

Hereditary and Acquired Angioedema: Heterogeneity of Pathogenesis and Clinical Phenotypes

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Keywords

Hereditary angioedema · Acquired angioedema · Mediators · Phenotypes · Differential diagnosis · Pathogenesis

Abstract

Recurrent angioedema (AE) without wheals is increasingly recognized as a clinical entity and a frequent cause of admission to the emergency room. The Hereditary Angioedema Working Group (HAWK) classification allowed the scientific community to go beyond the semantic confusion that dominated this topic for decades. This classification distinguishes hereditary and acquired forms of AE, either related or unrelated to C1 inhibitor deficiency. Recently, additional mechanisms have been involved in the AE pathogenesis, including the uncontrolled activation of factor XII, generation of vasoactive mediators that induce dysregulation of endothelial functions, and bidirectional interactions between mast cell-derived mediators and the plasma contact system. Thus, recurrent AE can be determined by multiple and concurrent mechanisms that may generate distinct clinical phenotypes of the disease. Frequency, severity, and the location of attacks are quite different from patient to patient and, even in

the same patient, they may change throughout the course of life. The severity of the clinical phenotype strongly influences the burden of the disease and patients' quality of life. Despite major advances in our understanding of recurrent AE, many unsolved questions remain, leaving several unmet needs for patients and caregivers. This review is focused on a description of different AE phenotypes and the concurrent mechanisms leading to their pathogenesis. A better definition of cellular and molecular pathways responsible for the distinct AE phenotypes may help to improve diagnosis and may lead to a personalized approach to prophylaxis and treatment of the disease.

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Introduction

Angioedema (AE) is a frequent clinical manifestation characterized by swelling of cutaneous and subcutaneous tissues, due to vascular reactions of deeper layers of skin

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and mucous membrane with increased blood vessel permeability [1]. AE is often associated with urticaria in the so-called urticaria AE syndrome: this association is important in a clinical setting since it is often caused by both allergic or nonallergic reactions. Recurrent AE presenting without significant urticaria should be diagnosed as a distinct disease. Whatever mechanism is determining AE, the basic pathophysiological event is a rapid vasodilation associated with increased vascular permeability in the deep dermis and submucosal vessels due to the local release of vasoactive mediators [2]. Mediators can be released by inflammatory cells resident in the tissue, e.g., mast cells, or recruited from blood, e.g., basophils and eosinophils. Alternatively, vasoactive mediators may be generated by the activation of plasma components such as the contact system, e.g., bradykinin (BK), or the complement cascade, e.g., anaphylatoxins C3 and C4. Histamine and BK are the best-studied vasoactive mediators of AE but other molecules contributing to AE are currently being sought.

The possible causes of AE without wheals are rather heterogeneous, ranging from hereditary or acquired conditions to drug exposure. The correct diagnostic approach, leading to the identification of the AE subtype is a fundamental step to plan the most appropriate attack treatment or prophylaxis in these patients.

Classification of AE

The current classification of AE without urticaria, recently published by Cicardi et al. [3], distinguishes 2 main forms of hereditary AE (HAE) and acquired AE (AAE; Fig. 1). Three types of HAE and 4 types of AAE are described as separate entities.

Hereditary AE

HAE is a rare autosomal dominant disease, resulting in recurrent attacks of potentially life-threatening acute edema that occur in members of the same family. Nevertheless, some cases of HAE develop as the result of a de novo mutation. This feature is very important for the clinician because the diagnosis of HAE should not be excluded in patients without a family history of AE.

In most patients with HAE, there are mutations in the C1 inhibitor gene (*SERPING1*), which result in the decreased synthesis of normal C1-INH (C1-INH-HAE type I) or expression of unfunctional C1-INH (C1-INH-HAE type II) [4]. However, mutations in the gene coding for coagulation factor XII (FXII) have been identified in a

subset of patients who present familial recurrent episodes of AE, but no abnormalities in complement parameters and no mutation in the *SERPING1* gene (FXII-HAE) [5]. Recently, a novel mutation in the angiopoietin-1 gene was associated with HAE [6]. However, in many families clearly with HAE, no genetic mutation has been identified so far and this variant is currently defined as unknown HAE (U-HAE) [3].

Acquired AE

The most frequent form of AAE is that induced by drugs. ACE inhibitors (ACEI) are the medications that most commonly cause AE without urticaria. This type of AAE is related to the inhibition of ACE, an enzyme involved in the breakdown of BK into inactive peptides. ACEI-AAE should be considered a side effect of this class of drugs and may present at any time – weeks or even years – after the initiation of treatment. Withdrawal of ACEI is not always associated with the immediate regression of AE episodes. If AE does not disappear within few months after stopping ACEI an alternative diagnosis should be considered [7].

Acquired C1 inhibitor deficiency (C1-INH-AAE) is a very rare condition in which the reduction of C1-INH is in some cases linked to autoimmune or lymphoproliferative diseases. An MGUS (monoclonal gammopathy of undetermined significance) is frequently associated with AAE [8]. Its pathogenesis is related to the consumption of C1-INH by neoplastic lymphatic tissues and/or the formation of anti-C1 inhibitor neutralizing autoantibodies [9]. Interestingly, the first AE attack often predates by several years the onset of hematological disease [10].

In a large group of patients, the cause of recurrent AE remains unclear (idiopathic AE). Therefore, they are classified as histaminergic (IH-AAE) or nonhistaminergic (InH-AAE) based on the improvement of symptoms in response to continuous treatment with antihistamines. While a role of mediators derived from mast cells and basophils is suggested in IH-AAE, BK and possibly other vasoactive mediators should be considered in the pathogenesis of InH-AAE.

