Review

Hereditary Angioedema

Cristina Tutunaru , Oana Ica * , George Mitroi , Daniela Neagoe , George Mitroi * , Simona Ianosi

Posted Date: 14 July 2023

doi: 10.20944/preprints202307.0996.v1

Keywords: hereditary angioedema guidelines; treatment; prophylaxis; management

Review

Hereditary Angioedema

Cristina Violeta Tutunaru [1], Oana Maria Ică [1,*], George F. Mitroi [2,*], Carmen Daniela Neagoe [3], George G. Mitroi [1] and Simona Laura Ianoși [1]

[1] Department of Dermatology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, 200349 Craiova, Romania
[2] Department of Urology, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, 200349 Craiova, Romania
[3] Department of Internal Medicine, Faculty of Medicine, University of Medicine and Pharmacy of Craiova, 200349 Craiova, Romania
* Correspondence: george.mitroi@umfcv.ro (G.F.M.); oana.maria.corici@umfcv.ro (O.M.I.); Tel.: +40-744547069 (G.F.M.); +40-727804474 (O.M.I.);

Abstract: Hereditary angioedema (HAE) is a very rare and potentially life-threatening genetic disease characterized by low levels of C1-INH inhibitor esterase and involving recurrent attacks of non-pruritic angioedema that do not leave subcutaneous or mucosal wells without the presence of hives. It occurs worldwide in 1 in 50,000 to 150,000 individuals and accounts for approximately 2% of clinical angioedema. It affects both sexes equally and can affect all races without ethnic differences. Methods: We conducted a review in Pubmed regarding this disease using keywords such as: hereditary angioedema, guideline, treatment, prophylaxis, management. Results: We analysed 195 articles and we focused our study on 17 reviews about type I of HAE published in English in the last 10 years. Conclusions: Screening among the family members of affected individuals (even if symptoms are absent) is mandatory, since it is a life-threatening condition. Developing solutions to diagnose and manage this condition has improved the life and treatment results of patients.

Keywords: hereditary angioedema guidelines; treatment; prophylaxis; management

1. Introduction

Hereditary angioedema (HAE) is defined as a genetic condition that occurs rarely but poses a threat to life having low levels of C1-INH inhibitor esterase and involving recurrent attacks of non-pruritic angioedema that do not leave subcutaneous or mucosal wells without the presence of hives. It occurs worldwide in 1 in 50,000 to 150,000 individuals and accounts for approximately 2% of clinical angioedema. It affects both sexes equally and can affect all races without ethnic differences. It is an autosomal dominant disease that requires mandatory screening among the family members of affected individuals (even in lack of symptoms), since it is a life-threatening condition. Developing solutions to diagnose and manage this condition has improved the life and treatment results of patients. [1]

We conducted a study focussed on this disease using keywords such as: hereditary angioedema, guideline, treatment, prophylaxis, management in Pubmed.

2. Materials and methods

We analysed 195 articles and we focused our study on 17 reviews regarding type I of HAE published in the last 10 years. This study aims to analyze the scientific literature of hereditary angioedema type I. Medline (PubMed) and ResearchGate electronic databases were used to search for articles written in English in the last 10 years. The research used keywords such as: hereditary angioedema, guideline, treatment, prophylaxis, management. The bibliography lists scientific papers of interest. Thus, the number of articles was limited by eliminating those that lacked direct relevance to our study.

 doi:10.20944/preprints202307.0996.v1

Exact phrases/ syntax and connectors used for database search/query were as follows: 'hereditary angioedema', 'guideline', 'treatment', 'prophylaxis', 'management'.

At first, articles were screened based on their title and duplicate records were removed. Article eligibility was evaluated based on their title and abstract and further exclusion took place for articles that were considered irrelevant. Articles without an abstract were not taken into consideration. Finally, full-text articles were screened for eligibility based on whether the articles referred strictly to type I of hereditary angioedema. Each article was afterwards studied independently for data extraction.

3. Discussions and results

Hereditary angioedema (HAE) (also called C1-INH esterase inhibitor deficiency, C1-INH inhibitor deficiency, HAE, HANE, hereditary angioneurotic edema, C1 complement inhibitor deficiency) is a very rare and potentially life-threatening genetic disease characterized by low levels of C1-INH inhibitor esterase and involving recurrent attacks of non-pruritic angioedema that do not leave subcutaneous or mucosal wells without the presence of hives. It occurs in various areas of the body such as hands, feet, genital area, stomach and face. C1-INH esterase deficiencies allow uncontrolled activation of the classical complement pathway and other systemic biochemicals including the bradykinin system.

J. L. Milton described HAE in 1876. In 1882 Quincke called the disease angioneurotic edema. Studies suggest that the name neurotic was used to describe the effect of mental stress as an exacerbating factor of this condition. In 1888, William Osler published the first paper describing a hereditary form of angioneurotic oedema; however, the biochemical basis of the disease was not discovered until several decades later. In 1963, Donaldson and Evans first described the absence of C1-INH esterase.

3.1. Epidemiological data

HAE occurs worldwide in 1 in 50,000 to 150,000 individuals and accounts for approximately 2% of clinical angioedema. It is a rare disease that affects both sexes equally and can affect all races without ethnic differences.

There are 3 types of hereditary angioedema types I, II and III which are differentiated by etiology and blood levels of C1 inhibitor. [2,3] Signs and symptoms are similar in all types. Type I is characterized by low levels of C1-INH inhibitor protein esterase due to an abnormal gene allele of the protein. Type II is characterized by increased or normal but dysfunctional levels of C1-INH. Again, one of the 2 allele genes is abnormal but in this case the alleles lead to the formation of non-functional protein. Type III has normal C1-INH levels and has been identified as an inherited estrogen-dependent form that occurs mostly in women with normal C1-INH levels. Type I is the most frequent in 80-85% of cases; type II is 15% of cases and type III is uncommon. Men and women are equally affected by HAE types I and II although women are prone to having more intense bouts.

