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Angioedema as a systemic disease

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Abstract Angioedema is a clinical entity defined as self-limiting edema localized in the deeper layers of the skin and mucosa and lasting for several days. Angioedema can be provoked by bradykinin and/or mast cell mediators, including histamine. Four types of acquired and three types of hereditary angioedema have been identified. The most obvious form of angioedema associated with other systemic disease is acquired angioedema due to C1-inhibitor deficiency. It is characterized by acquired consumption of C1 inhibitor and various underlying disorders, such as multiple myeloma, chronic lymphocytic leukemia, rectal carcinoma, and non-Hodgkin lymphoma. Suspected cases need an accurate differential diagnosis to exclude all other types of acquired and hereditary angioedema.

Introduction

Angioedema is a clinical entity defined as a self-limiting edema localized in the deeper layers of the skin and mucosa and lasting for several days. The disease was described for the first time by Heinrich Quincke (1842-1922) in 1882,[1] and since then, it is often referred to as Quincke edema.

Angioedema is characterized by a vascular reaction of deep dermal, subcutaneous, mucosal, or submucosal tissues with localized increased permeability of blood vessels resulting in tissue swelling.[2–6] Angioedema can be mediated by bradykinin and/or mast cell mediators, including histamine.[7]

A well-known and the most frequent manifestation of angioedema due to histamine and other mast cell mediators is the one that occurs as part of urticaria. It is characterized by the following two signs: (1) wheals, edema of superficial skin layers, and (2) angioedema, edema of deep skin layers.[8]

Bradykinin-mediated angioedema occurs either on a hereditary or acquired basis, due to a deficiency/defect of C1 inhibitor (C1-INH) or other mechanisms.[9,10]

It is obvious that the diagnosis of angioedema needs to be refined by the specification of its type. If angioedema recurs without significant wheals, the patient should be diagnosed having angioedema as a disease of its own. Because an accepted classification is absent, different types of angioedema are not well and easily identified.

Classification

According to the European Academy of Allergy and Clinical Immunology classification,[7] angioedema without wheals as a separate disease is classified on the basis of its cause, acquired or hereditary, and response to treatment. Four types of acquired (AAE) and three types of hereditary (HAE) angioedema are identified.

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AAE:

1. AAE with unidentified cause (idiopathic), responding to treatment with antihistamines (IH-AAE)
2. AAE with unidentified cause (idiopathic), nonresponding to treatment with antihistamines (InH-AAE)
3. AAE after treatment with angiotensin-converting enzyme inhibitors (ACEI-AAE)
4. AAE due to C1-inhibitor deficiency (C1-INH-AAE)

HAE:

1. HAE with autosomal-dominant inheritance and C1-INH deficiency (C1-INH-HAE; cause, mutations in *SERPING1* gene)
   1.1 Type 1 with decreased C1-INH plasma levels leading to an increase in bradykinin formation
   1.2 Type 2 with dysfunctional C1-INH protein
2. HAE with normal plasma levels of C1-inhibitors due to factor XII (FXII-HAE),[2] plasminogen,[3] or angiopoetin-1 mutations[4]
3. HAE of unknown reason (U-HAE)

Another similar classification of angioedema is based on the type of mediators responsible for symptom development,[11] including bradykinin-induced AE, mast cell mediator–induced AE, and AE due to unknown mediator.

Acquired angioedema

AAE is localized on the face, lips, tongue, extremities, or genital area. Edematous episodes may have various triggers, such as mild trauma, viral or bacterial infections, cold exposure, pregnancy, certain foods, or emotional stress. The incidence of edema episodes is unpredictable and can vary widely.

Acquired angioedema with C1-inhibitor deficiency

The most obvious form of angioedema related to other systemic diseases is the third form of AAE, namely C1-INH-AAE.[12] The disease was first described in 1972.[13] The first patient had C1-INH deficiency in combination with recurrent episodes of angioedema and lymphosarcoma. Currently, C1-INH-AAE is considered a subset of AAE. This form of AAE is characterized by acquired consumption of C1-INH associated with various underlying disorders.

