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Hereditary Angio-Oedema – A rare case report & review of management methodologies

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Abstract : *Hereditary angio-oedema (HAE) is a rare genetic condition causing episodes of swellings of the extremities including laryngeal oedema which may be life threatening. Episodes can be unpredictable, or triggered by factors such as trauma, drugs or dental treatment. HAE many times remains undiagnosed. Dental procedures, sickness, and surgery may trigger HAE attacks. There have been no known cases of HAE that have undergone dental surgical procedures reported in the Indian literature. We are presenting herewith a case who reported to our department with a positive history of HAE for whom surgical removal of an impacted third molar was carried out.*

Keywords: *Complement Component 1 Inhibitor Deficiency, Hereditary angio-oedema, laryngeal oedema*

I. Introduction

Hereditary Angioedema caused by C1-esterase inhibitor deficiency is an autosomal-dominant disease resulting from a mutation in the C1-inhibitor gene[1,2]. HAE is a disorder characterized by recurrent episodes of severe swelling (angioedema). The most common areas of the body to develop swelling are the limbs, face, intestinal tract, and airway[3]. Minor trauma or stress may trigger an attack, but swelling often occurs without a known trigger. Swelling in the airway can restrict breathing and lead to life-threatening obstruction of the airway. About one-third of people with this condition develop a non-itchy rash called erythema marginatum during an attack. This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Data regarding the epidemiology of angioedema is limited. Mortality rates are estimated at 15–33%, resulting primarily from laryngeal edema and asphyxiation. The incidence is approximately 1 in 50-100,000 with no ethnic variation. No sex or race predominance has been described[4,5].

II. Case History

A 30 year-old male patient (Figure 1) reported to department of Oral and Maxillofacial Surgery with chief complaint of pain in lower right third molar region. On intra oral examination pericoronitis in relation to the lower right third molar was noted. OPG (Figure 2) revealed an impacted right third molar. The patient revealed history of unexplained swellings over his extremities even with minor mosquito bites. Investigations of C1NH, serum complement C4 and C3 levels showed L1, <3.4mg/dl and 104.3mg/dl respectively. The patient insisted on having his third molar removed. He was informed of the possible risks involved and an appropriate consent was taken. Preoperative fresh frozen plasma was administered. The patient was taken up for the procedure under sedation with midazolam under lignocaine local anaesthesia without epinephrine General anaesthesia was avoided keeping into consideration the risk of intubation induced laryngeal oedema. Surgical removal of the tooth was carried out using a standard procedure (Figure 3). The patient was kept under observation postoperatively for five days and there were no signs of any life threatening oedema (figure 4 & 5).

III. Discussion

HAE accounts for only a small fraction of all cases of angioedema. Correct diagnosis of HAE is important to avoid potentially fatal consequences such as upper airway obstruction and unnecessary abdominal surgery.

The cardinal symptoms of HAE include[7,8] a positive family history, recurrent episodes of non-urticarial swelling lasting more than 24 hours and unresponsive to antihistamines, laryngeal oedema and recurrent unexplained abdominal pain and vomiting.

Often there is a family history, but new mutations also occur. Edema typically progresses slowly, peaks over the first 24 to 36 hours, and usually resolves within 72 hours, but can persist for as long as 1 week Attacks affecting the upper airways, however, can lead to obstruction and suffocation, and the manifestations of gastrointestinal edema can include intractable abdominal pain, vomiting, nausea, diarrhoea, and intestinal obstruction, and potentially can lead to hypovolemic shock[10,11].

Laryngeal edema presents the greatest risk to patients, and approximately 50% of patients with HAE have at least one laryngeal attack in their lifetime. In the past, fatality from asphyxiation during a laryngeal attack was reported in approximately 30% of patients with HAE[12]. The oedema is circumscribed and non-pitting. There is no urticaria or itching. The basic pathophysiology seems to be that the oedema is triggered by increased permeability of the blood vessels to bradykinin. The net result is episodes of massive local oedema, where the swelling is subcutaneous or submucosal rather than epidermal, so urticaria is absent. This is an important differentiating feature of HAE when compared with allergic reactions, which are primarily mediated by histamine. Mutations that cause hereditary angioedema type I lead to reduced levels of C1 inhibitor in the blood, while mutations that cause type II result in the production of a C1 inhibitor that functions abnormally. Without proper levels of functional C1 inhibitor, excessive amounts of protein fragments i.e. bradykinin are generated.