In 1963, Donaldson and Evans discovered that HAE is caused by a genetic deficiency of C1-INH (C1-INH). C1-INH deficiency is present from birth in HAE although there are few described cases of perinatal angioedema. Most often, symptoms appear during the two decades of life. Around 40% of people with HAE have the onset before the age of 5 years, while 3/4 before 15 years of age. Patients have mild symptoms that typically go unobserved but around puberty they become more serious. However, HAE with normal C1-INH levels occurs in the second decade of life and infrequently before puberty.

HAE is present throughout life even though in some cases improvement with age is seen. 5% of adult carriers of HAE are asymptomatic and are not diagnosed until their offspring become symptomatic.

 doi:10.20944/preprints202307.0996.v1

3.2. Etiopathogenesis

HAE is transmitted autosomal dominant. Children have a 50% chance of inheriting the disease if one parent has it. However, the lack of a family history of HAE does not exclude the diagnosis, as studies show that about 1/4 of cases is due to a spontaneous mutation of the C1 inhibitor gene at the time of conception. The gene that causes HAE is located on the long arm of chromosome 11 (11q12-q13.1).

C1-INH, an α2-globulin of approximately 105 kDa, is part of the serpin family of serine protease inhibitors, along with alpha trypsin, angiotensinogen and antithrombin III. These proteins exhibit strong abilities to inhibit their target proteases, resulting stable one-to-one complexes with the inhibited protein. C1-INH is encoded on chromosome 11 and it is produced primarily by hepatic cells but also by peripheral blood monocytes. Skin fibroblasts also synthesize this protein but their contribution to overall production under physiological conditions is unclear. Cytokines, in particular interferon γ, stimulate C1-INH synthesis in vivo. Interleukin-6 increases C1-INH release from HepG2 liver cells in vivo. This action is enhanced by IL-1 which independently has no impact on C1-INH. The regulation of C1-INH production is not fully known because there are patients that clinically have a positive response to androgen therapy despite having high C1-INH serum levels; it is thought that androgens might play a role in increasing C1-INH synthesis. They block activation of the lectin pathway by binding to MBL (mannose binding lectin) associated with serine proteases (MASP).

The main mediator involved in HAE is bradykinin. C1-INH plays an important role in the complement cascade (C1r, C1s, MASP-1, and MASP-2), coagulation and protease contact systems (plasma kallikrein and activated Hageman factor, coagulation factors XIIa and XIIf, the fibrinolytic protease plasmin and coagulation factor XIa. Finally, C1-INH is responsible for regulating bradykinin production. Thus, traumatic or stressful episodes can activate the contact and complement pathways. Increased bradykinin levels lead to recurrent episodes of angioedema. By binding to its receptor on endothelial cells, bradykinin might amplify vascular permeability causing angioedema. [4,5]

In the complement system, C1-INH inhibits the activated forms of several members of the complement pathways (C1r and C1s) by binding to them. If C1-INH is absent, C1, C2 and C4 are unrestrainedly activated before some others inhibitors, such as C4-binding protein and factors H and I, and can result in cascade blockage. [3]

The complement system encompasses nine components (C1-C9) and two pathways of activation (classical and alternative). C1 is a heterotetrametric trimolecular complex formed by 1 C1q, 2 C1r and 2 C1s connected by calcium molecules. The classical pathway involves the contact of the Fab fragment of immunoglobulin to the target antigen leading to complement activation started by C1q binding to the heavy regions of the Fc fragment. The complexes bind first to C1q and next to C1s resulting in C1r recruitment. Subsequently, C1s is activated gaining esterase activity and cleaves C4 causing the initiation of a cascade that generates a set of complement fragments called the membrane attack complex. The latter causes the destruction of the cell membrane with the lysis of target cells for specific immunoglobulins. C3a, C4a and C5a are produced during this process and cause increased permeability of the capillaries contributing to skin and organ oedema during an HAE attack.

In humans, it is thought that circulating C1 can be reactivated and is present in increased amounts when C1 INH is insufficient or absent. Inhibitors of C1-INH prevent autoactivation of circulating C1 by dissociating the C1q subunit and creating an inactive C1r2-C1s2-(C1-INH)2 complex. This complex cannot divide and neither activate the complement components, C4 and C2, so activated C1 substrates do not activate the classical pathway.

Studies have demonstrated that bradykinin is the mediator responsible for capillary extravasation. Bradykinin is accountable for most of the acute symptoms of HAE because: (1) activated kallikrein in large amounts is present in induced bullae in patients with HAE; (2) prekallikrein and high molecular weight kininogen levels are low during HAE attacks; (3) plasma bradykinin levels are significantly increased in individuals with acute HAE and those with ACE inhibitor treatment-induced angioedema; and (4) bradykinin blood levels were notably elevated in affected-induced compared to non-affected-induced individuals. It has been shown that clinical

 doi:10.20944/preprints202307.0996.v1

exacerbations correlate to high bradykinin blood levels and activation of the kinin system. Bradykinin results from the action of the plasma enzyme kallikrein on the high molecular weight substrate kininogen. It has proinflammatory proprieties and determines neutrophil chemotaxis, capillary dilation with plasma extravasation and relaxation of the smooth muscle and correlates with other forms of angioedema. Without a certain level of C1 inhibitor, bradykinin is generated in excess, promotes inflammation and is responsible for the episodes of cutaneous-mucosal oedema seen in patients with type I and type II AE.

In C1-INH-deficient animals, bradykinin and the receptor antagonist bradykinin prevent capillary extravasation.