The nature of C1-INH-AAE is nongenetic, which implies that no mutations in C1-INH gene (*SERPING1*) and no family history of angioedema are associated with this disease. In the absence of epidemiologic studies, the prevalence of C1-INH-AAE in the general population is estimated between 1:100,000 and 1:500,000, based on the experience of identifying one C1-INH-AAE patient for every 10 HAE patients.[7] Because the condition remains often unnoticed, the real prevalence is probably much higher. Persons of any race may suffer from C1-INH-AAE, and men and women are equally affected.

Studies on plasma from patients with C1-INH-AAE indicate consumption of C1-INH and classic pathway complement components and, during attacks, activation of contact system with release of bradykinin, which causes angioedema. The lymphoproliferative disease, frequently found in these patients, could directly contribute to the consumption of C1 and C1-INH.[7]

A few basic elements, characteristic for this type of AAE have been described:

- Negative family history for angioedema
- Age of onset after the fourth decade of life
- Acquired deficiency of C1-INH
- Hyperactivation of the classic pathway of human complement
- Recurrent angioedema episodes

C1-INH-AAE is grouped into the following two different types[14]: (1) Type I, associated with lymphoproliferative or autoimmune diseases, and (2) Type II, associated with autoimmune abnormalities.

C1-INH-AAE Type I and associated systemic diseases

Type I is most commonly related to B-cell lymphoproliferative disorders, but cases with associated T-cell lymphoma have also been described. Other reported neoplastic disorders for C1-INH-AAE Type I are multiple myeloma, chronic lymphocytic leukemia, rectal carcinoma, and non-Hodgkin lymphoma. There are some publications stating that myelofibrosis, Waldenström macroglobulinemia, essential cryoglobulinemia, erythrocyte sensitization, antiphospholipid syndrome, and infections with *Helicobacter pylo*ri or *Echinococcus granulosis* could serve as a trigger factor for this type of acquired angioedema. One patient has been associated with liver transplantation. The status of the liver donor was unknown, but it is speculated that the donor may have been C1-INH deficient.

The associated diseases may become evident years after the beginning of angioedema. A 2016 study reported that 62.5% of the patients were diagnosed with non-Hodgkin lymphoma at the onset of angioedema or up to 7 years later.[15] Patients with C1-INH-AAE Type I should be checked regularly for the development of malignancy.

The underlying disease may produce idiotype/anti-idiotype antibodies, or other immune complexes that downregulate C1-INH function. Increased consumption of C1q followed by C2 and C4 results in the subsequent release of vasoactive peptides that act on postcapillary venules. Another probable explanation for the development of angioedema is the overconsumption of C1-INH by neoplastic lymphatic tissue.[16]

C1-INH-AAE Type II and associated autoimmune abnormalities

AAE Type II is not a paraneoplastic syndrome. In Type II, a normal 105-kD C1-INH molecule is synthesized in adequate amounts. As a consequence of an unknown cause, a

subpopulation of B cells initiates synthesis of autoantibodies directed against C1-INH molecules. These autoantibodies might be of any of the major immunoglobulin classes. They attach to the epitopes of the reactive center of C1-INH and its regulatory capacity is weakened or nullified.[10] In all reported cases, C1-INH circulates in the blood in a form that has been cut down by target proteases to a 95-kD fragment. Due to the higher affinity of the autoantibody to native C1-INH, the 95-kD antibody/C1-INH complex dissociates, and the freed antibody can bind to another native C1-INH molecule, further depleting C1-INH.

In some cases, an overlap between Type I and II may occur. Patients with AAE Type I may initially present with autoantibodies to C1-INH, or the autoantibodies may develop as the disease progresses. Features of C1-INH-AAE Type I and II has been noted, particularly in patients with monoclonal gammopathy of undetermined significance.

C1-INH-AAE with autoantibodies and with lymphoproliferative diseases largely overlaps and should be considered the same disease. Other conditions, mainly Systemic lupus erythematosus (SLE), are reported in C1-INH-AAE, which appears as a syndrome with different possible associations; however, 20 out of 180 cases reported in the literature had no underlying disease associated with their C1-INH-AAE.[7]

AAE with C1-INH deficiency begins after the age of 40 years in 94% of patients. Family history of angioedema is never present.

