

Case Report

Usefulness of C1 Esterase Inhibitor Protein Concentrate in the Management of Hereditary Angioedema of Oropharyngeal Tissue

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ABSTRACT Hereditary angioedema is an autosomal-dominant disorder caused by mutation of the gene encoding the C1 esterase inhibitor (C1-INH). It manifests as painless, nonpruritic, nonpitting episodic swelling of the subcutaneous tissues, gastrointestinal, and upper respiratory tracts in the absence of urticaria. An attack typically takes 24 h to peak and resolves over 48–72 h. The most serious manifestation is a laryngeal attack associated with upper airway swelling. The aim of this case report is to describe the lifesaving use of a novel C1-INH protein concentrate in a patient with mild-to-moderate dyspnea caused by swelling of the upper airway (larynx) and tongue.

KEYWORDS: C1 esterase inhibitor protein, hereditary angioedema, laryngeal edema, oropharyngeal swelling

INTRODUCTION

Hereditary angioedema (HAE), also termed Quincke's edema, is an inherited disease caused by a deficiency in or dysfunction of the C1 esterase inhibitor (C1-INH) protein. It manifests as abdominal pain attributable to visceral swelling of the gastrointestinal tract, cutaneous angioedema, and/or oropharyngeal swelling without urticaria.^[1] The visceral swelling may cause abdominal pain, vomiting, and hypotension. Cutaneous angioedema presents as nonpitting nonpruritic swelling of the skin, usually affecting the face, limbs, and/or genitals. Swelling usually develops gradually over 24 h and may persist for ≥ 3 –4 days. Oropharyngeal swelling (including laryngeal swelling) is a much less frequent manifestation (<1% of all acute attacks).^[1-3] Laryngeal edema is a rare but potentially fatal manifestation of HAE, and death from asphyxiation may be the ultimate outcome. The mortality rate associated with this condition was 30% before the development of specific medications used to counter acute HAE attacks.^[1,4] Antihistamines, epinephrine, and corticosteroids have been used in the management of HAE, but the outcomes are unsatisfactory. Therefore, there is a need to consider using C1-INH protein concentrate to treat these

patients.^[4] Thus, we report a case of HAE involving the oral cavity and oropharynx that was successfully treated with C1-INH protein concentrate.

CASE REPORT

A 48-year-old female presented to our emergency department (ED) with oropharyngeal and facial swelling lasting 2 h. The patient was conscious but extremely anxious on physical examination. The patient's blood pressure was 100/60 mmHg, pulse rate was 98 beats/min, body temperature was 36.8° C, respiratory rate was 20 breaths/min, and oxygen saturation by pulse oximetry was 94% while breathing room air. Examination of the upper airway, including the oropharynx, revealed severe edema of the upper lip, uvula, and tongue [Figure 1]. Indirect laryngoscopy showed an inconspicuous laryngeal swelling. She complained of tightness in the throat. On admission, she did not exhibit shortness of breath or any difficulty breathing, suffering only from dysphagia. There was no history of trauma, food allergy, or any similar

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Figure 1: Direct visualization of the upper airway revealed edema of the upper lip and swelling of the soft palate, including the uvula and tongue



Figure 2: (a) the oropharyngeal and (b) facial swelling gradually resolved within 60 min after intravenous administration of C1 esterase inhibitor protein

complaint in any family member. She had not taken any drug such as an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor antagonist. Auscultation of the chest followed by abdominal palpation was normal.

We administered immediate intramuscular epinephrine, intravenous (IV) fluids, and IV antihistamines and steroids. However, no clinical response was achieved, and the edema did not become reduced in size. She experienced mild-to-moderate dyspnea approximately 2 h after admission. We then administered 1000 U of human C1-INH protein concentrate (reconstituted in 10 mL of saline) IV at a rate of 1 mL/min over 10 min. The clinical manifestations, including the oropharyngeal and facial swelling, rapidly improved, resolving completely within 60 min of administration of novel C1-INH protein concentrate [Figure 2]. Measurement of the complement C4 and C1q levels and of the C1-INH before the administration of C1-INH protein concentrate yielded the following: C4 12.7 mg/dL (normal: 16–38 mg/dL);

C1q 17.5 mg/dL (normal: 12–22 mg/dL), and C1-INH 14.3 mg/dL (normal: 18–32 mg/dL), respectively. The final diagnosis was HAE Type I caused by a deficiency of C1-INH protein. The patient was followed up in the ED, and the edema did not recur.

