Review Article:

Hereditary Angioedema: A Narrative Review

Rehnuma Nasim[1], Ankur Kumar Jindal[2], Dr. Towhida Noor[3]

1.National Institute of Cancer Research and Hospital, Dhaka
2. Manipal Hospital, Bengaluru, India
3. Matador Diagnostic and Wellness Center

Abstract

Hereditary angioedema (HAE) is mostly undiagnosed in most part of the world specially in developing countries like Bangladesh due to lack of awareness and diagnostic facilities. Swelling of face, eyes, lips, hands, feet, and genitals, abdominal pain, and life-threatening laryngeal oedema are the presenting features. HAE should be suspected in all patients who present with angioedema without wheals and who do not respond to antihistamines and/or steroids. C1 levels, C1-INH levels, and C1-INH function are the initial laboratory investigations for HAE. Management of HAE constitutes the treatment of acute attack and short-term and long-term prophylaxis. Self-administered plasma-derived C1-INH concentrate and recombinant human C1-INH (rhC1-INH), ecallantide, and icatibant is the first line treatment. Fresh frozen plasma, tranexamic acid, and attenuated androgens can be used where first line treatment is not available. Attenuated androgens have been shown to be effective in the prevention of attacks of HAE but cautions should be taken in children and in females. Hence, the treatment needs to be individualized considering the risk-benefit ratio of long-term prophylaxis. An overview of hereditary angioedema, its clinical feature, difference from histamine mediated angioedema, laboratory markers and management outline are summarized in this review.

Key word: Hereditary angioedema, Bradykinin, Histamine, Fresh frozen plasma, Tranexamic acid.

Introduction

Hereditary angioedema (HAE) is a potentially life-threatening genetic disorder. The estimated prevalence of HAE for the global population is 1 in 10,000 to 1 in 50,000.1 The diagnosis of HAE is relatively newer in this subcontinent and no epidemiological data is available. Considering the current population and the global prevalence, it is estimated that more than 3500 patients in Bangladesh and more than 30,000 patients in India with HAE are undiagnosed at present.[1]

Angioedema is defined as a deep-seated, ill-defined, nonpitting swelling of skin or mucosae that lasts much longer (2–3 days) than an average urticarial wheal, which is superficial, well-defined swelling of skin that usually lasts for few hours. Angioedema is not pruritic it can rather be painful whereas urticaria is intensely pruritic.[2] A tendency to involve nongravitational areas and asymmetric distribution differentiates angioedema from other causes of symmetrical gravitational oedema such as congestive heart failure, cirrhosis, and nephrotic syndrome causes symmetrical gravitational edema.[3]

Traditionally angioedema is classified according to the presence or absence of wheals.[4] Wheal associated angioedema is commonly encountered in patients having acute or chronic urticaria or anaphylaxis. Here the chief mediator is mast cell-released histamine, either through immunological pathway or by direct mast cells degranulation.[5]

Angioedema without wheals is a different entity, bradykinin being the most important mediator. Hereditary angioedema (HAE) is the most important

Corresponding author
Rehnuma Nasim, National Institute of Cancer Research and Hospital, Dhaka. Email: rehnuma2009@gmail.com, Mobile no: +880 1711-236561
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entity in this category followed by acquired angioedema (AAE). AAE may have multifactorial etiologies.[6]

Pathogenesis

The pathophysiology of HAE is described as bradykinin-mediated vasodilatation. C1-INH is a regulator of the complement and contact systems. If C1-INH is deficient or defective, as in types I and II HAE, the contact system will be activated, resulting in continuous production of kallikrein. This will lead to the uncontrolled proteolysis of high molecular weight kininogen and production of bradykinin.[7] Bradykinin will increase vascular permeability, causing oedema. Type 3 HAE leads to increased activation of factor XII by activating plasmin.[8]

A mutation in one or both alleles for the gene that encodes C1-INH (SERPING1) may cause HAE. Deletions and missense mutations make up the majority of SERPING1 variants.[9] Type 3 HAE has been shown to result in elevated estrogen levels, which also increases levels of activated factor XII, and has a variety of other mutations that can be seen in this subtype.[9,10,11] In the table 1, different genes associated with HAE has been discussed.