C1-INH-AAE is clinically characterized by episodes of transient nonpitting asymmetric edema. The lesions are nonpruritic and painless. Edema can occur anywhere in the body and typically last for several days. It is usually localized to the face, lips, tongue, extremities, and genitals. In C1-INH-AAE, swelling involves the face more often than the extremities, in contrast to HAE Type 1 and 2, where edematous changes of the extremities are more typical. Gastrointestinal edematous attacks are less common in C1-INH-AAE patients compared with C1-INH-HAE patients. In most of the patients, the edema of the subcutaneous and/or submucosal tissue appears without wheels, although a patient with a chronic lymphatic B-cell leukemia who suffered from both C1-INH-AAE and chronic spontaneous urticaria has been described.[17]

In patients with intestinal edema, colicky abdominal pain, nausea, vomiting, and diarrhea could be observed. This abdominal pain is less reported in AAE (30% to 50%) compared with HAE (up to 80%). Life-threatening edema of the upper respiratory tract as a clinical presentation of C1-INH-AAE has also been described. Approximately 50% of patients with C1-INH-AAE experience upper airway edema.[18]

Diagnosis. Testing for C1-INH deficiency is performed by measuring C1-INH antigen level, C1-INH function, and C4 levels in plasma. Qualitative and functional values of C1-INH should be obtained. Test results for acquired angioedema Types I and II indicate usually low C1-INH level, low C1q, and low C4 and C2 levels. AAE Type II shows positive immunoblot assay findings for the 95-kD C1-INH cleavage product. An enzyme-linked immunosorbent assay has been developed that measures the neutralizing capacity of anti–C1-INH antibodies in plasma.[19]

Other laboratory findings are related to the associated illnesses. During attacks of gastrointestinal edema, abdominal ultrasonography, or computed tomography scanning may show edematous thickening of the intestinal wall, a fluid layer around the bowel, and large amounts of free peritoneal fluid.

Histologic findings are indistinguishable from other angioedema types. Features include sparse perivascular mononuclear cell infiltrate and reticular dermal, subcutaneous, or submucosal edema. Vasodilation may be seen.

All patients diagnosed with C1-INH-AAE should be assessed for an underlying lymphoproliferative disorder. Regular check-ups are recommended if at the time of diagnosis, no lymphoproliferative disorder is found. C1-INH-AAE should always be considered in patients in the fourth decade of their life with recurrent episodes of angioedema without wheels and without family history for angioedema.

Treatment. Treatment of C1-INH-AAE should consider the underlying disease as well as the frequency and severity of angioedema. Curing the underlying disease can cure angioedema, and this option should be considered. Symptomatic treatment for angioedema recurrences can be provided using bradykinin-targeted drugs.

The edema is usually unresponsive to antihistamine therapy. AAE may stop if the underlying disease is treated, but some patients continue to experience episodes of edema despite the treatment. Treatment focuses on control of the clinical findings by regulating bradykinin activity using therapies found to be effective in HAE (C1-INH concentrate, icatibant, ecallantide, tranexamic acid, androgens).

Treatment for angioedema clinical manifestations in patients with C1-INH-AAE has used C1-INH replacement therapy. The majority of patients respond positively, but some may be resistant to this treatment due to an extremely rapid catabolism of C1-INH.

Avoidance of triggers (social stressors, trauma, exogenous estrogens, tamoxifen, ACEIs) prevents, or reduce the frequency.[7] Rituximab (monoclonal antibody against lymphocytes B-CD20) may be a promising therapy and has been used successfully in a few cases.

The prognosis depends on the control of the underlying disorder.[20] In the differential diagnosis all other forms of AAE should be considered.

