Case Report

Study of a Rare Case of Hereditary Angioedema in Bangladesh

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ABSTRACT

Hereditary angioedema (HAE) is a rare disease that is characterised by recurrent episodes of angioedema in the absence of urticaria or pruritus. It usually affects the skin and mucosa of the upper respiratory tract and the gastrointestinal tracts. It is usually a self-limited disease and resolves without treatment in a few days, although fatal asphyxiation may occur due to laryngeal involvement. The rarity, severity of the presentation and the need for appropriate treatment made a special interest to the clinicians for the disease. Early diagnosis can enable the attending physicians to administer an appropriate treatment to rescue the life of a patient. Our case is a 21-year-old medical student presented with recurrent attacks of angioedema involving lips, eyelids, and face for 12 years of age. Lack of appropriate diagnostic facilities made the diagnosis of her disease delayed.

Introduction

HAE is a rare genetic disease with a prevalence between one and nine per 100000, although the data has not been yet established in Indian subcontinent.1 It usually presents with recurrent attacks of oedema of the skin, subcutaneous tissue, mucous membranes, and visceral structures. Severity varies widely even among the same family members. Any organ system can be involved; however, involvement of extremities, face and intestinal tract are common. If the upper respiratory tract is involved, asphyxiation may result, which is the leading cause of death from the disease.2 Glottis oedema involves in 25 to 30% of cases and 13% of their fatalities result from asphyxiation.3,4 Therefore, early diagnosis and prompt treatment are necessary to reduce severe symptoms and minimise fatality.

HAE is not an allergic condition and doesn’t improve with epinephrine, antihistamines, and corticosteroids. The oedema is due to excess production of bradykinin to cause vasodilatation and increased vascular permeability, but the histamine and other mast cell mediators are not involved.5

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This mechanism explains the non-response of HAE to antihistamines and, thus, distinguishes it from histamine-mediated angioedema as seen in allergic reactions and urticaria. It is often misdiagnosed as an autoimmune disease or anaphylactic reaction. However, an association of HAE has been found with autoimmune diseases such as thyroiditis, SLE, Sjögren’s syndrome.6

Table 1: Classification of angioedema7

<table>
<thead>
<tr>
<th>Genetics</th>
<th>Disease</th>
<th>Pathogenesis</th>
<th>Prevalence</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mast cell mediated</td>
<td>Anaphylaxis</td>
<td>IgE-mediated</td>
<td>Common</td>
<td>Urticaria/pruritus; exposure to allergens (food, insects, drugs, etc); multisystem organ involvement</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>IgE-mediated</td>
<td>Common</td>
<td>Preceded by exposure to allergen; rapid onset of symptoms</td>
<td></td>
</tr>
<tr>
<td>Drug induced</td>
<td>IgE-mediated, enhanced prostaglandin synthesis</td>
<td>Common</td>
<td>Exposure to aspirin or NSAIDs; angioedema and bronchoconstriction; selective COX2 inhibitors okay</td>
<td></td>
</tr>
<tr>
<td>Bradykinin mediated</td>
<td>ACEI</td>
<td>Accumulation of bradykinin due to overproduction or impaired degradation</td>
<td>Common</td>
<td>ACEI (or ARS) therapy; higher incidence in African Americans; acute or delayed onset of symptoms</td>
</tr>
<tr>
<td>HAE type I (deficient C1-INH)</td>
<td>Mutant C1-INH gene on chromosome 11</td>
<td>Rare</td>
<td>Childhood/early adolescence onset; autosomal dominant; oedema, respiratory distress and abdominal pain</td>
<td></td>
</tr>
<tr>
<td>HAE type II (dysfunctional C1-INH)</td>
<td>Normal level C1-INH but dysfunctional</td>
<td>Rare</td>
<td>Childhood/early adolescence onset; autosomal dominant; oedema, respiratory distress and abdominal pain</td>
<td></td>
</tr>
<tr>
<td>HAE Type III (normal C1-INH)</td>
<td>Mutation in gene encoding coagulation factor XII</td>
<td>Rare</td>
<td>Autosomal dominant with low penetrance; primarily affects women (estrogen effect); symptoms later in life; face and tongue swelling</td>
<td></td>
</tr>
<tr>
<td>Acquired C1-INH deficiency type I</td>
<td></td>
<td></td>
<td></td>
<td>Age &gt;40 years; angioedema without urticaria; prodrome of erythema marginatum; underlying lymphoreticular disorders</td>
</tr>
</tbody>
</table>

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; HAE: Hereditary angioedema; C1-INH: C1-esterase inhibitor; NSAIDs: Non-steroidal anti-inflammatory drugs; COX: Cyclooxygenase; LPD: lymphoproliferative disorder

The most common form of HAE arises from deficiency or malfunction of C1 esterase inhibitor (C1-INH). However, there are other forms of HAE (Table I) in which C1-INH is normal. There may either be an absolute deficiency or abnormal function of C1-INH. Diagnosis of type 1 HAE is done by establishing low levels of C1-INH. Management of HAE is multifactorial, which includes patient education, avoiding inciting factors, management of acute attacks and prophylaxis.

