

Hereditary Angioedema: A Case Report and Literature Review

Nabeel Mushtaque Ahmed¹, Ashish S. Srivastava², Vinay Pandey³

ABSTRACT

Hereditary angioedema (HAE), also known as Quicke's disease, is an uncommon genetic disease. This is an autosomal dominant condition with a typical presentation of diffuse painless and non-pitting swelling of soft tissue. The disease manifests primarily in the face, airway, extremities, genitalia, abdominal viscera and trunk but swelling can affect any single part of the body or multiple sites. Because many symptoms of HAE overlap with those of other medical conditions, diagnosis may be delayed. It is characterised by either absence or functional deficiency of the C1 esterase inhibitor in plasma. Since it is not an allergic phenomenon, the patients often do not respond to hydrocortisone and adrenaline and this should arouse suspicion. Proper diagnosis and treatment are essential as this condition has the capacity of becoming life threatening due to potential airway embarrassment. Among untreated patients, death from asphyxiation during laryngeal attacks may be as many as 30% of cases. (Many HAE attacks are precipitated by trauma or stress. Symptoms typically worsen over 24 to 36 hours and resolve within 48 hours.) The diagnosis of HAE should be included when assessing patients who display the proper symptomology and family history of the similar condition. In conclusion, diagnosis and management of HAE is required to prevent a potentially fatal outcome.

INTRODUCTION

Hereditary angioedema (HAE) is a debilitating disease characterized by sudden attacks of brawny, non-pitting, and often painful edema(1) Any part of the body can be involved; however extremities, face and intestinal tract are the most common(2). HAE manifestations in the upper respiratory system, specifically involvement of the larynx, may lead to asphyxiation, which is the primary cause of death among HAE patients (3). Among untreated patients, death from asphyxiation during laryngeal attacks has been reported in as many as 30% of cases (4) and the possibility of asphyxiation from a first laryngeal attack is cause for concern. However, awareness of symptoms and effective interventions among physicians, patients, and families will reduce the risk of life-threatening crises.

It is caused either by absolute deficiency or improper function of C1 esterase inhibitor in plasma. Three types of HAE have been described (5, 6) on basis of levels of C1 esterase inhibitor. Type 1 HAE is caused by decreased production or absence of C1 esterase inhibitor (C1-INH). Type 2 HAE is characterized by normal or elevated C1-INH level indicating functional impairment (7). Type 3 HAE has been described in females only and presents as normal function C1-INH levels (8). However, this entity is controversial.

This condition is characterised by recurrent episode of swelling following a trivial trigger such as stress or trauma (9). There are many known HAE episode triggers, including oral surgical procedures such as tooth extraction. Such episodes can lead to laryngeal oedema, a life-threatening situation (3, 10).

Since HAE is not an allergic phenomenon pruritis does not occur concomitant with the swelling (10). Diagnosis can be established by low levels of C1 esterase Inhibitor(11,12). A low level of complement factor C4 is often. This condition usually first manifests in childhood and worsens during puberty affecting both sexes equally(12).As estrogen increases disease severity, women tend to have more severe disease than men. The severity of presenting symptoms varies widely, even among family members. There is also increased likelihood of developing autoimmune disease with age (13).

CASE REPORT

A 22year married female, house wife by occupation presented to JN Medical College Hospital Emergency with complaints of swelling of lips, face, both eye lids, dysphagia, throat tightness and mild respiraroty distress. All the symptoms began 6hours prior to reporting at casualty, following injury to her face over the area below left lower eye lid. The injury was trivial in form of drooping of mobile phone from her sons hand on her face while she was lying down on the bed. The swelling started over the area of trauma and gradually spread all over the face including both eye lids. She had no history of fever, nausea, vomiting, itching, pain abdomen, syncope, dizziness, chest pain or palpitation.

There is no history of any drug intake like OCPs. She had a history of similar but mild multiple attacks in the past (eight to ten times in last 4years) for which went to a local Private Practitioner where she was treated symptomatically and improved after 2-3days. No investigations were done at that time and the symptoms were thought to be due to some allergic condition.

Her vital signs were a blood pressure of 112/74 mm Hg in right arm; Pulse Rate of 114/min, regular; respiratory rate 30 per minute with oxygen saturation of 95% on room air; and Temp of 98.6F. Patient was awake and alert, well oriented to time, place and person but having mild difficulty in Breathing and choking sensation in throat. Her skin was warm and dry without cyanosis, rash or decreased turgor. Her face, eye lids and lips were swollen. Auscultation of lungs revealed bilateral vesicular breath sound without any added sounds. The cardiac examination demonstrated normal heart sounds without any murmurs. Her abdomen was soft and non-tender with normal bowel sounds. Her genital, extremity, and neurological examinations were unremarkable.

She was given symptomatic treatment with injections of diphenhydramine, hydrocortisone, adrenaline, oxygen and other supportive therapy but these measures did not show any significant improvement in her symptoms.