Hereditary angioedema type I and type II is caused by mutations in the SERPING1 gene. [6] This gene located on chromosome 11q12-q13.1 provides information on C1 inhibitor protein synthesis that regulates inflammation. C1 inhibitor blocks the activity of certain proinflammatory proteins. It seems that HAE is caused by around 300 different genetic mutations of which 25% occurs spontaneously. Mutations causing hereditary angioedema type I cause low levels of C1 inhibitors while type II mutations cause production of abnormally functioning C1 inhibitors. Low complement levels are also seen tin these types.

Type I AE is caused by gene mutations (mis-direction mutations, deletion or insertion) resulting in the formation of a truncated or misfolded protein. Therefore, a low antigenic and functional plasma level of normal C1-INH protein is seen. Although a normal allele is present, less than 50% (between 5% and 30%) of functional C1-INH is present. That may be due to the fact that levels of normal C1-INH are downregulated and this is supported by low C1-INH mRNA levels in patients with HAE. A possible explanation for the low level of C1-Inhibitor is that C1 inhibitor binds to the protein and causes inactivation and the complex is cleared from circulation. Half the normal level of C1-INH is considered insufficient to prevent angioedema attacks.

The reactive center of C1-INH is responsible for binding and cleaving target molecules. It is located at the Arg444-Thr445 site and between these 2 amino acids an intact peptide it is necessary to function. Some mutations in the C1-INH gene result in Arg 444 substitution of the C1-INH protein and are estimated to account for up to 70% of type II AE. These mutations cause an amino acid shift from arginine to cysteine or histidine at position 444.

The majority of HAE type II is caused by mutations involving the reactive center loop (RCL) except the mutation in the residual amino acid Lys251 that secondary to protein folding affects the functionality. These cause the formation of dysfunctional protein. The gene is defined by high allelic heterogeneity and around 748 mutations have been documented. Therefore, HAE type II is characterized by low levels of functional protein and normal or increased antigenic levels of dysfunctional mutant protein and. C1-INH deficiency permits C1 autoactivation with consumption of C4 and C2.

Type III is called HAE with normal quantitative and functional C1-INH. This type correlates with normal C1 inhibitor and normal complement level and usually begins in adult life. The connection between estrogen and angioedema is unknown and therefore the term "estrogen-dependent HAE" should not be used. It is postulated that estrogen may play a role in upregulating bradykinin production and reducing its degradation by angiotensin-converting enzyme (ACE). Type III of HAE is associated with increased kininogens activity leading to increased bradykinin levels. This type probably is an inherited deficiency of enzymes such as ACE, carboxypeptidase N and α2-macroglobulin or a phenotypic decrease of their function. Another option is the production of a yet unidentified substance that is not influenced by C1-INH and it produces bradykinin by cleaving large amounts of high molecular weight kininogen. Because C1 INH inhibits the activity of kallikrein and of factors XIIa and XII f and C1 INH level is normal in this case, the physiological defect responsible for angioedema is most likely due to decreased kallikrein levels.

Type III of HAE is caused by specific mutations in the F12 gene (missense, deletion and duplication mutations that are transmitted autosomal dominant with incomplete penetrance), in the plasminogen gene (transmitted autosomal dominant), in the angiopoietin 1 gene (transmitted AD), in the kininogen-1 gene (transmitted autosomal dominant) and in heparan sulfate-glucosamine 3

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 July 2023 doi:10.20944/preprints202307.0996.v1

sulfotransferase 6 (HS3ST6). [7] All these mutations in HAE type III appear to affect the kallikrein-kinin and fibrinolytic system pathways at different levels leading to bradykinin-mediated vascular extravasation and angioedema formation through activation of the bradykinin B2 receptor.

3.3. Signs and symptoms

Symptoms of hereditary angioedema typically begin in childhood (50% become symptomatic by age 7 while 66% before age 13) and worsen at puberty. Attacks in childhood are usually mild and rare and most often manifest as abdominal damage. Commonly, untreated patients report an attack every 1-2 weeks and most attacks last 3-4 days. [7,8] The frequency and duration of attacks varies greatly (from weekly attacks to years between attacks) in patients with hereditary angioedema and within the same families. In addition, the frequency of attacks increases after puberty. Patients with normal C1-INH are prone to more facial attacks.

In about 1/3 of those affected, the attack is preceded by an erythematous, flat, non-pruritic rash called erythema marginatum which can be mistaken for urticaria. Erythema marginatum is a non-pruritic form of erythema annulare more commonly associated with rheumatic fever. Lesions may be static or extend through the periphery centrifugally. Erythema marginatum which usually occurs on the trunk in patients with AE type I/II has not been reported in AE type III. In severe forms bullae or blisters may occur.[1]

Attacks are usually preceded by a prodrome with paresthesia in the affected area 1-2 hours earlier than the onset of oedema. Other symptoms reported before the attack is: sudden mood swings, anxiety, sensory changes or exhaustion.

Symptoms of HAE vary from individual to individual and include, in addition to angioedema (occurs in 80-99% of cases): abdominal pain, ascites, facial oedema and intestinal oedema (5-29% of cases).

The characteristic symptom is non-inflammatory cutaneous and mucosal oedema.

Patients often report that the oedema worsens within 12-24 hours with remission within 72 hours. Symptoms may last for up to 5 days and oedema may migrate to other areas. The oedema does not respond to antihistamines. Attacks are recurrent and often the disease-free period is several weeks.

Non-pitting skin oedema is the most common symptom and usually affects the extremities, genital area and the face. Patients first experience a sensation of constriction or paresthesia followed by angioedema that progresses over several hours.