Table 1: Gene Associated with HAE [12,13,14]

HAE type	Affected gene	Gene product
HAE Type 1	SERPING 1	C1-INH (mutations leading to deficiency of protein)
HAE Type 2	SERPING 1	C1-INH (mutations leading to deficiency of protein)
nC1-INH-HAE	F12	Coagulation factor XII
	PLG	Plasminogen
	KNG 1	Kininogen 1
	ANGPT 1	Angiopoitin 1
	HS35T6	Heparan sulfate-glucosamine: O-sulfotransferase 6
	MYOF	Myoferlin

Clinical features and subtypes

Hereditary Angioedema can present with different features and disease-inducing triggers. The usual presentation is acute episodic cutaneous or submucosal angioedema accompanied by abdominal pain.[16] Any case of angioedema in absence of wheals should be considered as HAE. Most episodes are spontaneous in onset, but in a few patients and physical trauma, mental stress, infections, and dental or other surgical procedure may act as a trigger. A typical episode of angioedema in patients with HAE lasts approximately 3–5 days and resolve spontaneously. Cutaneous swellings most frequently involve the limbs followed by face, genitals, and lips. Other sites like eyes, cheeks, hands, feet, genitals, gastrointestinal tract, tongue and larynx may also involve. Oedema is nonpitting and frequently involve nondependent areas of the limbs.[17]

In addition to cutaneous angioedema, the most commonly involved visceral structures are the gastrointestinal tract and respiratory tracts.[18] The cutaneous lesions may be most apparent but the visceral angioedema can be more bothersome to the patient and acts as key feature in diagnosing the disease.

Most patients with HAE are diagnosed before the age of [20]. The disease often remains asymptomatic in young children[20,22].

There is a prodromal phase before the acute attack. It is characterized by tingling, numbness, pain, and formation of faint, erythematous, serpiginous to annular, and most importantly, nonpruritic patches resembling chicken-wire on skin, called as erythema marginatum which are present in approximately 50% of HAE patients. [20,21] These skin lesions bear a striking similarity to erythema marginatum rheumaticum as seen in acute rheumatic fever and may be confused with urticaria as well. By the time patients present to the physicians and dermatologists' prodromal phase may disappear. Presence of prodromal symptoms is also more suggestive of bradykinin-mediated angioedema and should always be asked while evaluating a patient with suspected HAE.[6]

The acute angioedema episodes last between 2 and 5 days in most cases and additionally resolve spontaneously without the need for medical intervention26. This typical disease progression time frame can help exclude patients with chronic, non-episodic symptoms. Knowing the progression and typical disease pattern can also help appropriately diagnose these recurring episodes when combined with other clinical symptoms.[8]

Laryngeal oedema is one of the deadly visceral complications patients with HAE may encounter16. Approximately 50% patients experience episode of laryngeal oedema at least once in their lifetime. Rapidly progressing facial and lip angioedema may involve laryngeal edema.[19]

Angioedema can be divided into two subtypes, mast cell mediated and bradykinin mediated depending on the pathogenesis. Anaphylaxis, allergic reaction, drug induced angioedema is mast cell mediated angioedema. This angioedema is less severe than HAE and should be excluded at very beginning of the diagnosis. Mast cell mediated angioedema persists for less than 24 hours, and

there is no laryngeal or gastrointestinal involvement. Laryngeal oedema in HAE or bradykinin-mediated angioedema causes stridor; on the other hand, bronchospasm or wheezing is a feature of histaminergic-mediated angioedema. Table 2 describes the clinical differences between the two types of angioedema.

Bradykinin mediated angioedema is divided into ACEI induced, HAE, and acquired angioedema (AAE) type I C1-INH deficiency. HAE can be further divided into three subtypes- type 1, type 2, and type 3. All the subtypes of angioedema is briefly described in table 3.

Type 3 or normal-C1-INH-HAE is a rare entity. Clinical presentation of normal-C1-INH-HAE resembles type 1 and type 2 HAE. However, there are a few features that may help differentiate normal-C1-INH-HAE from other types. Relatively later age of onset, higher female predominance, more frequent involvement of face, tongue, and uvula; less frequent attacks overall, less frequent abdominal attacks are some distinguishing features.[23] Patients with angiopoietin gene mutation may have nail fold capillary abnormalities.[24] Haemorrhages and bruising have also been reported in the skin lesions of patients who have normal-C1-INH-HAE. Patients with factor XII gene mutation (most common type of normal-C1-INH-HAE) have marked sensitivity to estrogen and most attacks develop during pregnancy and with use of estrogen-containing oral contraceptives.[25,26]

There is an autosomal dominant mode of inheritance in HAE. However, approximately 25% of patients have a de novo mutation and have no family history.[27] Till date, de novo mutations have not been reported in normal-C1-INH-HAE. Most patients with AAE have onset of disease after the age of 40, whereas most patients with C1-INH-HAE have disease onset around adolescence or early adulthood. When constructing a differential diagnosis, urticaria is an important finding to consider for the exclusion of an HAE diagnosis.[28] Patients presenting with an HAE flare should not have urticaria on physical exam and the lesions present should not indicate an infectious process (warm or painful). [22,28]

In summarization, recurrent episodes of unexplained cutaneous or mucosal angioedema with recurrent abdominal colic or laryngeal swellings in absence of pruritus and urticaria should be think as HAE. A positive family history is important however, in absence of family history diagnosis of HAE cannot be excluded.