Idiopathic histaminergic acquired angioedema (IH-AAE)

Histamine-mediated AAE is often accompanied by an urticarial rash (Figure 1). The combination of spontaneous urticaria and angioedema with duration of more than 6 weeks belongs to the clinical spectrum of chronic spontaneous urticaria. This type of angioedema is provoked by allergic or nonallergic stimuli, which usually are unrecognized.

Because continuous administration of an antihistamine stops disease recurrences in a significant proportion of the patients, this this type of angioedema is defined as ‘histaminergic’. The term indicates for the significant role of the cutaneous

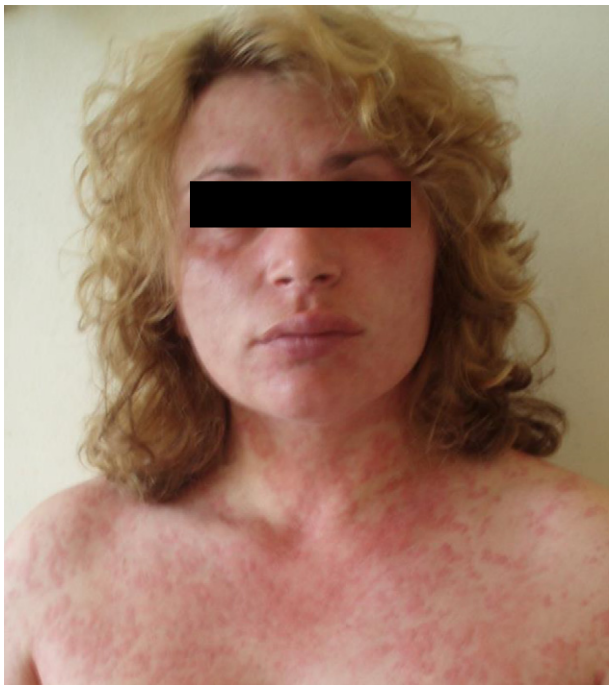

Fig. 1 Idiopathic histaminergic acquired angioedema accompanied by an urticarial eruption.

mast cells and/or the blood basophil degranulation and mediator release. Bradykinin or other vasoactive substances are not predominantly released.

Histamine release suggests an allergic cause. Very often, the starting point in the evaluation of patients with angioedema is to identify such a cause. Allergy is suspected if the recurrence of clinical manifestations is sequential, related to an exogenous stimulus and confirmed by a positive skin prick test and/or detection of clinically significant specific immunoglobulin E. Stimuli, such as medication and/or foods, insect bites/stings, or other environmental allergens are frequently involved in patients with acute angioedema, but only in a minority with recurrent attacks. Strong causal relationship between infection or autoimmune disease and angioedema is, however, frequently difficult to confirm. When allergy and other causes have been ruled out and an etiology cannot be identified, the histaminergic angioedema is defined to be idiopathic or spontaneous.

Clinical presentation. Data on clinical presentation of this form of angioedema are scarce. The following description is based on the discussion among experts[7]: IH-AAE develops rapidly; its maximum is within 6 hours; precipitating factors are not identified; drug history is irrelevant; the face is mostly affected; gastrointestinal and laryngeal mucosa are spared and death due to the angioedema has not been reported; there is no preferred age for onset; attacks are prevented by antihistamine and respond to corticosteroids and epinephrine as acute treatment; family history for angioedema is negative; and there are no associated diseases.

Diagnosis. Major diagnostic tools include exclusion of potential causes of angioedema based on the clinical features, including causative agents, associated autoimmune/infectious disease, C1-INH deficiency, and mutation in FXII. In the absence of an algorithm specific for angioedema, it is reasonable to implement urticarial diagnosis guidelines for diagnosis of urticaria.[8]

IH-AAE is the most common form of angioedema with some of its clinical and pathogenetic features similar to idiopathic recurrent urticaria. It is diagnosed on clinical features, exclusion findings, and therapeutic response. Antihistamine and corticosteroids represent the basic treatment.