HAE symptoms may recur and worsen. Triggering or aggravating factors can be: injury, intense pain, anxiety, surgery and dental surgery, viral diseases, stress or various physical activities. [9]

In women, menstruation and hormones can influence the symptoms of HAE. Some women report a higher frequency of attacks during menstruation. The literature shows that there is considerable variation in the frequency of attacks in pregnant women. The use of estrogen-derived drugs such as oral contraceptives and hormone replacement drugs is also associated with increased frequency and severity of attacks of HAE. However, often, the trigger factor remains unknown.

Pregnancy has been correlated with increased serum C1-INH levels even in the absence of HAE, so pregnancy does not increase the risk of attacks, but the opposite. This can be explained by the fact that the entire circulating amount of C1-INH increases during pregnancy, however a relative decrease in levels occurs as a consequence of the physiologically significant increase in plasma levels, especially in the last trimester. C1-INH levels are also low in pregnant women with pre-eclampsia and eclampsia and a significant proportion of pregnant women with HAE have premature births.

Angiotensin-converting enzyme inhibitors used to treat hypertension are known to increase the frequency and severity of attacks of HAE and should therefore be avoided.

However, only in about 40% of cases does the patient recognize a trigger.

Symptoms are present in the following areas: subcutaneous tissue (hands, legs, arms, genitalia and buttocks); abdominal organs (stomach, intestine, gallbladder and kidneys), upper respiratory tract (larynx) and tongue. Attacks usually occur in one area but subcutaneous, visceral and laryngeal

 doi:10.20944/preprints202307.0996.v1

involvement is common. The affected area typically becomes sore and painful, not erythematous or pruritic. Cutaneous urticaria is rarely present.

Symptoms associated with edema of the digestive system include: acute abdominal pain and/or other signs of obstruction such as dehydration due to intestinal edema along with nausea and vomiting. [10] They are the dominant symptom in about one quarter of HAE patients with and can occur occasionally in other forms of angioedema. Abdominal pain appears due to mucosal edema of the gastrointestinal tract and may be so intense as to mimic an acute abdomen. Ascites is often present in an abdominal attack associated with angioedema. Either diarrhea or constipation may occur. The attack subsides in 12-24 h. Pharyngeal or laryngeal oedema may cause coughing, dysphagia, dysphonia, stridor and asphyxiation. [11] Studies show that among the families affected by HAE, death due to laryngeal oedema accounts for about 30% of deaths. The risk to have a laryngeal attack in HAE patients is estimated at 70%. A trigger for laryngeal oedema can be local anesthetic for dental procedures but sometimes it can occur spontaneously. It should be noted that about half of patients with HAE have at least one episode of this type. Initially only voice change and swallowing difficulties may occur.

Hand and leg involvement is extremely painful and can interfere with daily activities.

Scrotal and penile oedema are relatively common in men. Similarly, some women show labial oedema. Urinary tract involvement may cause urinary condition of varying intensity. Intense headache, visual impairment (blurred vision, diplopia), ataxia and also painful muscle oedema with unilateral impairment of the hip or shoulder may occur.

Other rare signs reported include pleural symptoms with effusion, seizures and hemiparesis secondary to cerebral edema.

Patients with HAE have a predisposition to develop autoimmune diseases ranging from inflammatory bowel disease to systemic lupus, thyroiditis and although they are mild forms of the disease, they should be considered. Systemic lupus erythematosus affects around 2% of the patients. This association has a female predominance with significant skin lesions. Rarely, Sjogren's syndrome, drug-induced lupus, pernicious anemia, scleroderma and autoimmune aortitis have been associated with the disease.

Patients with HAE may have malaise but are afebrile. The priority is to ensure a clear airway. Patients with severe seizures may develop hypotension due to fluid sequestration in the extracellular space.

3.4. Diagnosis

It is based on a thorough clinical evaluation, family history and blood tests that detect low complement levels. If there are clinical suspicions and recurrent episodes of angioedema of unknown etiology genetic testing is indicated. Patients with HAE usually have normal results of the usual tests. Rarely an increased VSH or eosinophilia may be encountered. In this case another diagnosis should be considered. During attacks, patients may have hemoconcentration or prerenal azotemia reflecting intravascular volume loss. Leukocytes are usually normal although they sometimes increase during abdominal attacks.

There are 3 specific blood tests used to confirm the diagnosis of type I or II of HAE:

1. C1-Quantitative (antigenic) inhibitor
2. C1-Functional inhibitor
3. C4

- In case of HAE with normal C1-Inhibitor level it can be determined if there is a defect of one of the 6 genes that can cause HAE: factor XII (F12), plasminogen (PLG), angiopoietin 1 (ANGPT1), kininogen 1 (KNG1), myoferlin (MYOF) and heparan sulfate (HS)-glucosamine 3-O-sulfotransferase 6 (HS3ST6).
- Deficiencies in C1-INH lead to impairment of the complement cascade with low levels of functional C4, C1 INH and/or C1-INH and are seen at the onset and during an attack. Rarely the C4 level remains normal at the onset of the attack. Angioedema associated with

 doi:10.20944/preprints202307.0996.v1

lymphoproliferative diseases is often associated with low C1q level. In HAE with normal C1-INH, the level is normal at onset and during the attack.

The most accurate and accessible test for HAE is the serum C4 level. [12] It is almost always low at attack and typically decreased frequency episodes. The test should be redone if the suspicion of angioedema is high even if its value is within normal range. Patients with HAE have normal C3 and C1q levels, regardless of disease status.

During attacks, serum CH50 (total hemolytic complement) is characteristically low but when the attack subsides it returns to normal. This dosage is not very useful because deficiency of any complement component causes the CH50 to decrease.