Case history:

Our case is a 21-year-old female 5th year medical student of Rangpur Medical College. In June 2021, she got herself admitted through emergency department to medicine indoor. She came in with swelling and redness of her face (Figure 1) involving lips, nose, face, eye lids and forehead. She denied itching, pain, dyspnoea, cough, or gastrointestinal symptoms. She started suddenly over minutes to hours. On physical examination her vital parameters including pulse, BP, temperature, and respiration were normal. Apart from nervousness she was comfortable at rest without respiratory difficulty which excluded upper respiratory involvement. We regularly assessed her airway while inpatient to see any sign of laryngeal oedema. Initial treatment was given with intravenous steroid, antihistamine, but showed no immediate symptomatic improvement. Over the next couple of days with conservative management, her symptoms improved gradually (Figure 2). She stated that the disease manifested for the first time while she was studying in class six (age 12). She only experienced cutaneous attacks. Initially it was once or twice a year, but then the frequency had increased to several times a year. Before her presentation to us, she had developed similar skin manifestations involving hands and forearms that resolved in a few days without any treatment. Previous attacks were more or less similar compared to the last one. She denied history of oral ulceration, malar rash,
photophobia, arthritis, erythema nodosum or asthma. She was not aware of any particular cosmetic agent or food, or irritants related to the symptoms. She has no siblings, and her mother had history of seasonal conjunctivitis.

Above findings helped us decide to expand the search with the following tests:

Complement C4: 25.3 mg/dL (reference values: 10-40 mg/dL)

Complement C1q: 16.9 U/mL (reference values: ≥10 U/mL)

C1 INH: 164 mg/L (reference values: 195-345 mg/L).

Finally, the clinical information and laboratory findings (normal C1q level and low C1-INH) confirmed the diagnosis of HAE type I. After establishing the diagnosis, education regarding the characteristics and treatment of the disease was done along with the patient and family. Importance was given to identify and avoiding possible triggers such as trauma to face or respiratory tract, medications like ACE inhibitors etc. As our patient never had episode involving respiratory system, particularly laryngeal attack, and neither recombinant nor plasma derived C1-INH is available in our healthcare practice, and as our patient is in clinical remission, our priority was to prevent further attacks. We advised a three monthly follow up for her if she is in remission. The prognosis of HAE is variable. Once attacks have begun, they generally tend to continue throughout the patient's life.

For prevention of future attacks our plan is to start her on attenuated androgen - Danazol, and tranexamic acid. Regarding future plan, our advice was to administer fresh frozen plasma in case of emergency involving upper respiratory tract or severe gastrointestinal system involvement. If possible, we also advised to avail first line therapies like C1-INH concentrate.

Discussion:

A hereditary basis and autosomal dominant inheritance of angioedema or angioneurotic oedema was established in 1917 and its genetic nature with
a deficiency of the serum C1-INH was established in 1963. A C1 inhibitor (C1-INH) is an acute-phase reactant and is a member of the ‘serpin’ superfamily of serine protease inhibitors. Other proteins in this family are anti-thrombin III, α2-antiplasmin, and α1-antitrypsin. C1-INH downregulates steps in both classical and lectin complement pathways, as well as intrinsic coagulation, fibrinolytic, and kinin-generating pathways. Within these different pathways, C1-INH inhibits several plasma proteases e.g., C1r and C1s, mannose-binding lectin-associated serine proteases, factor XII, factor XI, kallikrein, and plasmin. The role of C1-INH in the kinin-generating pathway is related to the pathogenesis of HAE (Figure 3). In a state of decreased level or malfunctioned C1-INH in plasma, the kallikrein and the kinin-generating system become overactive which is the primary basis of angioedema. HAE is of three types based on C1-INH level. Type 1 HAE is the most common type and is evidenced by absent or low level of C1-INH. Type 2 HAE is less common than Type 1 and is evidenced by the dysfunctional C1-INH. In type 3 HAE the C1-INH level is usually normal, and it is rare and affects only females. However, this entity is controversial.

HAE usually presents by recurrent episodes of brownish, non-pitting, and sometimes painful oedema. Both sexes are equally affected. Usually starts in childhood and worsens during puberty.
Women tend to have more severe disease than men as oestrogen has a role to enhance the severity. There is also increased likelihood of association of autoimmune diseases. HAE is precipitated by numerous factors including physical injury, medical conditions, dental interventions, psychosocial stress, menstrual period, infections or medications such as oral contraceptive pills, and ACEi. Any part of the body can be involved but the commonly involved organs are extremities, oropharynx, larynx, face, intestinal tract, and genito-urinary tract. Death from asphyxiation due to laryngeal attacks is the leading cause of death in this disease and has been reported as many as 30% of the untreated patients. Pruritus does not occur in HAE as it is not an allergic condition, and therefore, it does not respond to epinephrine, antihistamines, and corticosteroids.