Idiopathic nonhistaminergic acquired angioedema

This is an angioedema type that is nonfamilial and nonhereditary. Known causes have been excluded as for IH-AAE, but recurrences persist upon antihistamine treatment. There are not many medical papers matching the terms idiopathic, nonhistaminergic, and angioedema. A number of experts believe strongly that it could encompass a distinct, homogeneous group of patients, which is why they are trying hard to provide a definition of this type.[7] For the first time the term is used for describing a group of patients with angioedema and a remarkable response to a prophylactic course of tranexamic acid.[21] A favorable effect of tranexamic acid was reported in another group of angioedema patients with similar characteristics, but defined as 'sporadic idiopathic bradykinin angioedema'.[22] The term "bradykinin-mediated" sometimes stands for 'nonhistaminergic' implying that bradykinin mediates this angioedema. Experimental evidence that bradykinin is involved in the pathogenesis of this type is still limited. Additional evidence supportive of bradykinin as the mediator comes from case reports showing efficacy of the bradykinin receptor antagonist icatibant in reverting angioedema, irresponsive to antihistamine.[7]

Clinical presentation. Only two limited series of patients are found in the literature to be considered representative of InH-AAE. There is a slightly higher frequency in men and age of onset is between 36 and 42 years. The most common clinical location is facial (Figures 2 and 3), followed by upper airway and abdominal involvement. Invasive management (endotracheal intubation) for upper airway edema was reported for a single patient in the Italian group.[23] The mean duration of clinical manifestations is less than 48 hours and the frequency of recurrences high, with more than half of the patients needing continuous prophylaxis with tranexamic acid.

Diagnosis. The first diagnostic step for this type of angioedema is the clinical history. The diagnosis is based on the patient's negative response to continuous antihistamine treatment.

Treatment. There is no conclusive evidence for an effective treatment for attacks of idiopathic nonhistaminic angioedema. Efficacy of tranexamic acid has been reported in the two previously mentioned case series, but no detailed data are available.

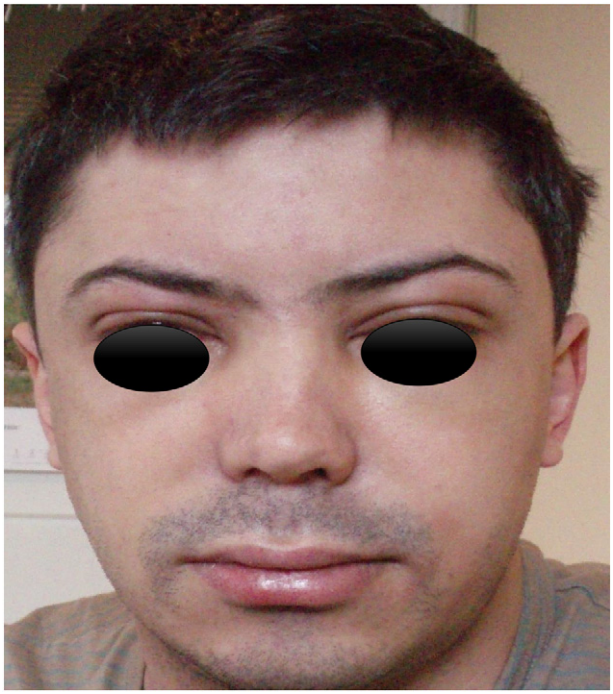

Fig. 2 Idiopathic nonhistaminergic acquired angioedema.

Acquired angioedema related to angiotensin-converting enzyme inhibitors (ACEI-AAE)

ACEIs are an unpredictable and important cause for the appearance of AAE. This is a well-known side effect as a result of the diminished break down of bradykinin. ACE is involved in the breakdown of bradykinin to inactive peptides. Its inhibition results in elevated plasma levels of bradykinin that further increase during ACEI-AAE. ACEI typically trigger angioedema without urticaria. Spontaneous recurrence of angioedema is possible even months after stopping the drug intake. Angioedema associated with angiotensin receptor blockers has been occasionally reported. Recently cases of angioedema were described after intake of ACEI and antidiabetic drugs (inhibitors of dipeptidyl peptidase-4). These drug combinations also lead to increased bradykinin levels in the blood. Other reasons for drug-induced angioedema are the neprilysin inhibitors, which also cause high bradykinin levels in the blood.