The current classification of AE has several limitations, mostly because many cases do not completely fit into this classification. The major problem concerns InH-AAE because the pathogenetic aspects of this condition remain largely unclear. There is strong evidence that this form of AE is heterogeneous and probably comprises variants of AE with different pathogenetic mechanisms. The lack of responsiveness to prophylaxis with antihistamines seems to support the role of nonmast cell-derived

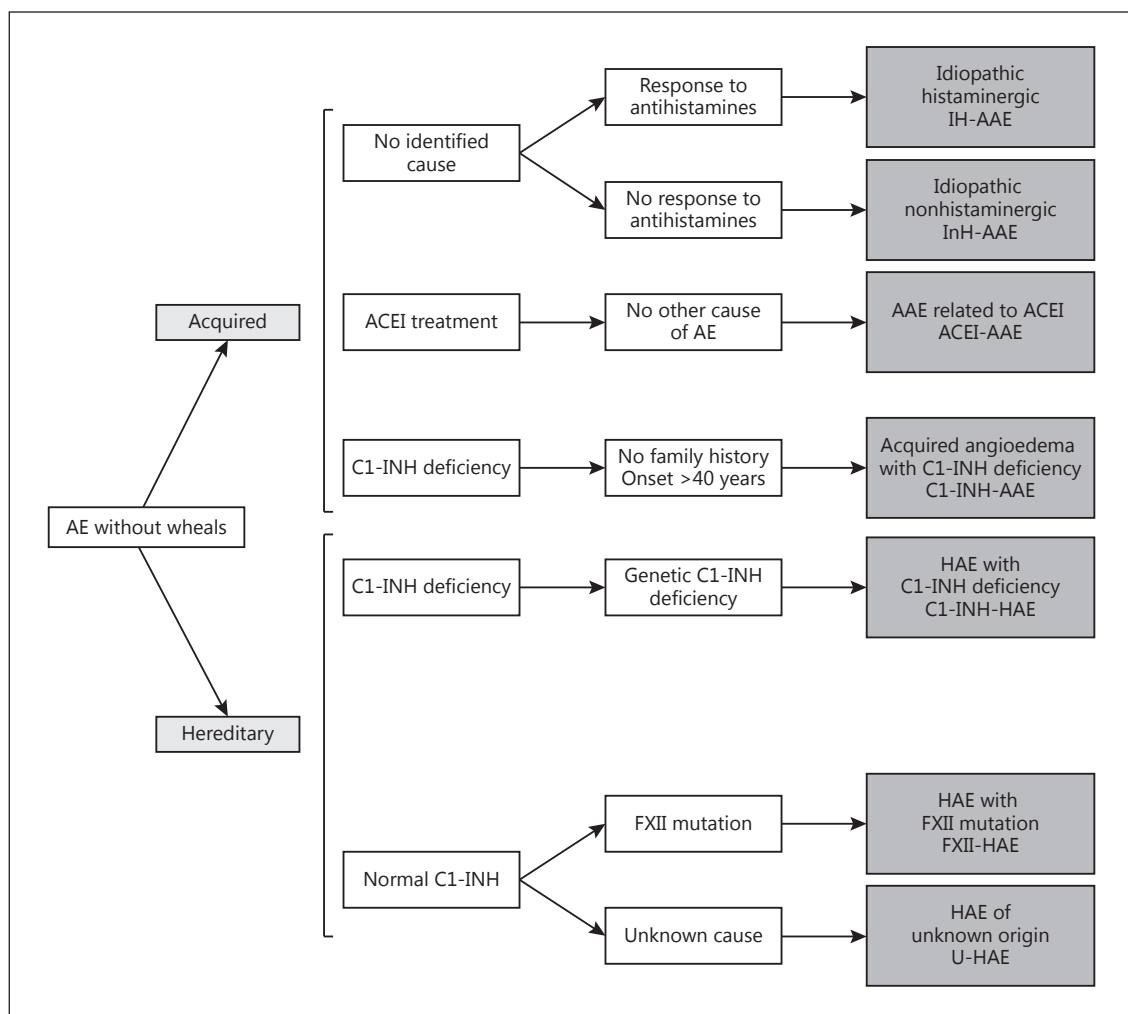


Fig. 1. Classification of AE without wheals (reproduced from Cicardi et al. [3] with permission granted by the publisher). HAE, hereditary angioedema; AAE, acquired angioedema.

mediators such as BK. Nonetheless, the positive response to treatment with anti-IgE (omalizumab) suggests a primary role of mast cells in a subset of patients with InH-AAE [11–13].

A revision of the HAWK (Hereditary Angioedema International Working Group) classification has been proposed by Prieto-García et al. [14], trying to define a clearer approach towards the idiopathic group. The hypothesis is that idiopathic AE should be considered a heterogeneous group and consequently the classification should include 2 or more subcategories based on the response to specific treatments.

Another classification focused on pathophysiological mechanisms of AE was proposed by Giavina-Bianchi et al. [15]. This classification was based on the identification

of 2 major groups, in which AE is mediated by mast cell and basophil degranulation or by the production of BK, respectively. However, this classification, based on a rigid pathogenetic dualism, still makes it difficult to categorize certain forms of idiopathic AE.

Pathophysiology of AE

Two main molecular mechanisms leading to AE have been identified: (1) an “allergic” pathway linked to the activation of mast cells and/or basophils, resulting in the release of histamine and other mediators, such as leukotrienes, prostaglandins, and platelet-activating factor, and (2) a “nonallergic” pathway leading to the generation of

BK. However, these 2 pathways may interact under certain circumstances since the activation of the contact system and generation of BK may be induced by mast cell-derived mediators such as heparin both in vitro and in vivo [16, 17]. These findings suggest a link between “allergic” and “nonallergic” AE pathways, but further studies are needed to confirm this hypothesis.

C1-INH is the main inhibitor of the components of the contact system and a poor control of local activation process of this system is believed to lead to BK formation. The contact system consists of the proteins FXII, prekallikrein, high molecular-weight kininogen (HMWK), and Factor XI. The activation of the contact system starts with the activation of FXII, which subsequently cleaves the prekallikrein to generate kallikrein. Kallikrein has 2 substrates: it activates additional FXII and liberates BK from HMWK [18]. BK is considered essential in the pathogenesis of C1-INH-HAE and represents the end product of the contact activation system and kallikrein-kinin system [19]. BK is a small vasoactive nonapeptide, acting on 2 types of receptor present on endothelial cells: B1R, an inducible receptor, and B2R, which is expressed constitutively on the cell surface. BK binds the B2R and activates various proinflammatory signaling pathways that increase vascular permeability. BK exerts its permeabilizing effect mainly through phosphorylation of VE-cadherin, the transmembrane adhesive protein expressed on the cell surface [20]. High levels of BK are detectable in the plasma of patients with HAE due to C1-INH deficiency during the attacks [21]. In plasma from HAE patients, but not normal donors, BK can also be generated directly from the prekallikrein-HMWK complex without activation of kallikrein mediated by FXIIa. C1-INH stabilizes the prekallikrein-HMWK complex and prevents BK formation [22, 23].