Table 2: Clinical differences between mast cell mediator–mediated angioedema and hereditary angioedema [29,30]

Characteristic	Mast cell mediated angioedema	Hereditary angioedema
Onset	Few seconds to a few minutes	Over several hours
Duration	Usually less than 24 hours	2–6 days
Itching/urticaria	Always seen	Not seen
Laryngeal attack	Rare	Common
Abdominal attack	Rare	Common
Prodrome	Never seen	Distinct feature
Family History	Rare	Common

Table 3: Subtypes of angioedema [15]

Disease	Subtype	Pathogenesis	Clinical features
Anaphylaxis	Mast cell mediated	IgE Mediated	Commonly seen. Urticaria/pruritus with preceding exposure to allergens such as insects, food, or drugs with multisystem organ involvement
Allergic reaction	Mast cell mediated	IgE Mediated	Commonly seen. Rapid-onset urticaria/pruritus with preceding exposure to allergens without multisystem organ involvement
Drug-induced	Mast cell mediated	IgE Mediated with increased prostaglandin formation	Commonly seen. Primarily angioedema and bronchoconstriction with preceding exposure to aspirin or Non-Steroidal Anti-Inflammatory Drugs
Angiotensin-converting enzyme inhibitor (ACEI)	Bradykinin mediated	Overproduction or impaired bradykinin degradation	Commonly seen. Acute onset or delayed angioedema with preceding ACEI or Angiotensin II receptor blocker therapy. Higher incidence in African Americans
HAE type 1	Bradykinin mediated	Mutant C1-INH gene on chromosome 11	Rare. Childhood or early adolescent onset with autosomal dominant inheritance. Clinical features of edema, respiratory distress, and abdominal pain
HAE type 2	Bradykinin mediated	Normal C1-INH levels, but dysfunctional	Rare. Childhood or early adolescent onset with autosomal dominant inheritance
HAE type 3	Bradykinin mediated	Typically, estrogen-dependent with normal C1-INH activity also may see several other mutations associated with this type	Rare. Affects women and appears later in life with autosomal dominant inheritance and low penetrance
Acquired type I C1-INH deficiency	Bradykinin mediated	Consumption of C1-INH by immune complexes	Rare. Age>40 years onset. Underlying lymphoreticular disorder with the presentation of angioedema without

Laboratory Investigation

Confirming the diagnosis of HAE in clinically suspected patient, C4, C1-INH protein, C1-INH functional levels are done. Patients with HAE usually have low C4, C1-INH protein, and C1-INH functional levels. Low C1-INH levels occur due to a deficiency without the SERPING1 gene.[28] If an HAE patient presents with a low circulating C1-INH level, they likely have type 1 HAE, whereas a normal circulating C1-INH level indicates type2 HAE. Testing for C4 levels alone is not a good screening test as it has a sensitivity of approximately 80% only. C4 levels are always normal in approximately 20% patients even when carried out at the time of an attack. Repeat test for C1-INH is advised if first test is normal and there is high clinical suspicion.[31]

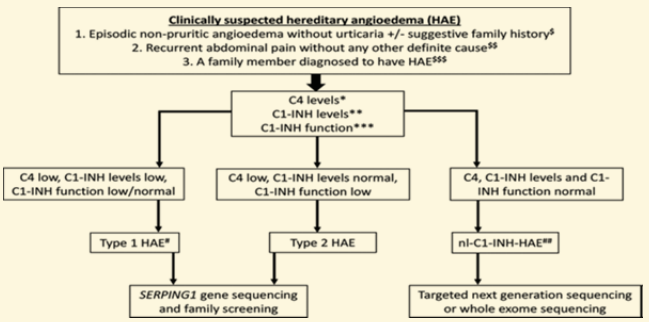

Figure 2: Simplified diagnostic algorithm for patients with clinically suspected HAE. $Family history of HAE may not be present in up to 20% of all patients with HAE. $$Recurrent pain abdomen may occasionally be the only clinical presentation of HAE. $$$Family members should be screened even if they are asymptomatic as late presentations and very mild presentations of HAE are known. *C4 levels are usually assessed using nephelometry, which may be normal in up to 20% of all patients even at the time of an acute attack. **C1-INH levels usually assessed using nephelometry. A repeat test is advised if the initial results are normal and there is high clinical suspicion of HAE. ***C1-INH function usually assessed using enzyme-linked immunosorbent assay (ELISA). Depending on the ease of accessibility, this test may be carried out at the time of initial presentation or after obtaining results of C4/C1-INH levels. Inappropriate storage or transport may affect the results of C1-INH functions. #A clinical possibility of acquired angioedema may be considered in patients with late-onset symptoms (>40 years of age) and if there is no family history. Low C1q levels may be suggestive of acquired angioedema due to the presence of autoantibodies against C1-INH protein (seen in autoimmune diseases). ##At present, there are no biomarkers for diagnosis of nl-C1-INH-HAE.[6]