Several treatments have been published for acute attack in patients with suspected or confirmed diagnosis of HAE. Treatment is divided into 3 categories: acute prophylaxis before triggers and procedures; acute treatment for attacks; long-term suppression[13,14,15]. Short-term prophylaxis and treatment of acute attacks apply to any HAE patient. Individuals who are eligible for long-term prophylaxis should be carefully selected[15]. Resolution of acute angioedema episodes can be obtained by increasing C1-inh levels in the serum. This can be administered to the patient in two different ways, as a plasma concentrate or as an intravenous infusion with FFP[16]. Intravenous administration of C1-INH concentrates 500 to 1,000 U 1 hour before surgery (nanofiltered C1-INH, CINRYZE; ViroPharma, Dublin, Ireland, Cinryze ™ brand of C1-inhibitor has been approved for preventing HAE attacks. Cinryze ™is delivered intravenously and is approved for home infusion. **Berinert®** brand of C1-inhibitor has also been approved for treating acute facial and abdominal HAE attacks. Berinert® is delivered intravenously[17]. The use of FFP has been shown to be effective in surgical prophylaxis. Treatment begins the night before the surgery with one unit of FFP. A second unit is administered before the surgery. FFP can be used if C1-inh concentrate is not available[13]. Bradykinin receptor antagonist can also be successfully used. (**Firazyr**® brand of bradykinin receptor antagonist has been approved for treating acute HAE attacks in patients 18 years and older. Firazyr® is delivered by subcutaneous injection and is approved for self-administration. Midazolam and propofol can be administered for sedation. These agents lessen anxiety and tension and promote relaxation. [18] Vasoconstrictors were not used with local anesthetics during the procedure. Epinephrine is the gold-standard vasoconstrictor; however epinephrine can trigger an attack of HAE.

Treatment in acute swelling attacks is initially supportive, but when the pharyngeal swelling occurs, Endotracheal intubation may be necessary to maintain airway patency[14]. Supportive management is usually by means of intravenous infusion of narcotics and anti-inflammatory drugs; these control pain and nausea and maintain the patency of the respiratory tract, respectively[19]. When abdominal involvement causes dehydration and hypotension, rehydration therapy is required[20]. When abdominal involvement causes dehydration and hypotension, rehydration therapy is required[19].

A new drug for the treatment of HAE acute attacks has been released recently. Ecallantide (**Kalbitor®** brand of plasma kallikrein inhibitor has been approved to treat acute HAE attacks in patients 16 years of age and older. Kalbitor® is delivered through subcutaneous injections) is a recombinant plasma kallikrein inhibitor. It can be administered to patients aged 16 and older in a subcutaneous form of three 10-mg (1-mL) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24-hour period[21]. Long-term prophylaxis aims to reduce the frequency and severity of attacks and is indicated in patients who have significant and/or frequent episodes (1 attack per month for at least 6 months) of Angioedema. Two types of drugs have been proven effective in this kind of prophylaxis: antifibrinolytic agents and androgen derivatives. [15] Androgen derivatives stanozolol and danazol have been used successfully[13]. HAE patients, after 1 week of high-dose danazol treatment (600 mg/day) are protected from swelling.11 danazol 600 mg/day 1 week prior the risk-inducing episode[20]. There is a risk of delayed HAE symptoms, and deaths have occurred even after minor dental work. Prophylaxis does not guarantee freedom from laryngeal oedema, so vigilance is always necessary during and after procedures.

IV. Figures

Figure 1: Pre operative extraoral photograph

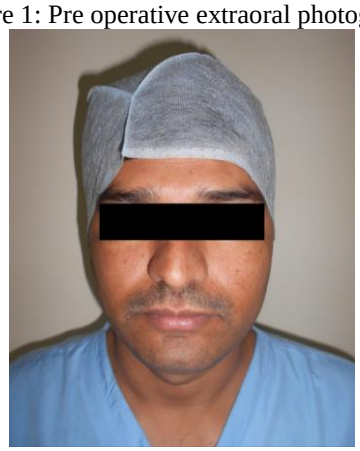


Figure 2: Orthopantomogram showing impacted third molar on right side mandible

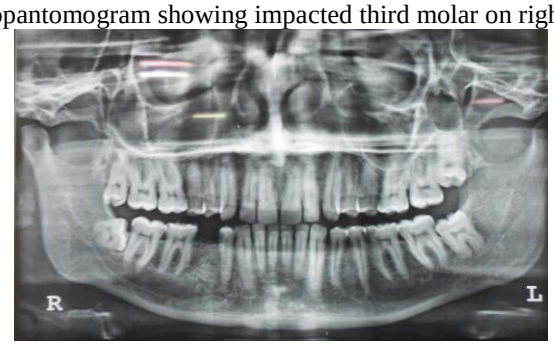


Figure 3: Intraoperative procedure

Figure 4: Post operative intraoral photograph

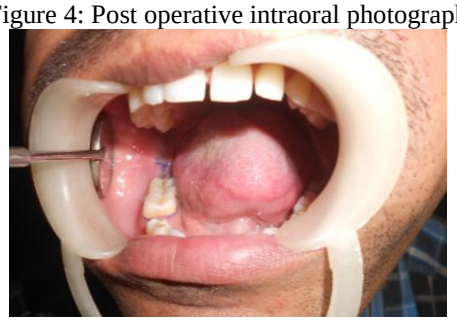
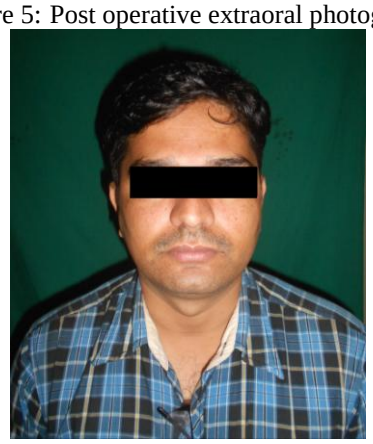


Figure 5: Post operative extraoral photograph



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