BK is not the only vasoactive mediator that regulates the permeability and vascular tone of small vessels. Other vasoactive mediators, such as endothelin-1, arginine vasopressin, adrenomedullin, vascular endothelial growth factors (VEGFs), and angiopoietins, are increased in C1-INH-HAE patients [24].

Moreover, plasma levels of VEGFs and angiopoietins, which are modulators of vascular permeability, were shown to be elevated in patients with a higher frequency of attacks even in the clinically silent phase between attacks. Therefore, it has been hypothesized that VEGFs and angiopoietins may induce a state of ‘vascular preconditioning’ that can predispose to AE attacks [24].

Endothelial cells are also emerging as active participants in the process of BK generation. The observation

that soluble E-selectin and eNOS plasma levels are increased in C1-INH-HAE patients strongly suggests that endothelial cell activation may have a role in the pathogenesis of attacks [25, 26]. Interestingly, endothelial cells stimulated by cytokines and estrogen release HSP-90 (heat shock protein-90) which, in turn, activates directly the prekallikrein-HMWK complex without the requirement of FXII. This is a potentially important mechanism to explain the focal nature of AE attacks [27, 28].

In fact, while the observation that swelling may occur at multiple sites during an AE attack suggests that systemic activation of the contact system is the precipitating event [29–31], the clinical expression of AE that is typically localized only at selected sites needs to be explained by a local mechanism generating BK at specific locations. In addition, the current pathogenetic hypothesis does not explain why certain organs, such as the lung, are always spared in BK-mediated AE.

Prolonged swelling observed in HAE attacks does not fit well with the rapid desensitization observed with B2R, the receptor actually considered to be responsible for mediating AE attacks. Zuraw and Christiansen [20] recently proposed that B1R, the inducible BK receptor, may have a role in sustaining the attacks. This receptor is readily induced by a variety of inflammatory stimuli, including BK itself, and it is slowly desensitized or downregulated. Interestingly, B1R signaling occurs constitutively but is greatly increased by binding of the BK metabolite des-Arg-kinin ligand. Participation of B1R to acute attacks is an attractive hypothesis that requires further investigation.

AE can be frequently elicited by drugs used for the treatment of high-prevalence diseases. The best characterized form is with ACEI, clearly due to their interference with BK degradation. Recent reports also show that a new class of oral antidiabetic agents could determine AE [32]. Dipeptidyl peptidase IV (DPP IV) inhibitors (also called gliptins) are emerging medications used in the treatment of type 2 diabetes that inhibit the degradation of glucagon-like peptide-1 (GLP-1), a factor stimulating the release of insulin from pancreatic islets. DPP IV is not specific for GLP-1, but also plays a role in the degradation of BK. It has been proposed that a reduction of DPP IV activity, either genetic or drug induced, may be a risk factor for AE. Further progress in understanding the mechanisms described here should provide new means to improve the diagnosis and treatment of all types of AE.

Clinical Features and Phenotypes of AE

Recurrent AE is clinically characterized by the appearance of circumscribed swelling, neither itchy nor erythematous, that is sometimes painful. It can involve one or more sites in the body, both cutaneous and mucosal (mostly upper airways and the gastrointestinal tract). The swelling may last from a few hours to several days and it disappears without any sequelae.

The clinical spectrum of the attacks, such as age of onset, localization, frequency and severity, differs among the different types of AE, but often a great variability is observed among patients affected by the same type of AE and even in the same patient in relation to the different stages of life. Depending on the underlying pathogenic mechanism, AE can begin early or late in life, may localize at a predominant body site (tongue, face, upper respiratory tract, abdomen, skin) and can be sporadic or recurrent with a different degree of severity [3].

C1-INH-HAE, both type I and type II, generally begins within the first or second decade of life. Swelling can affect the skin, gastrointestinal tract, and upper respiratory airways, although some patients present predominantly peripheral (hands, feet, face, lips, etc.) or mucosal (intestinal, laryngeal) locations. This type of AE may be preceded by nausea, malaise, fatigue and erythema marginatum. The development of swelling is slow (hours) and complete spontaneous remission occurs in 72–96 h. In many patients, particularly children, an attack can be induced by a local trauma that can be mechanical, physical, or associated with diagnostic or surgical procedures. In these cases, the location is typically, although not always, restricted to the site of trauma. Patients may also present a significant variability in the frequency of attacks over time, not always referable to identifiable factors. Furthermore, the frequency or severity of attacks may be worsened by stress, estrogen therapy or hormonal fluctuations, treatment with ACEI, and by acute or chronic infections. To date, more than 450 mutations of the C1-INH gene (*SERPING1*) have been identified. A possible genotype-phenotype correlation has been suggested, but no mutations have been strictly related to the clinical phenotype of HAE until now. Even within the same family, however, patients can present a different clinical course in terms of the site of involvement, and the number and severity of attacks. Finally, some patients can be asymptomatic throughout life, even when exposed to potential triggers. These data and the reported geographical differences in Europe regarding some clinical manifestations of AE (e.g., later onset disease in Ro-

manian patients, less often exhibited abdominal attacks in Hungarian patients, higher use of long-term prophylactic treatment in Greek patients) suggest that environmental factors might affect the variety of expression of *SERPING1* mutations [33]. It is also possible that polymorphisms in the BK receptor, contact system proteins, or variation in the kinin formation or metabolism could have a role in the variability of phenotypic expression of HAE.