Screening of family members

It is important to screen family members of a patient who has been diagnosed to have HAE. Sanger sequencing for a known variant in the SERPING1 gene may be a more cost-effective test for family screening as compared to C1-INH levels and C1-INH function.[32]

Management strategy for a patient with HAE

Management of HAE is usually divided into three broad categories:30

1. On-demand therapy (treatment of acute attack)
2. Short-term prophylaxis (STP) (prevention of attacks when they are anticipated)
3. Long-term prophylaxis (LTP) (prevention of attacks in patients with repeated angioedema attacks)

Treatment of acute attack or on demand therapy

In acute attack with out laryngeal oedema resolves within 3 to 5 days requiring no treatment[16]. But if there is laryngeal oedema, immediate treatment with C1-INH is essential to prevent the fatal asphyxiation. Self-administered plasma-derived C1-INH concentrate and recombinant human C1-INH (rhC1-INH), ecallantide, and icatibant is the drug of choice for patients with HAE in most developed countries.[29,33,34] Fresh frozen plasma (FFP) is still the best possible alternative where pd-C1-INH or other drugs are not available or accessible.[35] The recommended dose of FFP is 20 mL/kg[37,42] and contains 1 unit of C1-INH per ml. [36-40] Most patients respond within 1–12 h of administration of FFP[45,46]. Side effects associated with the use of FFP include infusion reactions and anaphylaxis, risk of transmission of viral infections such as hepatitis B, hepatitis C, and human immunodeficiency virus (HIV), and volume overload.41 Even though the guidelines recommend that each attack of HAE should be treated, because of potential side effects associated with use of FFP, its use may be suggested for the treatment of acute life-threatening attacks such as laryngeal oedema.

Short term prophylaxis

Short-term prophylaxis has been shown to reduce or prevent the attacks of angioedema in those at-risk[44-47]. It is indicated in those undergoing trauma or stress e.g., invasive procedures such as major dental work, oral surgery, endotracheal intubation, endoscopies, and anticipated stressful events.[42,43] The risk of development of angioedema remains during the procedure and 48–72hours after. Patients who are already using attenuated androgens may double the dose of drug 2 days prior to the anticipated date of procedure

and should be continued for 5 days after the procedure. If a patient is not taking attenuated androgen, then this may be initiated 2 days prior to the anticipated date of procedure and should be continued for 5 days after the procedure (Dose: stanozolol 2 mg/day). Where C1-INH therapy or Icatibant is easily available and can be used for patients with HAE when they develop angioedema. However, where all first-line treatment options are not available, the fresh frozen plasma can be used for prophylaxis.[47] FFP may be given (dose of 10 ml/kg twice daily) 1–2 days prior to the procedure and single dose on the day of procedure. FFP may be repeated after the procedure on a case-to-case basis (especially important for patients in whom laryngeal manipulation has been carried out).[6]

Long term prophylaxis

Initiating long-term prophylaxis (LTP) depends on the severity and frequency of attacks, impact on quality of life, access to treatment and comorbid conditions.[48] It is considered to start long-term prophylaxis in patients who have at least more than 1 episode of angioedema every month. The recommended doses for LTP with attenuated androgen and tranexamic acid are as follows:[35]

Stanozolol: 0.5 mg every other day up to 4 mg/day

Danazol: 100 mg every other day up to 600 mg/day

Tranexamic Acid: 30–50 mg/kg/day in two to three divided doses with a maximum daily dose of 3 g/day

International guidelines recommend lanadelumab (monoclonal antibody against plasma kallikrein) [300 mg subcutaneously every 2–4 weeks] or oral berotralstat (plasma kallikrein inhibitor) [150 mg once daily] or intravenous pd-C1-INH as first-line therapy for LTP[37].

In countries where the recommended first-line on-demand therapies are not available and FFP not easily accessible to all patients, it is advised to initiate long-term prophylaxis. However, risk v/s benefits of the available treatment options for long-term prophylaxis has to be considered[6].

Emergency card for patients with HAE

An 'Emergency card' that contains relevant information about clinical symptoms of HAE (especially laryngeal attack), emergency contact numbers and treatments (including on-demand therapy and requirement of tracheostomy/cricothyrotomy) must be kept.19Avoidence of ACEi and oestrogens must be maintained.[35]

Conclusion

Non itchy/ non-urticarial episodic swelling of any part of the body must be suspected as HAE. Complement C4, C1-INH are simple and sensitive screening test for patients with HAE. First line therapy plasma-derived C1-INH concentrate and recombinant human C1-INH (rhC1-INH) is not available currently in Bangladesh. Fresh frozen plasma, attenuated androgens, tranexamic acids are the alternative treatment. Patients should be encouraged to carry an emergency card.

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