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Review Article

Therapy of hereditary angioedema: is it time to focus on a different strategic approach? psychosocial issues and stress management

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ABSTRACT

Hereditary angioedema is an autosomal dominant genetic disorder due to the deficiency of CI esterase inhibitor with elevated levels of bradykinin. The disorder was named hereditary angioneurotic edema because of the associated mental stress which exacerbated the condition. It manifests most often as edema of the skin and mucosal surfaces. Laryngeal edema can cause fatal obstruction. The various treatment modalities available for HAE includes plasma derived C1-INH concentrate, ecallantide, icatibant, attenuated androgens and fresh frozen plasma. The drugs for HAE are efficacious, but with side effects and are expensive. Patients with HAE exhibit anxiety and depression, and the stressful state by itself predisposes to further attacks which in the long run forms a vicious cycle one leading on to the other. Considering the fact that HAE is a chronic disorder needing meticulous attention, together with the task of home therapy, availability of medication, adverse effects of drugs, the economic burden and the undue compromise on quality of life, there definitely arises a need for focus on a different strategic approach towards treatment. Currently the focus is on various treatment modalities targeting the complement system and the acute symptomatology of the condition, rather than on the "neurotic component or the stress factor" which might prove to be one major area of therapeutic benefit. Management of stress related factors, overcoming anxiety and depression through psychosocial modalities and simple alternative therapies like yoga as a part of routine activity can greatly reduce the disease, as well as the economic burden and improve the quality of life.

Keywords: Bradykinin, Chronic disorder, CI Inhibitor, Economic burden, New medications, Stress, Quality of life

INTRODUCTION

Hereditary angioedema (HAE) is an autosomal dominant genetic disorder. The disorder was first described by William Osler in 1888. The biochemical basis of the disease was explained much later by Donaldson and Evans in 1963. The disorder was named hereditary angioneurotic edema because of the associated mental stress which exacerbated the condition. Non-pruritic angioedema without urticaria is the hallmark of the condition. HAE is due to the deficiency of C1 Inhibitor [type 1] in about 85% of the patients and to a dysfunctional protein [type 2] in the remainder. A third type of HAE has been described in which C1 Inhibitor [C1-INH] function is normal, and the causal lesion is a mutant form of factor X11 which leads to generation of excessive bradykinin.[1]

C1-INH is a serine protease inhibitor whose target enzymes are C1r and C1s of the complement cascade, factor X11 of the coagulation pathway and the kallekrein system. These pathways are close linked, and their unregulated activation can give rise to vasoactive peptides like bradykinin.[2]

HAE is estimated to affect approximately 1 in 50000 persons, with no ethnic group differences.[3] Offspring's have a 50% chance of inheritance when one parent has

HAE.[4] Mortality secondary to laryngeal edema and asphyxiation has been reported in up to 30% of patients who were previously undiagnosed.[5] The disorder usually presents in the adolescence and has a female preponderance. A large proportion of affected woman report severe symptoms at puberty and while taking estrogen containing oral contraceptives, whereas progesterone-only oral contraceptive agents has been found to produce less severe form of disease.[6] Approximately 40% of people with hereditary angioedema (HAE) experience their first episode before age 5 years, and 75% present before age 15 years.[7]

CLINICAL MANIFESTATION AND DIAGNOSIS

The attacks of HAE may be spontaneous or it can be mediated through various other predisposing factors like minor trauma, surgical, medical or dental procedures, activity related mechanical pressures, emotional stress, drugs like ACE inhibitors, estrogen containing preparations, fatigue, febrile illness, alcohol, helicobacter pylori infection, and menstruation. It manifests after a prodromal phase associated with a tingling sensation involving a single part of the body or multiple areas at the same time. There is swelling of the skin and mucous surfaces typically non-pitting and most often non-pruritic involving areas of the face, upper airway, extremities, trunk, genitalia and the gastrointestinal tract. Episodes are often self-limiting. Involvement of the intestinal wall can cause severe abdominal pain.[8] Edema of the upper airways can result in serious life-threatening obstruction, a medical emergency which can prove to be fatal if appropriate measures are not taken immediately. Laryngeal attacks are associated with a substantial risk of death.[9] It may manifest as dyspnea, hoarseness of voice, dysphagia, stridor and erythema marginatum may precede the occurrence of edema in some patients. In 2% of HAE patients, edema may occur in atypical sites like the brain, urinary bladder, urethra, muscles, joints, kidney and rarely, even pericardial effusion or pleural effusion can occur during an attack.[10]