HAE with the normal C1 inhibitor may be linked to specific mutations in the coagulation FXII gene (FXII-HAE) or mutations in genes that are still unknown (U-HAE). It is prevalent in women and is characterized by a later age of onset (20–30 years) and fewer attacks/longer attack-free intervals compared to C1-INH-HAE. Swelling mostly targets the face, lips, tongue, and upper airways; multisite attacks are rare. Estrogens and pregnancy frequently exacerbate the disease.

ACEI-AAE is an acquired type of AE, prevalent in women, blacks, and smokers. It typically affects the tongue. The latency between starting ACEI therapy and the onset of swelling is highly variable; in 50% of cases it occurs within the first month of therapy, although a late onset is often described. The recurrence of AE after stopping ACEI should lead to the reconsideration of the initial diagnosis and the search for other forms of AE [34].

The onset of C1-INH-AAE is typically late (>40 years) and it is often related to underlying diseases (lymphoproliferative diseases, malignancies, anti-C1 inhibitor antibodies). The attacks mainly affect the face, the upper respiratory tract and abdomen, and the frequency of attacks is unpredictable. The rate of attacks is usually reduced by the treatment of the underlying disease [9].

The acquired types of AE of unknown causes can be classified into histaminergic and nonhistaminergic, depending on the clinical response to chronic therapy with antihistamines. It is sometimes difficult to distinguish between these 2 types of AE, mainly when clinical characteristics (timing, response to treatment, rarity of attacks) cannot help in evaluating the clinical response to antihistamines.

Therefore, although some features (familiarity, site, timing, worsening by ACEI, estrogen or pregnancy, underlying diseases, response to steroids and antihistamines) can guide the diagnosis, the clinical heterogeneity, which is not always predictable, can lead to a diagnostic delay and affect the therapeutic management. The treatment and prophylaxis of the various forms of AE have been recently updated and are described in excellent reviews [3, 4].

Table 1. Clinical features useful for a differential diagnosis of AE

	Mast cell-mediated AE	BK-mediated AE	
		acquired	hereditary
Speed of onset	Minutes	Hours	Hours
Time to resolution of symptoms	Minutes to a few hours	Days	Days
Age of onset	Any	4 decades 6 decades in ACEI-AAE	1–2 decades
Predominant location	Face (eyelids, lips), neck	Lips, tongue, uvula, and upper airways	Face, peripheral, upper airways, GI tract
Triggering factors	Known or probable allergens	Drugs	Trauma, infections, emotional stress, estrogen (FXII-HAE)
Family history	No	No	Yes
Inducing/exacerbating drugs	NSAIDs	ACEI, ARB, gliptins, sacubitril	ACEI, estrogen
Treatment of choice	Antihistamines Steroids Epinephrine	pd or rh C1-INH Icatibant Tranexamic acid (off-label treatments)	pd or rh C1-INH Icatibant

AE, angioedema; BK, bradykinin; ACEI-AAE, acquired AE related to ACEI; GI, gastrointestinal; FXII-HAE, hereditary AE with FXII mutations; NSAIDs, nonsteroidal anti-inflammatory drugs; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; C1-INH-AAE, acquired AE with C1-INH deficiency; pd C1-INH, plasma-derived C1 inhibitor; rh C1-INH, recombinant C1-INH.

Diagnosis

A diagnostic evaluation and an appropriate differential diagnosis are crucial in a disease with such a heterogeneous clinical phenotype. A correct clinical assessment requires a detailed and careful medical history; the clinical clues for potential diagnosis are listed in Table 1. A proposed diagnostic algorithm for patients with AE without urticaria is shown in Figure 2 [35].

In patients with recurrent AE attacks, the speed of onset and resolution of symptoms could help in the differential diagnosis. Mast cell-mediated AE usually appears very rapidly, occurring within minutes to a few hours after exposure to an allergen and resolving rapidly with treatment. Idiopathic histaminergic AE lasts about 8–24 h if untreated. By contrast, the clinical onset of AE induced by BK and/or other vasoactive peptides takes several hours to reach maximum intensity and improves over hours or days [3].

The sites involved during AE attacks are also very important, because a history of peripheral swelling and recurrent abdominal pain should alert the clinician to the

possibility of C1-INH-HAE or C1-INH-AAE. The preferential location of AE to the face, mouth, tongue, uvula, and upper airways is particularly suggestive of ACEI-AAE or HAE with normal C1-INH [36].

Trauma, infections, and emotional stress are the most common trigger factors. Interestingly, the relationship with estrogens, either exogenous or endogenous, is typical of HAE attacks, above all in patients with FXII-HAE [37].

Family history is present in most patients with C1-INH-HAE, supported by onset in the first or second decade, although about 25% of diagnosed patients are considered sporadic cases [38]. In the diagnosis of HAE with normal C1-INH (FXII- or U-HAE), a positive familial history is a key element. However, in FXII-HAE an estimated 3.4–30% of cases are estimated to have a lack of family history, mainly due to an incomplete penetrance in inheritance [39].

Furthermore, attention should be placed on drug history; not only on ACEI [40], angiotensin receptor blockers [41], ASA, and other NSAIDs [42], but also on glucose-lowering oral therapies (such as gliptins) that may

