angioedema should be considered when there is no heredity, all known causes of angioedema have been excluded, and symptoms persist despite treatment with high doses (up to four times the standard dose) of second-generation non-sedating antihistamines.[17] There is evidence that BK may be the mediator involved in idiopathic non-histaminergic angioedema. However, the evidence is not definitive, considering that other vasoactive mediators derived from mast cells or other cells, including cysteinyl-leukotrienes, prostaglandins, and platelet activating factor may play a role.[119] On the other hand, the involvement of mast cells/basophils does not exclude the participation of BK, as there is evidence that mast cells can increase vascular permeability by releasing heparin, which, in turn, induces the formation of BK. There are also indications of the participation of BK release in spontaneous chronic urticaria, with or without angioedema.[126,127] Among patients considered to have idiopathic non-histaminergic angioedema still there may be individuals with HAE-nC1-INH, with no family history and no known mutation, as well as some patients with histaminergic angioedema without wheals and resistant to antihistamines.[9,16,17,119] Therefore, the identification of the different forms of bradykinin-mediated angioedema can be better defined through specific laboratory and molecular aspects (Table 4).

Final considerations

HAE is an autosomal dominant genetic disease associated with recurrent angioedema that affects the subcutaneous tissue and submucosal tissue, mainly of the digestive tract and upper respiratory tract.[5,71,72]

Table 4
Laboratory and molecular features of bradykinin-mediated angioedema[119]

	HAE-C1-INH				
	HAE type I	HAE type II	HAE-nC1-INH	AEA-C1-INH	AEA-iECA
C1-INH	< 50%	Normal or increased	Normal	< 50%	Normal
Functional C1-INH	< 50%	< 50%	Normal	< 50%	Normal
C4	Low	Low	Normal	Low	Normal
C1q	Normal	Normal	Normal	Low (70% of cases)	Normal
Mutation	*SERPING1*	*SERPING1*	*FXII, PLG, ANGPT1, KNG1, MYOF, HS3ST6*	No	No
Ac anti-C1-INH	No	No	No	50% of cases	No

HAE = hereditary angioedema, HAE-C1-INH = hereditary angioedema with C1 inhibitor deficiency, HAE-nlC1-INH = hereditary angioedema with normal C1 inhibitor, AEA-C1-INH = acquired angioedema with C1 inhibitor deficiency, AEA-ACEi = angioedema acquired by angiotensin converting enzyme inhibitor, C1-INH = C1 inhibitor, anti C1-INH Ab = anti C1-INH antibody.

There are seven types of HAE defined by distinct pathogenic genetic variants: HAE-C1-INH, HAE-FXII, HAE-PLG, HAE-ANGPT1, HAE-KNG1, HAE-MYOF and HAE-HS3ST6. The most frequent mutations occur in the *SERPING1* gene, followed by mutations in the *F12* gene related to HAE-C1-INH and HAE-FXII, respectively.[20,53]

In many individuals with HAE, genetic variants causing the disease are not yet known, and these patients are diagnosed with HAE-U (HAE-unknown).[1]

Bradykinin is the main mediator associated with the clinical manifestations of HAE. The action of this mediator occurs due to the greater activity of the contact system and kallikrein-kinins system in most patients, while alterations in the endothelium have been described in others.[1,25,40,79]

Symptoms are most often triggered by stress situations, mechanical trauma, infections and medications, particularly estrogens, due to their actions to stimulate the contact system. Some patients have prodromal symptoms.[5,7]

Clinical manifestations are similar in the different types of HAE, being generally more frequent in HAE-C1-INH. Laryngeal edema is the most serious symptom that, although less frequent, can be the cause of death by asphyxia. HAE-C1-INH usually appears in childhood, and HAE-nC1-INH forms in adults.[20,105]

The initial screening test for the diagnosis of HAE is the serum C4 level. Then, the quantitative and functional measurement of C1-INH should be performed. In some cases with suspected AEA-C1-INH, it is necessary to measure C1q. In the absence of C1-INH alterations, the genetic study should be performed mainly in the absence of family history, or to characterize a specific type of HAE-nC1-INH.[5,71,72]

HAE can be confused with idiopathic histaminergic angioedema and also with recurrent angioedema with the use of drugs, especially ACE inhibitors, or with AEA-C1-INH.[7,17]

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Conflict of interests

Régis A. Campos, Faradiba S. Serpa, Maria Luisa O. Alonso, Pedro Giavina-Bianchi, Herberto José Chong-Neto, Eli Mansour, Eliana Toledo, Anete S. Grumach and Solange O.R. Valle received financial and/or honorary support from Takeda and CSL Behring. Anete S. Grumach is a CNPq productivity fellow and has also consulted for Catalyst. The following authors received financial and/or honorary support from Takeda: Camila L. Veronez, Jane da Silva, Marcelo V. Aun, L. Karla Arruda. The other authors deny conflicts of interest.

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