The diagnosis of HAE is suggested by a positive family history without pruritus and urticaria, presenting with recurrent gastrointestinal attacks of colic and episodes of laryngeal edema. Measurements of serum levels of C4, C1 inhibitor protein, and the C1 inhibitor functional activity are the major laboratory tests used to diagnose HAE. C4 is the single best screening test, however, C4 is not a definitive test because neither the sensitivity nor specificity are absolute.[11]

TREATMENT GOALS

The therapy of HAE is challenging. HAE is a chronic disorder aggravated most often by stress. It needs an individualized approach to care, as it causes a remarkable economic burden to the patient with a significant compromise in terms of quality of life. Thus, an effective treatment strategy would address all areas of concern. World allergy organization guidelines[12] emphasizes an individualized treatment protocol after thorough assessment (Table 1).

Primary prevention

A variety of conditions and events are known to trigger swelling attacks. Identifying and avoiding the predisposing etiological factors and stress management can provide the most effective modality of approach to treatment. Genetic counseling of the patients suffering from HAE, as well as their parents and siblings is mandatory.

Home therapy and self-administration

It has been demonstrated that home therapy decreases the severity of attacks, reduces morbidity and mortality and can improve quality of life. Home therapy can greatly reduce the cost of care as well. Geriatric patients and children are suited for effective home therapy. Advanced age is not a contraindication for home therapy, provided that patients and home therapy partners can safely and effectively administer treatment.[13]Women with HAE contemplating pregnancy should consider home self-administration training.[14,15] All patients should be educated to seek appropriate medical care immediately after self-administration of medication for an acute attack.

Drug treatment of acute episodes

The various measures undertaken for acute management of HAE on conventional basis include adrenaline, corticosteroids, antihistamines, fluids for hypotension with hemodynamic instability, pain management and fresh frozen plasma. Administration of antihistamines, glucocorticoids, or epinephrine have been reported to be of no proven benefit because of the non-histaminergic etiopathogenesis of the condition. Progressive laryngeal obstruction mandates intubation or tracheostomy. Specific treatment of acute attacks include plasma derived C1-INH concentrate, ecallantide and icatibant (Table 2).

Plasma derived C1-INH concentrate

It has been 30 years, since the effectiveness of C1-INH therapy in acute attacks of HAE has been reported**.** The C1-INH is a replacement protein which is purified and concentrated from pooled human plasma. Human plasma–derived concentrate (pd C1-INH Cinryze) was approved in 2008.[16] It is a nano filtered, lyophilized intravenous preparation free of viral and other potential pathogens. Another C1-INH concentrate (Berinert) is a pasteurized, nano filtered, and lyophilized concentrate derived from human plasma for intravenous injection, that received its approval in 2009 for the management of angioedema attacks of the face and abdomen in adult and adolescent patients.[17] In January 2012, Berinert received approval for an additional indication of self-administration and acute attacks of HAE.[18,19]

Table 1: World Allergy Organization recommendations.