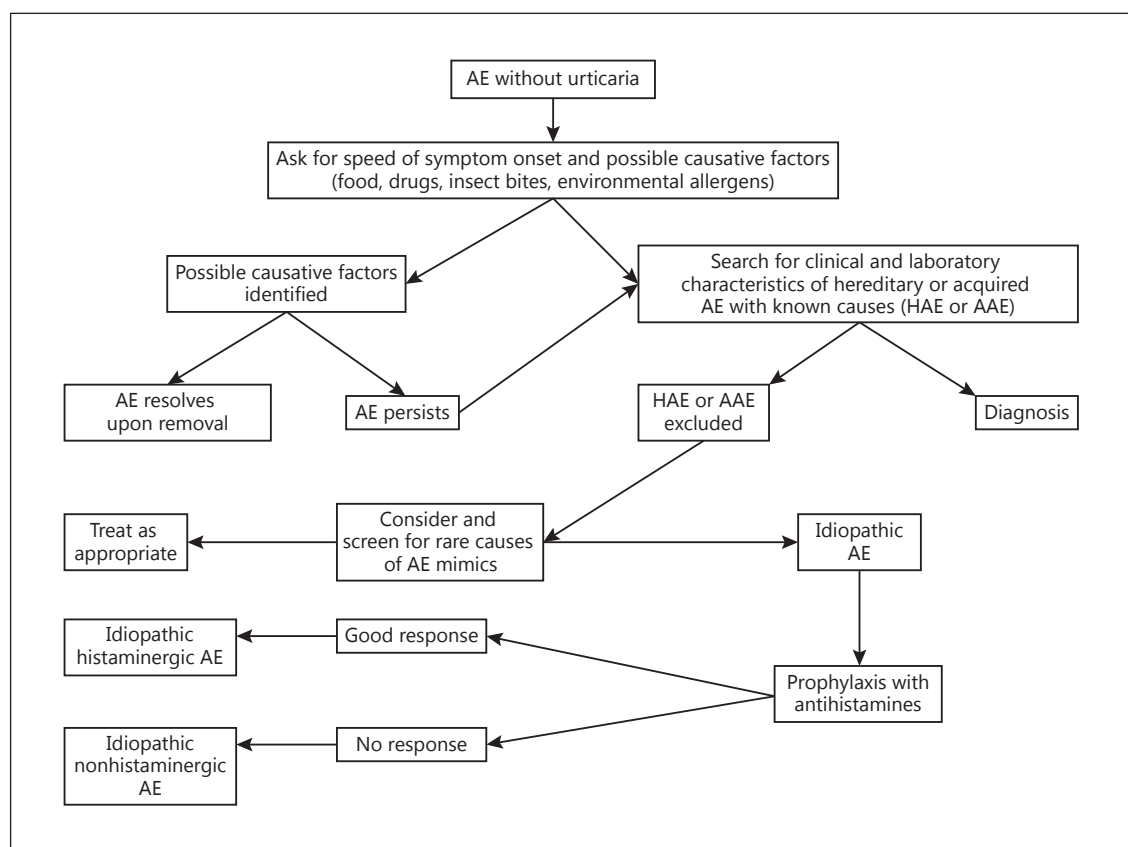


Fig. 2. Diagnostic algorithm for patients with AE without urticaria. HAE, hereditary angioedema; AAE, acquired angioedema.

occasionally precipitate AE [43]. Recently, the novel drug (sacubitril) that is an inhibitor of neprilysin has been introduced in the treatment of moderate to severe heart failure, and it seems to enhance the rate of AE attacks when associated with valsartan [32]. Furthermore, it is useful to investigate other related diseases, such as autoimmune or lymphoproliferative ones, that may suggest a C1-INH-AAE [44]. The response to treatments is crucial in the diagnostic approach, bearing in mind that lack of response to epinephrine, antihistamines, or corticosteroids is typical of BK-mediated AE.

Elucidating the cause of AE also involves an appropriate laboratory testing. If mast cell-mediated AE is suspected, experts suggest employing the guidelines for the diagnosis of urticaria [45]. On the contrary, in any patients with suspected BK-mediated AE, complement factors should be determined [35]. First-line screening for C1-INH-HAE, indeed, should be performed by determining C4 concentrations, which are low in about 96% of cases [46]. However, affected patients with normal C4

have been reported [47] and, if clinical suspicion is high, concentrations of quantitative and functional C1-INH should be requested simultaneously.

C1-INH and C4 determinations are not available in all hospital settings on a routine basis, so results are usually obtained a few days or weeks later. Recently, Bork and Witzke [48] showed that a shortened activated partial thromboplastin time (aPTT) may help to diagnose C1-INH-HAE and C1-INH-AAE when other tests are not available. aPTT is a routine and easy screening test for the “intrinsic” and “common” pathways of blood coagulation [49].

Nevertheless, a correct diagnosis of C1-INH-HAE should still be based on 2 readings, separated by 1–3 months, of low C4, plasma C1-INH levels below 50% of the normal values, or reduced functional C1-INH [3]. The latter measure is not routinely performed in the majority of hospital laboratories and this is probably the main reason why C1-INH-HAE type II has a higher diagnostic delay than type I in Europe [50].

C1-INH gene testing should be performed to confirm the diagnosis of C1-INH-HAE in case of uncertainty, although mutations can be identified in approximately 95% of cases [51]. A recently published study reported that C1-INH plasma levels have a very good correlation with genetic analysis, also in children below 1 year of age, so it is not necessary to look for *SERPING1* mutations to diagnose C1-INH-HAE in newborns [52]. Genotyping of *F12* is, indeed, mandatory in the suspicion of HAE with normal C1-INH [37].

About 70% of C1-INH-AAE patients show low C1q levels, due to the activation of the classical complement pathway [53]. These patients need a careful screening to rule out underlying lymphoproliferative diseases and MGUS. The role of testing for anti-C1 inhibitor antibodies in the diagnosis of AAE is also important, being present in most C1-INH-AAE patients [53].

Beside the correct diagnosis of AE, an open question is the identification of disease-specific biomarkers that could reflect disease activity. The most promising sources of suitable biomarkers appear to be the components of the plasma contact system, endothelial cell-related and inflammatory factors. Currently, plasma levels of cleaved HMWK [54], levels of VEGFs, and angiopoietins have been associated with disease severity [24]. It was suggested, indeed, that some polymorphisms/mutations of possibly AE-related genes, such as BK receptor B2R, FXII, MBL2, neprylisin, and aminopeptidase P, might also be associated with disease severity. Other potential biomarkers have been recently reviewed by Farkas et al. [55]. However, the rarity of the disease and its complexity makes it difficult to find a biomarker that is really useful in clinical practice.

Finally, the differential diagnosis must be aware of rare diseases that can present with symptoms mimicking AE, such as:

- Gleich's syndrome, a subtype of hypereosinophilic syndromes [56];
- NERDS syndrome, characterized by the association of synovial nodules, eosinophilia, rheumatism, dermatitis, and swelling [57];
- Clarkson syndrome or idiopathic capillary leak syndrome, characterized by a rapid plasma extravasation, sometimes life-threatening [58].