DISCUSSION

This case demonstrates the importance of early treatment with C1-INH protein concentrate to counter a life-threatening laryngeal HAE attack associated with upper airway swelling caused by an inherited C1-INH deficiency. Angioedema (a synonym of angioneurotic edema) is mediated by various pathophysiological pathways, including those involving histamine and bradykinin. The most common pathophysiology is mediated by histamine; however, less common bradykinin-mediated pathophysiology is also known.^[5,6] Bradykinin-mediated angioedema may be caused by hereditary defects in C1-INH protein production, may be a side effect of ACEis, or may reflect an acquired C1-INH protein deficiency.^[5,7] Bradykinin-mediated angioedema associated with ACEi use was unlikely in the present case, as the patient was not taking an ACEi or an angiotensin II receptor antagonist. Thus, we ruled out ACEi-induced angioedema.

Three distinct forms of HAE have been described: Types 1, 2, and 3, caused by a deficiency in or dysfunction of the C1-INH protein. Type I HAE is defined by a low plasma concentration of functional C1-INH, low C4 level, and normal C1q level; it occurs in 80%–85% of all HAE patients. Type II HAE is characterized by the presence of a normal or elevated concentration of functionally impaired C1-INH protein, low C4 level, and normal C1q level. Type III HAE has recently been identified as an estrogen-dependent inherited form of the condition, occurring principally in females with normal levels of functional C1-INH protein.^[1,6,8]

Inherited C1-INH deficiency or dysfunction is rare, accounting for only 5% of all cases of angioedema in which urticaria is absent and for only 1% of all cases of angioedema.^[3] Diagnosis of the specific type of angioedema is essential in terms of appropriate treatment.^[9] Acquired angioedema and HAE may be distinguished by the levels of complement components. Acquired angioedema is characterized by a low plasma C1-INH protein level, low plasma C4 level, and reduced plasma C1q level; these parameters aid in diagnosis when a relevant family history is absent, as in the present case.^[4,7] The majority of patients with angioedema due to acquired C1-INH deficiency have reduced plasma C1q whereas C1q levels are generally normal in HAE.^[10] The low C1-INH level combined with the low C4 and normal

C1q levels suggested that an inherited C1-INH protein deficiency was in play, consistent with our diagnosis of Type I HAE.

Bradykinin- and histamine-mediated angioedema require different treatments. Antihistamines, epinephrine, and corticosteroids are ineffective in patients experiencing bradykinin-mediated edematous HAE episodes.^[6,8] A human nanofiltered C1-INH protein concentrate, Cinryze® (ViroPharma Inc., Exton, PA, USA), administered IV (1000 U/dose), is the only product that both prevents and manages acute HAE attacks (abdominal, facial [tongue and oropharynx], or laryngeal) in adults. The concentrate inhibits the actions of factor XII and kallikrein, thus reducing bradykinin production.^[11]

CONCLUSION

HAE is a rare but potentially life-threatening disorder, and asphyxiation may be the ultimate outcome if a laryngeal attack is associated with upper airway swelling. Early diagnosis and prompt treatment are essential. HAE should be suspected when a patient presents with angioedema without urticaria and does not respond to antihistamines, corticosteroids, or epinephrine. IV administration of 1000 U of the C1-INH protein concentrate is effective and safe during the management of acute HAE attacks, particularly laryngeal attacks, in ED patients. We recommend that hospital EDs routinely stock this agent.

Consent

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand her name and initial will not be published and due efforts

will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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