Review

Management of patients with hereditary angio-oedema in dental, oral, and maxillofacial surgery: a review

T. Uzun *

Trabzon Oral and Dental Health Hospital, Department of Oral and Maxillofacial Surgery, DDS, Trabzon, Turkey

Abstract

Hereditary angio-oedema (HEA) is an autosomal dominant, life-threatening genetic disorder that is caused by insufficiency or dysfunction of the C1 esterase inhibitor that develops coincidentally with recurrent oedema in the skin, internal organs, and upper respiratory tract. Increased production of bradykinin secondary to increased plasma kallikrein activity is the primary cause of attacks. Dental procedures cause emotional stress and mechanical trauma and may also initiate attacks. The most feared complication is asphyxiation as a result of laryngeal oedema. Cases that resulted in death after tooth extraction have been reported, so dentists and oral and maxillofacial surgeons should take maximum care in the treatment of patients with HAO, consult with the patient's doctor, and ensure that prophylaxis is given before the procedure. They should work as atraumatically as possible and use procedures to minimise stress. In the event of an attack of HAO, despite all the correct measures having been taken, the procedure should be terminated immediately and treatment of the attack started as soon as possible. The first drugs for the treatment of acute attacks are C1-INH (C1 inhibitor), ecallantide, or icatibant.
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Keywords: Hereditary angio-oedema; Dental; Oral and maxillofacial

Introduction

Hereditary angio-oedema (HAO) is an autosomal-dominant, life-threatening genetic disorder that develops when the C1 esterase inhibitor is insufficient or does not function correctly coincidentally with recurrent oedema of the skin, internal organs, and upper respiratory tract. Its incidence ranges from 1/50 000 to 1/100 000.[1] The disease does not discriminate between sexes or among races.

Classification

Three types of the disease have been described: type 1, type 2, and HAO with normal C1-inhibitor (C1-INH) activity. A total of 85% of all cases are type 1, and present with low C1-INH activity. Type 2 includes the remaining 15% of cases, and the C1-INH activity of this type may be normal or raised, but the present C1-INH is non-functional.[2] In the HAO with normal C1-INH activity all measurements are normal, but attacks of angio-oedema are similar to those of type 1 and type 2. This type is more common in women and is often triggered by oestrogen.[3,4] The gene encoding the C1-INH protein is localised on chromosome 11 (11q12-q13.1) and more than 450 mutations for it have been identified.[5–9] While autosomal dominant inheritance is seen in 75% of the patients, there is no family history in the remaining 25%.[10–13] These cases are thought to occur as a result of de novo mutation.

* Tel.: +90 5468634022.
  E-mail address: tugce–nur@hotmail.com

Pathophysiology

C1-INH is a serine protease inhibitor that is synthesised mainly in the liver (SERPING1 family).[14] This inhibitory protein not only inhibits C1s and C1r (the components of the classical complement pathway), but also inhibits the mannan-binding lectin pathway of the complement system, FXIa, FXIIa, thrombin, plasmin, and kallikrein.[15–21] Increased bradykinin production secondary to increased plasma kallikrein activity is the primary cause of attacks of HAO.[22] Bradykinin is a vasodilator and causes an increase in vascular permeability.[23] As a result, fluid accumulates in deep dermal, subcutaneous, or mucosal/ submucosal tissue.

Clinical presentation

Patients with HAO usually have their first attacks during childhood, and the frequency of attacks increases in puberty when the disease is usually diagnosed.[24] Local trauma and emotional stress are the most important triggers of attacks, but mechanical compression, infection, dental procedures, menstruation, ovulation, drugs such as angiotensin-converting enzyme inhibitors (ACE), angiotensin II receptor blockers (ARB), and oestrogen may also cause attacks.[7,25,26] Inhibition of ACE causes angio-oedema through an accumulation of bradykinin.[27] It has been reported that attacks associated with ACE inhibitors are more common in Black/Afro-Caribbean patients than in the general population.[28,29] Allergy does not cause HAO.

Diagnosis of the disease may be delayed because it is rare and heals itself.[30] Patients may talk about sudden deaths in their family history, for which reasons are not understood. During the attacks of HAO, non-pitting, non-pruritic swellings usually occur in the extremities, abdomen, face, and upper respiratory tract. It is painful, but rarely itches. Patients complain about ẗightnessäs a result of stretching in the skin. Some may experience prodromal symptoms such as nausea before the attack, fatigue, myalgia, joint pain, tingling, erythema marginatum, and numbness.[31–33] The resulting swelling increases within hours and usually resolves spontaneously within 2–5 days. Pain, vomiting, ascites, and diarrhoea may occur during abdominal attacks.[23] Symptoms may mimic conditions such as appendicitis, small bowel obstruction, inflammatory bowel disease, gall bladder disease, or diverticulitis.[34] Computed tomography and ultrasound can be used to diagnose gastrointestinal angio-oedema.[35] Acute abdominal symptoms may result in unnecessary surgical intervention as a result of misdiagnosis.[36] Abdominal swelling and peripheral oedema after tooth extraction have also been reported.[37] Attacks of HAO can be differentiated from allergic and idiopathic angio-oedema by the absence of urticaria, the fact that they do not respond to antihistamines and corticosteroids, and are of relatively long duration (72–96 hours).[38]