Review of her family history revealed, her father and uncle (father's brother) died of similar episode at the age of 35-40years because of similar and severe attack. No diagnosis was established for the same. Her cousin also had multiple episodes of similar attack and he was also admitted in a hospital for a moderate- severe attack and improved after 3-4days.

The Complete blood counts (CBC), blood chemistry, and urinalysis were all within normal limit except mild iron deficiency anaemia. Erythrocyte sedimentation rate, Absolute eosinophil count and C-reactive protein were normal. Chest radiography revealed no abnormalities. Ultrasound abdomen was within normal limit (no abdominal organ oedema seen).

Given the patient's repeated episodic attacks, strong family history and presence of precipitating event in the form of physical trauma, the possibility of Hereditary Angioedema (HAE) was kept. Patient was admitted in ICU for monitoring and managed conservatively with intravenous fluids, antihistaminic and four units of fresh frozen plasma(FFP). The patient condition improved significantly following FFP transfusion. Considering possibility of HAE blood sample was sent for C4 level (sample taken before FFP transfusion) which was low (<8 mg/dl, normal 10-40 mg/dl) which makes the diagnoses of HAE likely. C1 esterase inhibitor level was also ordered which also came to be low (38mg/L, normal 195-345mg/L) which confirmed the diagnosis of HAE. On the basis of history, physical examination, past history of similar attacks, family history and laboratory investigations, she was diagnosed as a case of Hereditary angioedema (HAE).

Gradually her condition improved and was shifted to critical care ward (CCW). The patient recovered fully and was discharged from the hospital on day5 with no symptoms. The patient and family members were educated regarding avoidance of triggering factors and early reporting to the hospital if the symptoms develop. She was prescribed danazol for prophylaxis, oral Iron therapy for iron deficiency anaemia on discharge and was scheduled for regular follow up.



Fig:1 (At initial presentation)



Fig:2 (After FFP transfusion)



Fig: 3 (At discharge)

DISCUSSION

Hereditary Angioedema (HAE) is a rare genetic disorder and the reported incidence varies from 1:10000 to 1:50000(14). The incidence in India has not been established yet. The diagnosis of hereditary angioedema is important because unlike other forms of mucocutaneous oedema secondary to allergy, HAE does not respond to epinephrine, antihistamines and corticosteroids. There are many known HAE episode inciting factors, including physical injury, medical or dental operations, psychological stress, menstruation, infections or certain medications – a list that includes contraceptive pills and angiotensin-converting enzyme (ACE) inhibitors (10). Face oedema may be limited to the eyelids only or may extended to its entire surface, the lips, oral cavity (tongue and soft palate) or may lead to Life-threatening laryngeal oedema. Life-threatening laryngeal oedema can be an HAE patient's initial presenting HAE symptom, or it may follow face or extremity oedema, or it could appear during every episode in a specific HAE patient.

C1 esterase inhibitor protein regulates the level of C2 and C4 complement (15). However it also affects the kinin generating system by inhibiting kallikrein, and this is the primary basis for occurrence of angioedema in patients with HAE (16). Though diagnosis of HAE is by a detailed history, past medical and family history; determination of C4 level and C1 esterase inhibitor level also aids in the diagnosis of HAE.

These patients do not respond to antihistaminic, corticosteroids or epinephrine as was the case in our patient. The treatment of acute attack is largely supportive and priority is given to securing an adequate airway (17). C1 esterase inhibitor concentrate is available in western countries where it has become the therapy of choice for life threatening attacks (18,19). An intravenous infusion of 500 to 1000 U has an onset of action of 30 minutes to 2 hours and last for 3 to 5 days. If C1 esterase inhibitor concentrate is not available then an infusion of 2 to 4 U of fresh frozen plasma is useful in replacing inhibitor levels (20). Our patient improved after FFP transfusion and the condition resolved over 4-5 days.

Management of HAE is multifactorial and consists of medical management of acute angioedema episodes (acute phase), long-term maintenance/ prophylaxis, avoidance of situations or activities known to incite episodes in the specific patient, prophylaxis prior to dental or medical procedures (short-term prophylaxis). If one excludes C1-INH, fresh frozen plasma (FFP) is used for treatment of acute phase. However, FFP administration has two disadvantages: possible transmission of contagious disease, including hepatitis B, C and HIV infection, amongst others, because it is a biological product; and secondly, anaphylactic shock or resurgence of angioedema due to the fact that FFP consists of supplement factors, including C4 (7,10).

Recent evidence showing that bradykinin is the main mediator of HAE causing vasodilatation and permeability of vessels has led to the development of novel agent which either inhibits bradykinin or blocks its receptors. First agent Ecallantide which is a kallikrein inhibitor and another drug Icatibant which is a bradykinin receptor antagonist have been approved for acute management (21,22). HAE prevention measures include attenuated androgen administration (danazol-stanozolol), and antifibrinolytic factors such as E-aminocaproic acid and tranexamic acid. Corticosteroids and antihistamines administration is not helpful in HAE patients (23).