Type I HAE is characterized by:
- Low level of C1-inhibitor esterase
- Low level of C4 and C2
- Normal C1q level

Type II HAE is characterised by:
- Normal or increased level of C1-inhibitor but dysfunctional
- Low level of C4 and C2
- Normal C1q level

Type III HAE is characterized by:
- Normal level of C1-inhibitor esterase
- Normal level of functional C1-INH
- Normal level of C4 and C1q
- Factor XII mutation may be present.

Diagnosis in HAE with normal C1-Inhibitor level is based on the following criteria: (i) history of recurrent angioedema in the absence of urticaria or medication that may cause angioedema, (ii) normal or almost normal level of C4, antigenic and functional C1-INH and (iii) mutation of factor XII that is associated with the disease or positive family history of angioedema and lack of efficacy of high dose antihistamines (cetirizine 40 mg/day or equivalent for at least one month or 3 angioedema attacks)

Imaging studies which can sometimes be useful in the diagnosis of AE:
- Abdominal X-ray: during gastrointestinal angioedema, features of ileus may be present
- Chest X-ray: pleural effusions are uncommon
- Abdominal ultrasound or CT scan: thick bowel wall due to edema, a slurry of fluid around the bowel and free peritoneal fluid in large amounts of may sometimes be seen.[13]

Histologically, angioedema in HAE is identical to that in other forms of angioedema. Characteristically, a perivascular mononuclear infiltrate and dermal oedema are present. These features are also seen in chronic urticaria or other types of angioedema. Reticular, subcutaneous or submucosal dermis show edema but no inflammatory cellular infiltrate is present. Vasodilation may also be seen.

3.5. Differential diagnosis

- Other types of angioedema without urticaria are called acquired angioedema. Acute non-inherited angioedema affects the skin and mucous membranes. It may be a response to an allergen and is treated as urticaria. In some cases, the pathophysiology is similar to HAE. It usually resolves itself in 1-2 days. Triggers can be allergens such as drugs, insect stings, foods (nuts, seafood, eggs). Some people develop anaphylactic reactions which can lead to angioedema of the respiratory tract. There are 2 types of acquired angioedema. Acquired angioedema type I appears in patients suffering from rheumatologic and hematological disorders such as B-cell lymphoproliferative diseases (chronic lymphocytic leukemia, lymphosarcoma, multiple myeloma) or macroglobulinemia and essential cryoglobulinemia. [14] Rarely, lupus anticoagulant, Churg-Strauss vasculitis, erythrocyte sensitization, livedo reticularis, infections (HIV, hepatitis B and C, Echinococcus granulosis virus, and Helicobacter pylori), chronic sinusitis, dental infections have been reported. This happens due to circulating

 doi:10.20944/preprints202307.0996.v1

anti-idiotypic antibodies against immunoglobulins expressed on the surface of B cells. Other acquired oedemas may occur in various surgeries such as mastectomy, malignancies and/or autoimmune diseases. Acquired angioedema can occur at any age but most commonly after the fourth decade while HAE occurs in 90% of cases by the second decade of life. Like acquired AE, acquired anemia has low C1-INH activity and presents with similar clinical features. However, the 2 forms differ. Acquired angioedema is due to (1) an autoantibody that inhibits C1-INH function (monoclonal gammopathy), (2) overuse of normal C1-INH due to numerous antibody-antigen complexes or (3) factors formed by lymphoid tumors that destroy C1-INH activity. Usually, acquired angioedema is associated with decreased levels of C1q while HAE has normal levels of the protein. Though HAE is curable, drugs used for other forms of angioedema are ineffective. When angioedema is not accompanied by urticaria or when cutaneous or laryngeal attacks are unresponsive to common treatment, HAE should be suspected. While the incidence of angioedema caused by ACE inhibitors is less than 1%, in blacks the incidence increases to 2.8-6%. Other factors that increase risk include smoking, older age and female gender while diabetes reduces the risk. It is believed to be due to inhibition of kininase II which cleaves bradykinin and converts angiotensin I to angiotensin II in the renin-aldosterone pathway. Unpredictable episodic angioedema usually occurs in the head and neck, especially in the tongue and oropharynx. Even though the majority of cases appear within the first seven days of treatment with ACE inhibitors, sometimes they occur after years of treatment. This type of angioedema remits on discontinuation of therapy and reappears on re-exposure. ACE inhibitors can also prevent other types of angioedema. Angioedema rarely occurs in angiotensin II receptor antagonists. Occasionally it occurs a few hours after NSAID ingestion. Sometimes rheumatological disease may be considered, usually when the oedema is periarticular and causes limitation of mobility. Other forms of angioedema are episodic angioedema with eosinophilia, pressure or vibration induced angioedema. [14,15]

- Cutis laxa is a group of rare diseases of connective tissue defined by laxity of the skin. Thickening and hyperpigmentation of the affected site may be seen. The disease is diagnosed at birth or early in childhood. The first symptom is commonly facial oedema and may be mistaken for HAE. Cutis laxa progresses and causes changes in the skin and blood vessels.
- Immediate hypersensitivity reactions (IgE mediated)
- Different types of urticaria: cholinergic, chronic spontaneous with angioedema, contact, vasculitis, dermographism, solar, pressure urticaria.
- Drug eruptions
- Other affections such as facial cellulitis, dermatomyositis, cutaneous Crohn's disease and systemic lupus erythematosus.
- Histamine-mediated angioedema - associated with urticaria and pruritus. Trigger factors include viruses, drugs, food; still in the majority of chronic cases an external eliciting agent often autoimmune mediated is responsible. Histamine can be released by mastocytes s via Ig E or non-Ig E hypersensitivity mechanisms such as opioids, contrast agents, vancomycin and physical factors like cold, heat, vibration, pressure, water or sun. Distinction from bradykinin-mediated diseases is made by minimal abdominal symptoms, presence of urticaria, response to antihistamines, rapid onset and remission and sometimes presence of anaphylactic signs and symptoms. [15]

3.6. Prognosis

Although AE is a rare disease, it can have fatal outcome: laryngeal oedema can lead to asphyxia, abdominal attacks causing severe pain may prompt unnecessary surgeries, diagnostic delays, and opioid dependence. HAE attacks affecting the subcutaneous tissues result in disfigurement and disability, decreasing quality of life.