Incidence. Analysis of large cohorts of hypertensive patients suggests angioedema to occur in less than 0.5% of patients taking ACEI but 3- to 4.5-fold more often in black than in Caucasian subjects.

Clinical manifestations. Acquired angioedema related to ACEI is more frequent in women than in men and in individuals over 65-years old. The latency between the initiation of ACEI therapy and the onset of clinical manifestations can vary greatly from a few hours to several years, but it is more likely to occur earlier after initiation of ACEI therapy. AAE related to ACEI is usually observed on the face, followed by lips, eyelids, tongue, neck, and upper airway. ACEI-induced gastrointestinal angioedema has rarely been reported. Deaths from laryngeal edema due to ACEI-AE have been reported. The episodes of angioedema may persist for several months after withdrawal of the ACEI without undermining the validity of the drug-related diagnosis.

Diagnosis. There is no test specifically modified during ACEI-AAE, and therefore, it is diagnosed upon manifestation of not otherwise explained angioedema in patients taking ACEI.

Therapy of ACEI-AAE. To prevent ACEI-AAE recurrences, the drug should be immediately discontinued. ACEI withdrawal is not, however, 100% effective. Continued use of ACEI in spite of angioedema results in a marked increase in the incidence of recurrent angioedema with serious morbidity. The reason for persistence of angioedema after ACEI

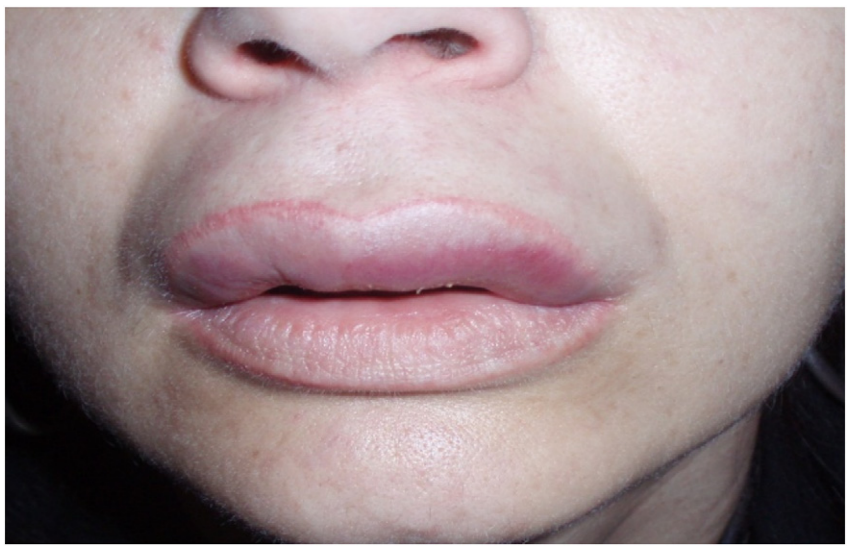

Fig. 3 Idiopathic nonhistaminergic acquired angioedema.

withdrawal is not clear. Pathophysiology suggests that bradykinin-targeted drugs, licensed to treat HAE due to C1-INH deficiency, could be effective to reverse clinical manifestations in ACEI-AAE. Due to the lack of efficacy of corticosteroids and epinephrine, some of them have been used off-label in ACEI-AAE.[7]

In most patients with ACEI-AAE, clinical manifestations disappear or are drastically reduced after stopping the ACEI. Individuals who do not improve even after several months of stopping the ACEI are likely to have an alternative cause for their angioedema and were coincidentally taking an ACEI. There are no routine investigations to distinguish responders from nonresponders to ACEI withdrawal. If the ACEI is responsible but is not withdrawn, the attacks may become more severe and frequent. ACEIs are contraindicated in patients with a history of angioedema and an alternative antihypertensive drug should be substituted.