Furthermore, several disorders may manifest with subcutaneous or submucosal swelling that can be confused with AE [59], such as Melkersson-Rosenthal syndrome [60], facial cellulitis, Crohn disease, superior vena cava syndrome, systemic amyloidosis, eosinophilic fasciitis, and infections.

The Importance of a Correct Diagnosis to Use the Right Therapy

The rarity of HAE means that this condition is frequently misdiagnosed, resulting in a mean diagnostic delay of 8–16 years depending on different countries. The diagnosis of HAE may be difficult, especially if a familial history is silent or in patients only showing gastrointestinal involvement without cutaneous localization. A recent survey showed that two thirds of patients affected by HAE received a misdiagnosis, the most frequent being allergic reactions and appendicitis [61]. Sometimes abdominal symptoms of AE, such as crampy or extreme pain with or without nausea/vomiting or diarrhea, can be misdiagnosed with several abdominal conditions. This can result in unnecessary surgical interventions, such as appendectomy [62, 63].

Some patients may experience chest pain/dyspnea or dysphagia: these may be misdiagnosed as panic attack or speech disorders. More rarely (in approx. 5%), some patients could suffer from headaches, seizures, and visual disturbances when the brain is involved [64, 65], or urinary retention due to AE of urethral mucosa [64]. While patients are looking for a correct diagnosis of HAE, a life-threatening attack may occur: it has been demonstrated that mortality by asphyxiation is higher in patients with undiagnosed C1-INH-HAE than in patients with diagnosed C1-INH-HAE. Furthermore, the average lifespan of asphyxiated patients with undiagnosed C1-INH-HAE is shorter than those patients with undiagnosed C1-INH who died of other causes. This observation underscores the need to identify these patients more rapidly in order to prevent a fatal attack [61]. When AE is recognized, it is beneficial to start the correct therapy to avoid useless or damaging treatment, e.g., corticosteroids or epinephrine in BK-mediated forms.

Unmet Needs and Future Directions

Major improvements in the diagnosis and treatment of recurrent AE have been achieved over the last 20 years. A novel assay for the diagnosis of HAE types I and II based on the inhibition of BK-forming enzymes has been recently proposed. It seems to perform better than both the commonly used ELISA and the chromogenic assay as well [66].

Several new drugs for prophylaxis and the treatment of acute attacks of AE are now available, particularly for hereditary forms due to C1-INH deficiency. Clinical and experimental studies contributed to the elucidation of

several mechanisms that can be responsible for AE development in vivo, including new pathways leading to uncontrolled activation of FXII, novel mediators dysregulating endothelial cell functions, and the bidirectional interference between mast cells and the contact system. Despite these advances in our understanding of AE, many unsolved questions remain, leaving patients with several unmet needs.

Recurrent isolated AE can be linked to multiple causes, and, even in the same type, it may show distinct phenotypes. The frequency, severity, and location of attacks deeply differ from patient to patient and in the same patient during different periods of life. Thus, the development of a specific phenotype influences the burden of the disease and patients' quality of life. Understanding better the real triggers of AE attacks will help to explain why they develop only at certain times and at specific locations. This information will be helpful to design new agents that can

be used for effective prophylaxis of the different forms of AE. Further research is needed to identify biomarkers in order to distinguish the disease type and predict disease severity. There is clearly the need for identifying clinical and laboratory parameters to allow an early recognition of acute attacks, which is mandatory to implementing rapid and effective treatments. A better knowledge of the AE pathogenesis can lead patients with different phenotypes to receive a correct diagnosis and the most appropriate therapy within a shorter period of time.

Disclosure Statement

The authors have no relevant conflicts of interest relating to the contents of this review and have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed.