Early-onset HAE patients have a more severe course of the disease in comparison with those with late-onset attacks.

 doi:10.20944/preprints202307.0996.v1

Before the discovery of effective treatment, the mortality rate from HAE was 20-30%. With adequate prophylactic treatment, the prognosis is nowadays very good. An appropriate usage of androgens can lead to decreased side effects on both short and long term.

3.7. Standard treatment

Although this disease is treatable and preventable, its complications are unresponsive to standard treatment for angioedema, so establishing the right diagnosis is crucial. The most accurate screening test for HAE is the serum C4 level.

Treatment of AE is based on 3 pillars: treatment of acute angioedema attacks (on-demand treatment), short-term (preprocedural) prophylaxis, and long-term prophylaxis. [1 Hypotensive patients due to fluid sequestration in the extracellular space may require iv fluids for hemodynamic balancing. Abdominal pain is treated with narcotics. In case of laryngeal oedema tracheostomy or intubation is sometimes required. In HAE type I and II, the preferred treatment in acute attacks is replacement of C1-INHibitor with existing concentrates, kallikrein inhibitor or bradykinin receptor antagonist type 2. If no specific treatment is available, fresh frozen plasma (FFP) can be used, but because plasma can be used as a substrate for bradykinin generation, attacks may worsen before improvement. Give 2 units of PPC to support complement control and prevent the development of angioedema. PPC is not recommended for the treatment of acute attack. [17]

In 2008, the Food and Drug Administration (FDA) approved Cinryze, a C1-INHibitor for the prophylaxis of angioedema attacks in adults and adolescents with AE. This was the first drug approved in the U.S. for HAE. In June 2018, it was also approved in the pediatric population over the age of 6. There are studies that show that Cinryze C1-INH nano filtered concentrate shorten the duration of attacks and reduce their frequency. The nanofiltration process is an additional effort to maximize protection against viral diseases such as Creutzfeldt-Jakob disease. A dose of 1000 units (10 ml) is administered every 3-5 days. It is category C in pregnancy and is also approved for self-administration. Hypersensitivity reactions and thrombotic events have been reported. [18]

In September 2009, the FDA approved Berinert (C1-INH concentrate) for acute abdominal attacks and facial oedema in adults and adolescents with HAE. It is human plasma-derived protein. In January 2012, it was also additionally approved for laryngeal angioedema. In 2016, it became the first and only pediatric treatment for AE. Symptom relief occurs within 30-60 min; it is not approved for long-term prophylaxis. Hypersensitivity reactions, laryngeal edema and thromboembolic events have been reported. However, the most frequently reported adverse event is dysgeusia.[18]

Also in December 2009, the FDA approved Kalbitor (ecallantide) for the treatment of potentially life-threatening acute oedema associated with HAE. During attacks of HAE, irregular plasma kallikrein activity results in the excessive generation of bradykinin which causes oedema. Kalbitor is a *highly specific recombinant plasma* kallikrein inhibitor that is injected subcutaneously into individuals over 12 years of age with HAE. This drug slows C1-INH catabolism rate, therefore C1-INH concentrations are more efficacious. [19]

In 2011, Icatibant (Firazyr) - a selective antagonist of the bradykinin B2 receptor - was approved for acute attacks of HAE in patients over the age of 18. [20]

In 2014, the FDA approved Ruconest, a C1 esterase recombinant inhibitor for the treatment of acute attacks in adult and adolescent patients with HAE. It is a C1 esterase inhibitor purified from genetically modified (transgenic) rabbit milk. It is administered as a 5-minute infusion. [21]

In 2017, the FDA approved Haegarda (C1 inhibitor) administered subcutaneously for the prevention of HAE attacks in adolescents and adult patients, although its efficacy in HAE patients with laryngeal attack has not been established.

In August 2018, the FDA approved lanadelumab (Takhzyro) for the prophylaxis of HAE attacks in patients over 12 years of age. It is a monoclonal antibody that works by binding to plasma kallikrein and decreasing and blocking its activity. It is administered every 2-4 weeks. [22]

In 2020, the FDA approved Orladeyo (berotralstat) for stroke prevention in patients over 12 years of age. Orladeyo is a capsule to be taken once daily. [23]

 doi:10.20944/preprints202307.0996.v1

For prevention of angioedema attacks associated with surgery, dental procedures and other triggers, short-term treatment is recommended prior to procedures.

HAE management involves the treatment of acute attacks and their prevention (prophylaxis). C1-INHibitor concentrates, kallikrein inhibitor and fresh frozen plasma infusion represent therapeutic options for acute attacks of HAE types I and II. Sometimes acute attacks that affect upper respiratory airways require intubation if stridor or any sign of respiratory distress is present. Prophylaxis may include regular C1-INHibitor injections, long-term androgen therapy or antifibrinolytics.

In 2013 the World Allergy Organization (WAO) made the next recommendations on the management of HAE type I and II as shown in Table 1

Table 1. Recommendations on the management of HAE type I and II according to the World Allergy Organization (WAO) made in 2013.