Prophylaxis is recommended for those patients who experience recurrent attacks of laryngeal edema. The duration of prophylactic treatment usually depends on the severity of disease and toxicities associated with drug therapy (24, 25). It is essential to increase the awareness in addition to the development of treatment options to identify the disease earlier so that the quality of life of these patients can be improved. It is also important to educate the patients regarding avoidance of triggering factors and early reporting to the hospital if the symptoms develop.

REFERENCES

- [1] Frank MM. Hereditary angioedema: the clinical syndrome and its management in the United States [review]. *Immunol Allergy Clin North Am.* 2006;26(4):653-668.
- [2] Pearson KD, Buchignani JS, Shimkin PM, Frank MM. Hereditary angioneurotic edema of the gastrointestinal tract. *Am J Roentgenol Radium Ther Nucl Med.* 1972; 116: 256-261.
- [3] Bork K, Barnstedt SE. Laryngeal edema and death from asphyxiation after tooth extraction in four patients with hereditary angioedema. *J Am Dent Assoc.* 2003 Aug;134(8):1088-94. Review. [Medline: 12956349] [Free Full Text]
- [4] Agostoni A, Aygoren-Pursun E, Binkley KE, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol.* Sep2004;114(3 suppl):S51-S131.
- [5] Khan DA. Hereditary Angioedema: Historical aspects, classification, pathophysiology, clinical presentation and laboratory diagnosis. *Allergy Asthma Proc.* 2011; 32(1): 1-10.
- [6] Frank MM, Gelgand JA, Atkinson JP. Hereditary Angioedema: the clinical syndrome and its management. *Ann Intern Med* 1976; 84: 589-93.
- [7] Maeda S, Miyawaki T, Nomura S, Yagi T, Shimada M. Management of oral surgery in patients with hereditary or acquired angioedemas: review and case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2003 Nov;96(5):540-3. Review. [Medline: 14600687] [doi: 10.1016/j.tripleo.2003.08.005]
- [8] Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet.* 2000 Jul 15;356(9225):213-7. [Medline: 10963200] [doi: 10.1016/S0140-6736(00)02483-1]
- [9] Hereditary Angioedema: the clinical syndrome and its management. *Ann Intern Med* 1976; 84: 589-93.
- [10] Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. *Arch Intern Med.* 2001 Nov 12;161(20):2417-29. Review. [Medline: 11700154]
- [11] Hereditary Angioedema: the clinical syndrome and its management. *Ann Intern Med* 1976; 84: 589-93.
- [12] Zuraw BL. Clinical Practice. Hereditary Angioedema: the clinical syndrome and its management. *N Engl J Med* 2008; 359(10): 1027-36.
- [13] Neilsen EW, Gran JT, Straume B. Hereditary angioedema: New clinical observations and autoimmune screening, complement and kallikrein-kinin analysis. *J Intern Med.* 1996; 239(2): 119-30.
- [14] Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet.* 2000 Jul 15;356(9225):213-7. [Medline: 10963200] [doi: 10.1016/S0140-6736(00)02483-1]
- [15] Ziccardi R. A new role of C1 inhibitor in homeostasis: control of activation of the first component of complement. *J Immunol* 1982; 128: 2505-2508
- [16] Davis AE. Biological effects of C1 inhibitor. *Drug News Prospect.* 2004; 17: 439-446.
- [17] Tsou TJ, Dixon MD, Akinwale B, Nouth H, Hardin E. Unusual presentations of hereditary angioedema and acquired angioedema. *J Emergency Med Acute Primary Care* 2006; 234(14): 891-1047.
- [18] Christiansen SC, Zuraw BL. Update on therapeutic developments of hereditary angioedema. *Allergy Asthma Proc.* 2009; 30(5): 500-5.
- [19] Morgan BP. Hereditary Angioedema-therapies old and new. *N Engl J Med* 2010 5; 363(6): 581-3
- [20] Papamantinos M, Matiakis A, Tsirevelou P, Kolokotronis A, Skoulakis H. Hereditary Angioedema: Three cases report, Members of the same family. *J Oral Maxillofac Res* 2010; 1(1): e9.
- [21] Schneider L, Lumry W, Vegh A, Williams AH, Schmalbach T. Critical role of kallikrein in hereditary angioedema pathogenesis: A clinical trial of ecallantide, a novel kallikrein inhibitor. *J Allergy Clinical Immunol* 2007; 120(2): 416-22.
- [22] L onghurst HJ. Management of acute attacks of hereditary angioedema: potential role of Icatibant. *Vascular health risk manag* 2010; 6: 795-802.
- [23] Socker M, Boyle C, Burke M. Angio-oedema in dentistry: management of two cases using C1 esterase inhibitor. *Dent Update.* 2005 Jul-Aug;32(6):350-2, 354. [Medline: 16117356]
- [24] Bork K, Schneiders V. Danazol induced hepatocellular adenoma in patients with hereditary angioedema. *J Hepatol.* 2002; 36: 707-709.
- [25] Reshef A, Leibovich I, Goren A, Kidon M. Hereditary angioedema: new mechanisms and therapeutic options. *Harefuah* 2009; 148(8): 529-34