S. No.	Description
1.	All patients suspected to have HAE-1/2 (i.e., recurrent angioedema in the absence of a known cause) should be assessed for blood levels of C4, C1-INH protein, and C1- INH function, and these tests, if abnormally low, should be repeated to confirm the diagnosis.
2.	All attacks that result in debilitation/dysfunction and/ or involve the face, the neck, or the abdomen should be considered for on-demand treatment. Treatment of attacks affecting the upper airways is mandatory.
3.	All attacks are treated as early as possible.
4.	HAE attacks are treated with C1-INH, ecallantide, or icatibant.
5.	Intubation or tracheotomy is considered early in progressive upper airway edema.
6	Patients with attacks receive adjuvant therapy when indicated (pain management, intravenous fluids, and supportive care), but specific therapies should be used without delay when indicated.
7.	Oral antifibrinolytics are not to be used as on-demand treatment.
8.	All patients should have on- demand treatment for 2 attacks.
9.	All patients should carry their on-demand treatment at all times.
10.	The administration of short-term prophylaxis should be considered before surgeries, especially dental/intraoral surgery, where endotracheal intubation is required, where upper airway or pharynx is manipulated, and before bronchoscopy or endoscopy.
11.	Before the initiation of long-term prophylaxis with androgens, measurements of complete blood count, urine analysis, liver function tests, lipid profile, assessment of cardiac risk factors, and liver ultrasound should be performed. While using androgens for long-term prophylaxis and for 6 months after stopping therapy, complete blood count, urine analysis, lipid panel, liver function tests, and blood pressure should be monitored every 6 months and an ultrasound of the liver should be done yearly to assess for adverse events associated with androgens and contraindications to androgens.
12.	Screening children for HAE-1/2 should be deferred until the age of 12 months, and all offspring of an affected parent should be tested.
13.	The preferred on-demand therapy for HAE-1/2 attacks in children is pdC1-INH.
14.	During pregnancy and lactation, pdC1-INH is the preferred therapy.
15.	All patients with HAE should have an action plan and product available to treat an attack of HAE.
16.	All patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer.
17.	All patients should be provided with an HAE identification card.
18.	All patients with HAE should have at least 1 annual assessment by an HAE specialist.
19.	Family members of patients with HAE should be screened so that appropriate therapy can be available for treatment, especially because the first event may be of the upper airway and fatal without appropriate therapy.
20.	Hepatitis A and B vaccination should be administered to HAE-1/2 patients receiving blood products, including pdC1-INH. All patients should receive influenza vaccine.

Ecallantide

The kallikrein inhibitor ecallantide is a recombinant protein and a reversible inhibitor of plasma kallikrein which acts by preventing conversion of high molecular weight kininogen to bradykinin. The recommended dose of ecallantide is 30 mg delivered subcutaneously. FDA has extended the approval from 16 years to above 12 years of age and older individuals recently. It belongs to pregnancy category C and use in lactating woman has been cautioned as facts on excretion in breast milk and developing infants are not known. It can cause hypersensitivity reactions.[20]

Icatibant

Icatibant is a bradykinin B2 receptor antagonist for treatment of acute HAE attacks in adults and for subcutaneous self-administration in patients aged 18 years or older. The most common adverse effects reported with the use of icatibant are localized, mild erythema and edema at the injection site, burning sensations and itching.[21]

Prophylactic management

The prophylactic therapy may be directed to short term or procedural prophylaxis and long-term prophylactic therapy for patients with severe, frequent attacks with compromise on quality of life. The drugs used in short term prophylaxis include C1-INH concentrate, attenuated or modified androgens such as danazol and fresh frozen plasma. C1 esterase inhibitor [human] has been approved for routine prophylaxis of HAE attacks above 12 years of age. Solvent/detergent-treated plasma (SD-plasma) can be used if C1-INH concentrate is not available.[22]

Attenuated androgens such as methyl testosterone, danazol

and stanozolol, prevent symptomatic attacks of HAE. Danazol is the commonly used drug. Attenuated or modified androgens have been found to increase the levels of endogenous complement proteins and correct the biochemical defect providing prophylactic protection. The daily recommended dose is 600 mg [200 mg three times a day] for one week before and after planned procedures.[23]

Attenuated androgens are contraindicated during pregnancy, lactation, in children and in patients with prostate cancer. They can produce virilizing side effects in women, menstrual irregularities, hot flashes, edema, weight gain, loss of libido in men, gastrointestinal upset, elevated liver enzymes, hypertension, and increased atherogenesis. Hepatocellular adenomas and hepatocellular carcinoma have been reported in patients taking danazol for 10 or more years.[24] In children, antifibrinolytics have been used as first-line drugs because of the adverse effects of attenuated androgens.[25]

Fresh frozen plasma (FFP), which contains C1-esterase inhibitor, has been used for short term prophylaxis therapy and may help abort most episodes of acute HAE. The other drugs that have been found to be useful in treatment of HAE prophylaxis include the antifibrinolytic agent epsilon aminocaproic acid and tranexamic acid. Epsilon aminocaproic acid has been used for preoperative prophylaxis. It is avoided in patients with thrombotic predisposition and ischemia due to arterial atherosclerosis.