Recommendations on the management of HAE type I and II according to the World Allergy Organization (WAO) made in 2013
• C4, C1 and C1-INH level and C1-INH function should be tested in all patients suspected for type I and II HAE
• Attacks of HAE that (1) cause debilitation/dysfunction and/or (2) affects the face, neck and abdomen might need treatment on demand; upper airway attacks require treatment
• HAE attacks require as early as possible therapy with C1-INH, allantide or icatibant; oral antifibrinolytics are not candidates for treatment on demand.
• Oedema of the upper airway may require intubation or tracheostomy
• Depending on the case the patient will benefit from either adjuvant therapy or specific treatment
• Plasma-derived C1-INH is the choice of on-demand treatment for seizures in children and pregnant and breastfeeding women
• HAE patients should carry an identification card an also treatment for the attack to be carried along
• Patients who require treatment approved for self-administration should be trained in this regard
• An annual assessment by an HAE specialist should be done for all patients

3.8. Prophylaxis

Prophylactic treatment is needed if serious attacks occur more often than once every 3 months. This includes attenuated androgens or C1-INH protein products such as Cinryze. If androgenic therapy is used, the dose should be decreased to minimize the adverse effects of the medication. The most commonly used drug in this class is danazol but all are effective. The usual recommendation is 200mg/day or less but it can be up to 800mg. Stanazole is given 2mg daily or every 2 days but can be increased to 12mg per day and methyltestosterone to 10 to 30mg per day. The most important long-term adverse effect is hypertension. The 17-alpha alkylated androgens (danazol or stanazol) can rarely cause hepatotoxicity and liver tumors. Monitoring is recommended. Adverse effects include: masculinization, alopecia, acne, vasomotor symptoms, decreased breast size, irregular menses, low libido, changes in lipid profile (atherogenesis) and risk for hepatic adenoma, necrosis or cholestasis, hypertension. Therefore, they are not recommended in patients under 16 years of age. Major contraindications include prostate malignancy, pregnancy, infancy and breastfeeding. [24]

Antifibrinolytic agents (plasmin inhibitors) like epsilon aminocaproic acid (1-2g 3 times daily) or tranexamic acid are not as effective as androgens but can still be an option for prophylactic

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 14 July 2023 doi:10.20944/preprints202307.0996.v1

treatment . They are an option for pregnant women and children. Tranexamic acid inhibits the fibrinolytic activity of plasmin. Aminocaproic acid is a derivative of the amino acid lysine that suppresses fibrinolysis by inhibiting plasminogen-activating factors and less by antiplasmin activity. Inhibition time is 1-2h; several days of treatment are required and it can be used po or iv. These agents are recommended when other agents such as anabolic steroids are not tolerated. Side effects include myalgia (with or without increased creatine phosphokinase or aldolase secondary to rhabdomyolysis), fatigue and clotting disorders.

Cytotoxic agents and immunosuppressants (usually cyclophosphamide) and glucocorticoids including or not plasmapheresis are useful in lowering autoantibody synthesis in HAE type II.

Short-term prophylaxis for surgery is needed. C1-INH infusion may be administered one day prior or just before the intervention. Antifibrinolytics and androgens can be used 5 days before surgery and 2-5 days afterwards. Fresh frozen plasma can be administered the day before and the day after the procedure. [25]

The 2013 WAO recommendations on HAE preventive treatment and screening are shown in Table 2.

Table 2. The 2013 WAO recommendations on HAE preventive treatment and screening.

The 2013 WAO recommendations on HAE preventive treatment and screening
• Short term preventive treatment should be given in the case of dentistry and airways intervention.
• Prior to prescribing androgen therapy, there should be an assessment for heart conditions including usual blood test, lipid profile and liver ultrasound.
• During a long-standing preventive treatment with androgens including half year after finishing the course, full blood count, urine examination, liver transaminases, lipid profile and blood pressure every 6 months and liver ultrasound annually should be performed.
• Defer screening of children with HAE type I/II until 12 months of age, all the family members of the affected individual should be screened.
• Hepatitis A and B vaccines should be administered to patients with HAE receiving blood products including plasma-derived C1-INH, influenza vaccine should be administered to all patients with HAE

Treating underlying infections of the HAE attack such as Helicobacter pylori can induce remission. In addition, the patient may have medications such as contraceptives, hormone replacement therapy or ACE inhibitors that can trigger an attack.

Investigational agents - some protease inhibitors have an overlapping function with C1-INH (antithrombin III, beta-macroglobulin and alpha1 antitrypsin) and might serve as a therapeutic means.

4. Conclusions

Hereditary angioedema (HAE) is defined as a genetic condition that occurs rarely but poses a threat to life having low levels of C1-INH inhibitor esterase and involving recurrent attacks of non-pruritic angioedema that do not leave subcutaneous or mucosal wells without the presence of hives. Screening among the family members of affected individuals (even in lack of symptoms) is mandatory, since it is a life-threatening condition. Developing solutions to diagnose and manage this condition has improved the life and treatment results of patients.