The differential diagnoses of AAE include also the forms of HAE as mentioned below. Because the pathophysiology and the management of these clinical forms are different from those of AAE, it is important to determine the correct diagnosis

Hereditary angioedema

Different forms of HAE are currently recognized and identified genetically. The forms of HAE with normal C1-INH (HAE-FXII, Hereditary angioedema with mutation in the angiopoietin-1 gene (HAE-ANGPTI), Hereditary angioedema with normal C1-inhibitor levels due to a mutation in plasminogen (HAE-PLG), Hereditary angioedema due to unknown mutations (HAE-UNK)) share some clinical features and, possibly, therapeutic options.[11]

Hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE)

C1-INH-HAE is an autosomal-dominant orphan disease with minimal prevalence varying from 1.09 in 100,000 to 1.51 in 100,000 inhabitants.[24] C1-INH-HAE is due to one of more than 450 different mutations in one of the two alleles of the *SERPING1* gene, which codes for C1-INH. Several homozygous mutations were described, predominantly in patients with parents who are close blood relatives. Structural abnormalities in these patients are very heterogeneous, and prevalence of *de novo* mutations is approximately 25% of cases.

C1-INH is a serine protease inhibitor and the major inhibitor of several complement proteases (C1r, C1s, MASP 1 and 2, and contact-system proteases [plasma kallikrein and coagulation FXIIa]), as well as a relatively minor inhibitor of the fibrinolytic protease plasmin. Mutations in *SERPING1* result in reduced plasma levels of C1-INH and facilitated release of bradykinin, which is the key mediator of this type of angioedema.[10]

Two phenotypic variants have been described:

- Type I is a quantitative decrease in C1-INH with a consecutive diminished functional activity (C1-INH-HAE Type I).
- Type II is distinguished by normal or high levels of dysfunctional C1-INH.

Clinical presentation and systemic involvement. C1-INH-HAE is clinically manifested by recurrent, localized subcutaneous or submucosal edema lasting for 2 to 5 days. The most commonly involved organs are the skin and upper respiratory and gastrointestinal tracts. The clinical expression is highly variable from asymptomatic cases to patients suffering from disabling and life-threatening attacks. Because nearly all patients with C1-INH-HAE present recurrent episodes of abdominal pain due to temporary bowel obstruction as a consequence of mucosal edema, it is common that they often undergo unnecessary surgery misdiagnosing for surgical emergency a gastrointestinal angioedema.[25,26]

Diagnosis. C1-INH-HAE is suspected on the basis of the previously mentioned clinical manifestations and a positive family history (although this may not be present in up to 25% of patients), onset of clinical manifestations in childhood or adolescence, failure to respond to antihistamines, glucocorticoids, or epinephrine, presence of prodromal signs or clinical manifestations before swelling, and/or the absence of urticaria (wheals). Diagnosis, however, needs laboratory confirmation. Measurements of serum or plasma levels of C1-INH function, C1-INH protein, and C4 are used. In HAE-I, which comprises approximately 85% of patients, both, the concentration and function of C1-INH are low. In HAE-II, C1-INH concentrations are either normal or elevated, whereas C1-INH function is reduced. Patients with C1-INH-HAE present with low C4, and to a lesser extent low C2, because consumption due to the activation of the classical complement pathway lacking its physiologic inhibitor C1-INH. Measurement of C4 levels is used for screening of C1-INH-HAE, because it is decreased even in between attacks and only exceptionally can be normal. C4 levels are usually low in HAE-I/II patients, but its sensitivity and specificity are limited. Diagnosis is confirmed by the evidence of plasma C1-INH levels below 50% of the normal values.[27]

Sequencing of the *SERPING1* gene can be supportive in the diagnostic workup of some HAE-I/II patients (including prenatal diagnosis); however, biochemical C1-INH testing is effective and less expensive than genetic testing.[11]

The World Health Organization's first international standards for C1-inhibitor, plasma, and concentrate was established in 2011.[28] Diagnosis of C1-INH-HAE should be based on two reduced readings of C4 and quantitative and/or functional C1-INH, separated by 1 to 3 months. The constellation for the diagnosis of C1-INH deficiency has a specificity of 98% to 100% and a negative predictive value of 96%.[29,30]