References

- Lang DM, Aberer W, Bernstein JA, Chng HH, Grumach AS, Hide M, et al: International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol* 2012;109:395–402.
- Kaplan AP, Greaves MW: Angioedema. *J Am Acad Dermatol* 2005;53:373–388.
- Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, et al: Classification, diagnosis and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy* 2014;69:602–616.
- Cicardi M, Suffritti C, Perego F, Caccia S: Novelty in the diagnosis and treatment of angioedema. *J Invest Allergol Clin Immunol* 2016;26:212–221.
- Björkqvist J, de Maat S, Lewandrowski U, Di Gennaro A, Oschatz C, Schöning K, et al: Defective glycosylation of coagulation factor XII underlies hereditary angioedema type III. *J Clin Invest* 2015;125:3132–3146.
- Bafunno V, Firinu D, D'Apolito M, Cordisco G, Loffredo S, Leccese A, et al: Mutation of the angiotensin-converting enzyme 1 gene (*ANGPT1*) associates with a new type of hereditary angioedema. *J Allergy Clin Immunol*, in press.
- Beltrami L, Zanichelli A, Zingale L, Vacchini R, Carugo S, Cicardi M: Long-term follow-up of 111 patients with angiotensin-converting enzyme inhibitor-related angioedema. *J Hypertens* 2011;29:2273–2277.
- Cicardi M, Zanichelli A: The acquired deficiency of C1 inhibitor: lymphoproliferation and angioedema. *Curr Mol Med* 2010;10:354–360.
- Zanichelli A, Azin GM, Wu MA, Suffritti C, Maggioni L, Caccia S, et al: Diagnosis, course, and management of angioedema in patients with acquired C1-Inhibitor deficiency. *J Allergy Clin Immunol Pract* 2017, Epub ahead of print.
- Castelli R, Delilieri DL, Zingale LC, Pogliani EM, Cicardi M: Lymphoproliferative disease and acquired C1 inhibitor deficiency. *Haematologica* 2007;92:716–718.
- Sands MF, Blume JM, Schwartz SA: Successful treatment of 3 patients with recurrent idiopathic angioedema with omalizumab. *J Allergy Clin Immunol* 2007;120:979–981.
- Von Websky A, Reich K, Steinkraus V, Breuer K: Complete remission of severe chronic recurrent angioedema of unknown cause with omalizumab. *J Dtsch Dermatol Ges* 2013;11:677–678.
- Ozturk AB, Kocaturk E: Omalizumab in recurring larynx angioedema: a case report. *Asia Pac Allergy* 2014;4:129–130.
- Prieto-García A, Marcos C, Caballero T; Spanish Group for Study of Bradykinin-Mediated Angioedema: Classification of angioedema without wheals. *Ann Allergy Asthma Immunol* 2016;116:177.
- Giavina-Bianchi P, Aun MV, Motta AA, Kalil J, Castells M: Classification of angioedema by endotypes. *Clin Exp Allergy* 2015;45:1142–1143.
- Oschatz C, Maas C, Lecher B, Jansen T, Björkqvist J, Tradler T, et al: Mast cells increase vascular permeability by heparin-initiated bradykinin formation in vivo. *Immunity* 2011;34:258–268.
- Sala Cunill A, Björkqvist J, Senter R, Guilarte M, Cardona V, Labrador M, et al: Plasma contact system activation drives anaphylaxis in severe mast cell-mediated allergic reactions. *J Allergy Clin Immunol* 2015;135:1031–1043.
- Kaplan AP, Ghebrehiwet B: The plasma bradykinin-forming pathways and its interrelationships with complement. *Molecular Immunol* 2010;47:2161–2169.
- Fields T, Ghebrehiwet B, Kaplan AP: Kinin formation in hereditary angioedema plasma: evidence against kinin derivation from C2 and in support of "spontaneous" formation of bradykinin. *J Allergy Clin Immunol* 1983;72:54–60.
- Zuraw B, Christiansen C: HAE pathophysiology and underlying mechanisms. *Clin Rev Allergy Immunol* 2016;51:216–229.
- Cugno M, Zanichelli A, Foeni F, Caccia S, Cicardi M: C1-inhibitor deficiency and angioedema: molecular mechanisms and clinical progress. *Trends Mol Med* 2009;15:69–78.
- Joseph K, Tholanikunnel BG, Kaplan AP: Factor XII-independent cleavage of high-molecular-weight kininogen by prekallikrein and inhibition by C1 inhibitor. *J Allergy Clin Immunol* 2009;124:143–149.
- Joseph K, Tholanikunnel BG, Bygum A, Ghebrehiwet B, Kaplan AP: Factor XII-independent activation of the bradykinin-forming cascade: Implications for the pathogenesis of hereditary angioedema types I and II. *J Allergy Clin Immunol* 2013;132:470–475.
- Loffredo S, Bova M, Suffritti C, Borriello F, Zanichelli A, Petraroli A, et al: Elevated plasma levels of vascular permeability factors in C1 inhibitor-deficient hereditary angioedema. *Allergy* 2016;71:989–996.