References

1. Longhurst HJ, Bork K. Hereditary angioedema: an update on causes, manifestations and treatment. Br J Hosp Med (Lond). 2019 Jul 2;80(7):391-398. doi: 10.12968/hmed.2019.80.7.391. PMID: 31283393.
2. Kesh S, Bernstein JA. Isolated angioedema: A review of classification and update on management. Ann Allergy Asthma Immunol. 2022 Dec;129(6):692-702. doi: 10.1016/j.anai.2022.08.003. Epub 2022 Aug 19. PMID: 35988876.
3. Longhurst HJ, Zanichelli A, Caballero T et al.; IOS Study Group. Comparing acquired angioedema with hereditary angioedema (types I/II): findings from the Icatibant Outcome Survey. **Clin Exp Immunol**. 2017a Apr;188(1):148–153. https://doi.org/10.1111/cei.12910
4. Levi M, Cohn DM. The Role of Complement in Hereditary Angioedema. Transfus Med Rev. 2019 Oct;33(4):243-247. doi: 10.1016/j.tmrv.2019.08.002. Epub 2019 Aug 29. PMID: 31676220.
5. Caccia S, Suffritti C, Cicardi M. Pathophysiology of hereditary angioedema. **Pediatr Allergy Immunol Pulmonol**. 2014 Dec;27(4):159–163. https://doi.org/10.1089/ped.2014.0425
6. Bork K, Wulff K, Steinmüller-Magin L, Braenne I, Staubach-Renz P, Witzke G, Hardt J. Hereditary angioedema with a mutation in the plasminogen gene. **Allergy**. 2018 Feb;73(2):442–450. https://doi.org/10.1111/all.13270
7. Fijen, L.M., Bork, K. & Cohn, D.M. Current and Prospective Targets of Pharmacologic Treatment of Hereditary Angioedema Types 1 and 2. Clinic Rev Allerg Immunol 61, 66–76 (2021). https://doi.org/10.1007/s12016-021-08832-x
8. Bernstein JA. Severity of hereditary angioedema, prevalence, and diagnostic considerations. Am J Manag Care. 2018;24(14 Suppl):S292–8.
9. Sinnathamby ES, Issa PP, Roberts L, Norwood H, Malone K, Vemulapalli H, Ahmadzadeh S, Cornett EM, Shekoohi S, Kaye AD. Hereditary Angioedema: Diagnosis, Clinical Implications, and Pathophysiology. Adv Ther. 2023 Mar;40(3):814-827. doi: 10.1007/s12325-022-02401-0. Epub 2023 Jan 7. PMID: 36609679; PMCID: PMC9988798.
10. Iwanami K, Okano T,Ohara O, et al. Recurrent acute abdomen as the main manifestation of hereditary angioedema. *Intern Med* 2019;58:213–6.doi:10.2169/internalmedicine.1559-18pmid:http://www.ncbi.nlm.nih.gov/pubmed/30146609
11. Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. **J Allergy Clin Immunol**. 2012 Sep;130(3):692–697. https://doi.org/10.1016/j.jaci.2012.05.055
12. Jindal AK, Bishnoi A, Dogra S. Hereditary angioedema: Diagnostic algorithm and current treatment concepts. Indian Dermatol Online J. 2021;12(6):796
13. Wilkerson RG, Moellman JJ. Hereditary Angioedema. Emerg Med Clin North Am. 2022 Feb;40(1):99-118. doi: 10.1016/j.emc.2021.09.002. Epub 2021 Oct 29. PMID: 34782094.
14. Jacobs J, Neeno T. The importance of recognizing and managing a rare form of angioedema: hereditary angioedema due to C1-inhibitor deficiency. Postgrad Med. 2021 Aug;133(6):639-650. doi: 10.1080/00325481.2021.1905364. Epub 2021 Jul 6. PMID: 33993830.
15. Maurer M, Magerl M, Ansotegui I et al.. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. **Allergy**. 2018 Aug;73(8):1575–1596. https://doi.org/10.1111/all.13384
16. Caballero T. Treatment of Hereditary Angioedema. J Investig Allergol Clin Immunol. 2021 Feb;31(1):1-16. doi: 10.18176/jiaci.0653. PMID: 33602658
17. Wentzel N, Panieri A, Ayazi M, Ntshalintshali SD, Pourpak Z, Hawarden D, Potter P, Levin ME, Fazlollahi MR, Peter J. Fresh frozen plasma for on-demand hereditary angioedema treatment in South Africa and Iran. World Allergy Organ J. 2019 Oct 12;12(9):100049. doi: 10.1016/j.waojou.2019.100049. PMID: 31641402; PMCID: PMC6796769.
18. Henry Li, H., Riedl, M. & Kashkin, J. Update on the Use of C1-Esterase Inhibitor Replacement Therapy in the Acute and Prophylactic Treatment of Hereditary Angioedema. Clinic Rev Allerg Immunol 56, 207–218 (2019). https://doi.org/10.1007/s12016-018-8684-1
19. Shire. Kalbitor prescribing information. 2015. http://www.shirecontent.com/PI/PDFs/Kalbitor_USA_ENG.pdf. Accessed August 21, 2017.
20. Farkas H. Icatibant as acute treatment for hereditary angioedema in adults. Expert Rev Clin Pharmacol. 2016;9:779-788.

21. Riedl M. Recombinant human C1 esterase inhibitor in the management of hereditary angioedema. Clin Drug Investig. 2015;35:407-417.
22. Betschel S, Badiou J, Binkley K, Borici-Mazi R, Hebert J, Kanani A et al (2019) The International/Canadian Hereditary Angioedema Guideline. Allergy Asthma Clin Immunol 15:72. https://doi.org/10.1186/s13223-019-0376-8
23. Longhurst H, Moldovan D, Bygum A, Cicardi M, Huissoon A, Aygoren-Pursun E, et al (2019) Oral plasma kallikrein inhibitor BCX7353 is safe and effective as an on-demand treatment of angioedema attacks in hereditary angioedema (HAE) patients: results of the ZENITH-1 Trial. Paper presented at the AAAAI, San Francisco CA. https://ir.biocryst.com/static-files/2b3e13b9-ad24-432c-9ac5-15711d954d88
24. Greve J, Strassen U, Gorczyza M, Dominas N, Frahm UM, Mühlberg H, Wiednig M, Zampeli V, Magerl M. Prophylaxis in hereditary angioedema (HAE) with C1 inhibitor deficiency. J Dtsch Dermatol Ges. 2016 Mar;14(3):266-75. doi: 10.1111/ddg.12856. PMID: 26972189.
25. Frank MM. Hereditary angioedema: short-term prophylaxis for surgery. Allergy Asthma Proc. 2012;33:303-304.