Treatment. Treatment objective of C1-INH-HAE patients is to avoid mortality and reduce morbidity. Several international consensus papers, released since 2004, guide the treatment of C1-INH-HAE.[11,31–35]

Upon being diagnosed as C1-INH-HAE, all patients should have readily available a drug of proved efficacy in reverting

attacks. The first step to disease control is to administer this drug as soon as the patient realizes that angioedema clinical manifestations have started to develop. If reduction of disease burden and significant improvement of the quality of life are not achieved by this approach, continuous prevention treatment should be considered. Antifibrinolytic agents, attenuated androgens, and plasma-derived C1-INH are available for this approach.

Plasma-derived C1-INH, given at doses effective for on-demand and as close as possible to the procedure, appears as the most rational approach, because it is promptly effective and has a sufficient half-life.[7]

Hereditary angioedema with normal C1 inhibitor and factor XII mutation (FXII-HAE) and of unknown origin (U-HAE)

From 1985 to 2006, patients of both sexes with HAE and normal C1-INH have been described. They were members of 11 families. Patients presented with recurrent angioedema of the skin associated with relapsing episodes of abdominal pain attacks and episodes of upper airway obstruction. In 2006, a new group of patients with HAE and normal C1-INH was identified. The cause of the disease in this case is believed to be two different missense mutations. The location of these mutations was the same locus, as the Hageman factor, or coagulation *F12* gene.[7]

Clinical presentation. The clinical manifestations include recurrent skin swelling, abdominal pain attacks, tongue swelling, and upper airway edema. No difference in clinical manifestations due to the presence of *F12* gene mutations has been identified.[36]

Urticaria does not occur at any time in any of these patients. The skin swelling typically lasts 2 to 5 days; they affect mainly the extremities and the face. The abdominal attacks also last 2 to 5 days and are manifested as severe crampy pain.[7]

Diagnosis. Diagnosis of U-HAE is based on clinical findings and requires that patients have the specified clinical manifestations, one or more family members, affected with these clinical manifestations, do not have familial and hereditary chronic urticaria with urticaria-associated angioedema, normal C1-INH activity and protein in plasma, and no HAE-associated mutation in *F12* gene. FXII-HAE has analogous clinical criteria, but with the presence of an HAE-associated mutation in *F12* gene.

The laboratory diagnosis of FXII-HAE is purely genetic, whereas there are no confirmatory laboratory tests for U-HAE.

Therapeutic approach. Patients with U-HAE/FXII-HAE do not respond to corticosteroids and antihistamines. Based on the presumed pathophysiology, several potential treatment options are available, including C1-INH agents, icatibant, ecallantide, progesterone, danazol, and tranexamic acid.[7,11]

The 2017 revision and update of the international World Allergy Organization/European Academy of Allergy and Clinical Immunology guideline for the management of hereditary angioedema[11] describes three levels of treatment of HAE.

On-demand treatment. It is recommended that all attacks be considered for on-demand treatment, and any attack affecting or potentially affecting the upper airway should be treated as early as possible. HAE attacks may be treated with C1-INH, ecallantide, or icatibant. Intubation or surgical airway intervention is considered early in progressive upper airway edema. It is recommended that all patients have sufficient medication for on-demand treatment of two attacks and carry on-demand medication at all times.

Preprocedural (short-term) prophylaxis. Short-term prophylaxis before procedures that can induce an attack is recommended.

Long-term Prophylaxis. Long-term prophylaxis should be considered for patients who face events in life that are associated with increased disease activity. Patients are evaluated for long-term prophylaxis at every visit. Use of C1-INH for first line long term prophylaxis is recommended. Androgens as second-line, long-term prophylaxis are suggested.

Conclusions

Among the many clinical forms of angioedema, only the AAE due to C1-INH deficiency has a direct link to other systemic diseases, such as multiple myeloma, chronic lymphocytic leukemia, rectal carcinoma, and non-Hodgkin lymphoma. In such cases, a precise differential diagnosis should be made to exclude all other types of AAE and HAE.

Conflict of interest

The authors declare no conflict of interest.

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