Long-term prophylaxis is considered in all severely symptomatic HAE patients with previous history of acute attacks involving any of the organ systems without regard to the frequency of episodes. Only 2 agents are currently approved for long-term prophylaxis of HAE attacks namely human C1-INH concentrate and the attenuated androgen danazol. None of the current prophylactic modalities are capable of preventing upper airway edema with certainty.[26] Recently a plasma derived concentrate of C1 esterase inhibitor (Haegarda) has been approved for prophylactic therapy in June 2017 that can be used subcutaneously.[27]

OBSTETRICAL AND GYNECOLOGICAL IMPLICATIONS OF HAE

The expert committee guidelines support the use of C1-INH (pdC1-INH) during pregnancy.[28] Vaginal delivery is preferred for patients with HAE. If surgery is mandatory, epidural anesthesia is preferred to avoid intubation procedures. Lactation by itself can precipitate attacks of angioedema and pdC1-INH can be used in women who wish to breastfeed. Menstruation, ovulation and estrogen containing replacement therapy during menopause including phytoestrogens, can predispose to the occurrence of acute events.[29]

Stress and HAE: Is it time to focus on psychosocial and mental health?

The currently available therapy for the treatment of HAE are efficacious, but with their own limitations and side effects and more importantly carries a heavy economic burden as it is a chronic disease entity.

Table 2: Drugs for management of HAE.

Drug class	Drugs	Route	Indication
HAE specific agents	Plasma derived C1-INH concentrate [Cinryze]	iv	Acute attacks Prophylaxis
	Plasma derived C1-INH concentrate [Berinert]	iv	Acute attacks Prophylaxis
	Recombinant human C1-INH [Ruconest]	iv	Acute attacks
	Plasma derived C1-INH [Haegarda]	sc	Prophylaxis
Kallikrein inhibitor	Ecallantide	sc	Acute attacks
Bradykinin B_2 receptor antagonist	Icatibant	sc	Acute attacks
Attenuated androgens	Danazol, stanozolol, oxandrolone	oral	Prophylaxis
Antifibrinolytics	Epsilon aminocaproic acid[a]	oral, iv	
	Tranexamic acid		
Others	Fresh frozen plasma[b]	iv	

iv intravenous, sc subcutaneous, a not routinely recommended, b alternative when other agents are not available

Patients with HAE exhibit an increased tendency for anxiety and depression not only due to the burden of the chronic disease and its intense compromise on quality of life but the stressful state by itself predisposes to further attacks which in the long run forms a vicious cycle one leading on to the other. The associated stress can result in the activation of the immune system which in turn may be a contributing factor responsible for the excessive levels of bradykinin. Chronic stress may itself elicit a prolonged secretion of cortisol, to which white blood cells might produce a counter regulatory response by down regulating their cortisol receptors. This down regulation, in turn, reduces the cells capacity to respond to anti-inflammatory signals and allows cytokine-mediated inflammatory

processes to flourish.[30]

It has been pointed out from several studies that the inflammatory process that is etiologically responsible for HAE may in itself be a risk factor for depression. Yogic practices probably inhibit the activity of the para ventricular nuclei of the hypothalamus, which in turn affects the anterior pituitary gland to produce less ACTH. The decrease in ACTH decreases the synthesis of cortisol from the adrenal glands.[31] More studies focusing on stress related factors, immune response mechanisms associated to HAE attacks and routine yogic practices can provide better insight into much fruitful treatment options for HAE.

CONCLUSION

Considering the fact that HAE is a chronic debilitating disorder needing meticulous attention on part of the health care provider, together with the task of mastering the art of home therapy by the patient himself along with his attending family, the availability of the medication in farfetched and remote areas , the associated adverse effects of the drugs and the heavy economic burden together with reduced quality of life, there definitely arises a need for focus on a different strategic approach towards HAE treatment which can prove to be beneficial. Currently the focus is on various modalities of drug treatment targeting the complement system and acute symptomatology of the condition rather than on the "neurotic component or the stress factor" which might be one major area of therapeutic focus that should be considered seriously. Management of stress related factors, overcoming anxiety and depression through psychosocial modalities and simple alternative therapies like yoga as a part of routine activities can greatly improve day to day wellbeing, bring forth a reduction in the disease as well as the economic burden and may greatly improve the quality of life.

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