- 25 Demirturk M, Gelincik A, Cinar S, Kilercik M, Onay-Ucar E, Colacoglu B, et al: Increased eNOS levels in hereditary angioedema. *Int Immunopharmacol* 2014;20:264–268.
- 26 Kajdacs E, Jani PK, Csuka D, Varga LA, Prohaszka Z, Farkas H, et al: Endothelial cell activation during edematous attacks of hereditary angioedema types I and II. *J Allergy Clin Immunol* 2014;133:1686–1691.
- 27 Joseph K, Tholanikunnel BG, Kaplan AP: Heat shock protein 90 catalyzes activation of the prekallikrein-kininogen complex in the absence of factor XII. *Proc Natl Acad Sci USA* 2002;99:896–900.
- 28 Joseph K, Tholanikunnel BG, Kaplan AP: Cytokine and estrogen stimulation of endothelial cells augments activation of the prekallikrein-high molecular weight kininogen complex: implications for hereditary angioedema. *J Allergy Clin Immunol* 2017;140:170–176.
- 29 Hofman ZL, Relan A, Zeerleder S, Drouet C, Zuraw B, Hack CE: Angioedema attacks in patients with hereditary angioedema: local manifestations of a systemic activation process. *J Allergy Clin Immunol* 2016;138:359–366.
- 30 Dunn JT, Kaplan AP: Formation and structure of human Hageman factor fragments. *J Clin Invest* 1982;70:627–631.
- 31 Joseph K, Tholanikunnel T, Kaplan AP: Treatment of episodes of hereditary angioedema with C1 inhibitor: serial assessment of observed abnormalities of the plasma bradykinin-forming pathway and fibrinolysis. *Ann Allergy Asthma Immunol* 2010;104:50–54.
- 32 Bas M, Greve J, Strassen U, Khosravani F, Hoffman TK, Kojda G: Angioedema induced by cardiovascular drugs: new players join old friends. *Allergy* 2015;70:1196–1200.
- 33 Speletas M, Szilagyi A, Psarros F, Moldovan D, Magerl M, Kompoti M, et al: Hereditary angioedema: molecular and clinical differences among European populations. *J Allergy Clin Immunol* 2015;135:570–573.
- 34 Toh S, Reichman ME, Houstoun M, Ross Southworth M, Ding X, Hernandez AF, et al: Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch Intern Med* 2012;172:1582–1589.
- 35 Grigoriadou S, Longhurst HJ: Clinical Immunology Review Series: an approach to the patient with angioedema. *Clin Exp Immunol* 2009;155:367–377.
- 36 Bernstein JA, Moellman J: Emerging concepts in the diagnosis and treatment of patients with undifferentiated angioedema. *Int J Emerg Med* 2012;5:39.
- 37 Bork K, Wulff K, Hardt J, Witzke G, Staubach P: Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. *J Allergy Clin Immunol* 2009;124:129–134.
- 38 Germeis AE, Speletas M: Genetics of hereditary angioedema revisited. *Clin Rev Allergy Immunol* 2016;51:170–182.
- 39 Firinu D, Bafunno V, Vecchione G, Barca MP, Manconi PE, Santacroce R, et al: Characterization of patients with angioedema without wheals: the importance of *F12* gene screening. *Clin Immunol* 2015;157:239–248.
- 40 Bas M, Adams V, Suvorova T, Niehues T, Hoffmann TK, Kojda G: Nonallergic angioedema: role of bradykinin. *Allergy* 2007;62:842–856.
- 41 Strassen U, Bas M, Hoffmann TK, Knopf A, Greve J: Treatment of angiotensin receptor blocker-induced angioedema: a case series. *Laryngoscope* 2015;125:1619–1623.
- 42 Kozel MM, Mekkes JR, Bossuyt PM, Bos JD: Natural course of physical and chronic urticaria and angioedema in 220 patients. *J Am Acad Dermatol* 2001;45:387–391.
- 43 Byrd JB, Shreevatsa A, Putlur P, Foretia D, McAlexander L, Sinha T, et al: Dipeptidyl peptidase IV deficiency increases susceptibility to angiotensin-converting enzyme inhibitor-induced peritracheal edema. *J Allergy Clin Immunol* 2007;120:403–408.
- 44 Wu MA, Castelli R: The Janus faces of acquired angioedema: C1-inhibitor deficiency, lymphoproliferation and autoimmunity. *Clin Chem Lab Med* 2016;54:207–214.
- 45 Zuberbier T, Asero R, Bindslev-Jensen C, Canonica WG, Church MK, Giménez-Arnau A, et al: EAACI/GA²LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. *Allergy* 2009;64:1417–1426.
- 46 Zanichelli A, Arcoleo F, Barca MP, Borrelli P, Bova M, Cancian R, et al: A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy. *Orphanet J Rare Dis* 2015;10:11.
- 47 Tarzi MD, Hickey A, Förster T, Mihammadi M, Longhurst HJ: An evaluation of tests used for the diagnosis and monitoring of C1 inhibitor deficiency: normal serum C4 does not exclude hereditary angioedema. *Clin Exp Immunol* 2007;149:513–516.
- 48 Bork K, Witzke G: Shortened activated partial thromboplastin time may help in diagnosing hereditary and acquired angioedema. *Int Arch Allergy Immunol* 2016;170:101–107.
- 49 Reshef A, Zanichelli A, Longhurst H, Relan A, Hack CE: Elevated D-dimers in attacks of hereditary angioedema are not associated with increased thrombotic risk. *Allergy* 2015;70:506–513.
- 50 Zanichelli A, Magerl M, Longhurst H, Fabien V, Maurer M: Hereditary angioedema with C1 inhibitor deficiency: delay in diagnosis in Europe. *Allergy Asthma Clin Immunol* 2013;9:29.
- 51 Czuka D, Szilagyi A, Farkas H: Hereditary angioedema due to C1-inhibitor deficiency from a genetic point of view. *Hered Genet* 2015;4:e112.
- 52 Pedrosa M, Phillips-Angles E, López-Lera A, López-Trascasa M, Caballero T: Complement study versus C1NH gene testing for the diagnosis of type I hereditary angioedema in children. *J Clin Immunol* 2016;36:16–18.
- 53 Zingale LC, Castelli R, Zanichelli A, Cicardi M: Acquired deficiency of the inhibitor of the first complement component: presentation, diagnosis, course, and conventional management. *Immunol Allergy Clin North Am* 2006;26:669–690.
- 54 Suffritti C, Zanichelli A, Maggioni L, Bonanni E, Cugno M, Cicardi M: High-molecular-weight kininogen cleavage correlates with disease states in the bradykinin-mediated angioedema due to hereditary C1-inhibitor deficiency. *Clin Exp Allergy* 2014;44:1503–1514.
- 55 Farkas H, Veszeli N, Kajdacs E, Cervenak L, Varga L: “Nuts and bolts” of laboratory evaluation of angioedema. *Clin Rev Allergy Immunol* 2016;51:140–151.
- 56 Khoury P, Herold J, Alpaugh A, Dinerman E, Holland-Thomas N, Stoddard J, et al: Episodic angioedema with eosinophilia (Gleich syndrome) is a multilineage cell cycling disorder. *Haematologica* 2015;100:300–307.
- 57 Butterfield JH, Leiferman KM, Gleich GJ: Nodules, eosinophilia, rheumatism, dermatitis and swelling (NERDS): a novel eosinophilic disorder. *Clin Exp Allergy* 1993;23:571–580.
- 58 Duron L, Delestre F, Amoura Z, Arnaud L: Idiopathic and secondary capillary leak syndromes: a systematic review of the literature (in French). *Rev Med Interne* 2015;36:386–394.
- 59 Andersen MF, Longhurst HJ, Rasmussen ER, Bygum A: How not to be misled by disorders mimicking angioedema: a review of pseudoangioedema. *Int Arch Allergy Immunol* 2016;169:163–170.
- 60 Klii R, Chebbi W: Melkersson-Rosenthal syndrome: a rare entity not to ignore. *Pan Afr Med J* 2015;21:33.
- 61 Lunn ML, Santos CV, Craig TJ: Is there a need for clinical guidelines in the United States for the diagnosis of hereditary angioedema and the screening of family members of affected patients? *Ann Allergy Asthma Immunol* 2010;104:211–214.
- 62 Aamir AM, Borum ML: Hereditary angioedema: what the gastroenterologist needs to know. *Clin Exp Gastroenterol* 2014;7:435–445.
- 63 Ohsawa I, Nagamachi S, Suzuki H, Honda D, Sato N, Ohi H, et al: Leukocytosis and high hematocrit levels during abdominal attacks of hereditary angioedema. *BMC Gastroenterol* 2013;13:123.
- 64 Bork K, Meng G, Staubach P, Hardt J: Hereditary angioedema: new findings concerning symptoms, affected organs and course. *Am J Med* 2006;119:267–274.
- 65 Lasek-Bal A, Holecki M, Handzik-Orlik G, Smetka M, Dulawa J: Hereditary angioedema with dominant cerebral symptoms finally leading to chronic disability. *Clin Neurol Neurosurg* 2015;135:38–40.
- 66 Joseph K, Bains S, Tholanikunnel BG, Bygum A, Aabom A, Koch C, et al: A novel assay to diagnose hereditary angioedema utilizing inhibition of bradykinin-forming enzymes. *Allergy* 2015;70:115–119.