Clinicians in emergency department may not be familiar with the disease because of its rare prevalence. Therefore, high suspicion is necessary to diagnose HAE in someone who presents with recurrent attacks of angioedema, non-anaphylactic laryngeal oedema, and repeated episodes of self-limited abdominal pain. Serum complements levels help in diagnosis as follows:

- Low C1-INH level,
- C1q level usually normal, low level suggest acquired angioedema,
- C1-INH functional assessment,
- HAE type III- normal or high C1 level,
- Low levels of C4 may be associated with HAE.

The diagnostic flowchart of angioedema can be depicted as in the Figure 4.

The patients may benefit from a wallet card with details of previous attacks and treatments. The first-line therapies for HAE include the following:

- pdC1-INH: Human plasma-derived C1 inhibitor concentrate,
- rhC1-INH: Recombinant human C1 inhibitor,
- Icatibant: bradykinin B2-receptor antagonist,
- Ecallantide: kallikrein inhibitor.

As laryngeal swelling progress rapidly and can result in fatal asphyxiation, immediate airway
assessment is necessary. Features include dyspnoea, increased respiratory rate, stridor and low saturation. Prodromal symptoms include fatigue, nausea or other gastrointestinal symptoms, myalgias and flu-like symptoms.

Mental or physical stress and dental procedures are the most common triggers or exacerbating factors. Other triggers include infection (e.g. viral respiratory infection), certain drugs such as tamoxifen and hormonal changes in women.

Intubation may be needed in patients with stridor or respiratory distress, because first-line therapies even take approximately 30 minutes or more to start action. If possible expert airway management is necessary.

Where first-line agents are not available which is true for our setting, the type and severity will guide the approach to treatment:

- For patients who has laryngeal oedema or gastrointestinal attacks, solvent-detergent-treated plasma or, if not available, fresh frozen plasma.
- For patients who has mild gastrointestinal symptoms, rehydration and other supportive therapy.
- Treatment with a first-line therapy is commended for those with severe gastrointestinal symptoms or severe cutaneous manifestations that would likely result in dysfunction or lost days from school or work. The choice of agent is based on availability and severity of disease.
- No treatment is necessary for patients with cutaneous attacks not involving skin adjacent to the airway.

After an acute attack, it is necessary to review the risk factors which might have precipitated it. It is of great significance to find out specific precipitants or triggers to prevent future attacks. The clinician should review the care plan whether the patient was able to access care quickly.

The three groups of agents are used for long-term prophylaxis; these are attenuated androgens, antifibrinolytics, and regularly injected pdC1-INH or rhC1-INH concentrate. Attenuated androgens and C1-INH concentrate are both highly effective. However, androgens cause adverse effects in some patients, and C1-INH concentrate is expensive. Synthetic 17-alpha-alkylated androgens include danazol, oxandrolone, stanozolol, oxymetholone, methyltestosterone and tibolone. Since differences among drugs are not well-characterised, the choice of androgen is based largely on availability and the adverse effects. Danazol is widely available throughout the world. Oxandrolone and tibolone may be less virilizing than other agents. A double-blind controlled study of nine subjects showed that high dose androgen therapy (danazol 600 mg) reduces the risk of at least one attack in a one-month treatment period from 94 to 2 percent and the recurrence rates from monthly to 1 in every 10 months. Other studies also concluded that androgens were effective for prevention of attacks. Most HAE patients are well controlled with doses of danazol ranging from 50 to 200 mg daily or every alternate day. There are two ways of administering androgens for long-term prophylaxis: starting with a low dose and gradually increasing or starting with a high dose and then tapering. Antifibrinolytics are inexpensive and usually well-tolerated but significantly less effective than androgens or C1-INH. Corticosteroids, antihistamines, and epinephrine are not helpful in HAE. Methyltestosterone is another alternative. In Bangladesh there was no previous case report on HAE. However, there is a case report in India where a 22 year female presented with facial swelling predominantly periorbital area, throat tightness, and breathlessness. Symptoms started hours after she sustained minor trauma below her left eye by a mobile phone.

**Conclusion:**

HAE is a rare disease but can be fatal if diagnosis is delayed. There are possibilities of late diagnosis or erroneous diagnosis as the clinical picture can
mimic other pathologies. Our patient had experienced recurrent episodes which was initially misdiagnosed as urticaria or anaphylaxis at the emergency department. So, it is important to review details of past attacks and if suspected; determine serum complement levels.

**Declaration of patient consent:**

The patient has given her consent in appropriate consent forms for her images and other clinical information to be shared in the journal. Due efforts were made to conceal her identity, but anonymity cannot be guaranteed.

**References:**