Laryngeal and lingual oedema

The most feared complication of the disease is asphyxiation as a result of laryngeal oedema, and more than half of all patients with HAO have an attack at least once in their lifetime.[39] This can result in death if it is not properly diagnosed and treated, and is the most common cause of death in patients with HAO.[41] In the past, 30% of patients with HAO have been reported to have died from laryngeal oedema.[41] During the attack, there may be changes such as deepening of the sound, wheezing, and aphonia, but swelling usually develops slowly within hours and gives time for medical intervention However, asphyxia-related deaths as the result of quickly-increasing oedema have also been reported.[42] When laryngeal oedema-induced asphyxia does occur, intubation of the patient or insertion of a surgical airway may be required.[43] Cricothyroidotomy is preferred when intubation or tracheostomy is not possible, because it is relatively simple and has a low risk of complications.[44]

Before cricothyroidotomy, patients should be placed supine with the head in extension, and the positions of the thyroid cartilage, cricoid cartilage, and cricothyroid membrane should be confirmed. A 1 cm transverse incision should be made along the cricothyroid membrane and then the larynx penetrated. The incision area can be widened with the help of a curved haemostat. The patient is ventilated by inserting a tracheostomy or endotracheal tube.[45]

Laryngeal oedema can present alone, or it can develop together with oedema of the face and tongue. In the differential diagnosis of lingual oedema, we should consider congenital conditions such as haemangioma, lymphangioma, Beckwith-Wiedemann syndrome, Down syndrome, and hypothyroidism; together with acquired conditions such as infiltration of a tumour, amyloidosis, myxoedema, and acromegaly; and acute conditions such as haemorrhage, infection, infarction, and oedema.[46] HAO should be considered in patients with lingual oedema who do not respond to antihistamines and corticosteroids, who have no history of exposure to an allergen, or who have a history of physical or emotional trauma that may lead to the development of oedema. It should also be considered in those who have patients in their own family who have experienced similar symptoms (that may even have resulted in death) and the necessary tests should be requested.

Laboratory tests

The most commonly used tests for hereditary angioedema are the C4 and C1-INH activity and the C1-INH function test. Serum C4 activity is low in type 1 and type 2 HAO, and is within normal limits in those with allergic angio-oedema and HAO with normal C1-INH activity.[47] The concentration of C1 inhibitor protein is low in patients with type 1 HAO, and within normal limits or high in patients with type 2 HAO. For the diagnosis of patients with type 2 HAO, C1

inhibitor activity should also be measured. Complement C3 and CH50 concentrations are within normal limits in HAO and measurement does not generally help.[48] Sequencing of the SERPING1 gene may support the diagnosis of HAO 1 and 2, but biochemical tests are less costly and more effective.[49]

Management of an attack

There are three stages in the management of HAO: treatment of the acute attack (on-demand treatment), short-term prophylaxis, and long-term prophylaxis (Table 1). Early intervention is essential in attacks of HAO. When the interval between the onset of the attack and the beginning of the treatment is shortened, the resolution of the symptoms is facilitated and the total duration of the attack is shortened.[50–53]

Oedema that develops in patients with HAO does not respond to antihistamines, corticosteroids, or epinephrine. Epinephrine may provide short-term relief, but does not alter the course of the attack.[54–56] In their 2017 guidelines, the World Allergy Organization (WAO) and the European Academy of Allergy and Clinical Immunology (EAACI) recommended the use of C1-INH, ecallantide (a kallikrein inhibitor), or icatibant (a bradykinin receptor antagonist) in the treatment of acute attacks.[46] When these drugs are not available, attacks should be treated with solvent detergent-treated plasma, or fresh frozen plasma if it is not available. The use of antifibrinolytic agents (tranexamic acid) or androgens (danazol) is not recommended because their effects in on-demand treatment have had little to no effect.[57] Icatibant is a bradykinin receptor antagonist that can be given subcutaneously by the patients themselves for the acute treatment of hereditary angioedema if they are over 18 years old.[58] Self-injection of the drug may reduce the severity of the attack by shortening the time between the onset of symptoms and treatment.[58]

Prophylaxis

Dental procedures, oral and maxillofacial surgery, and endotracheal intubation may result in swelling of the lips and tongue, and obstruction of the airway by laryngeal oedema. Cases that resulted in death after tooth extraction have been reported.[42,59–61] Patients who died had often been misdiagnosed as having allergic angio-oedema, had been treated with adrenaline, steroids, and antihistamines, and (as these drugs are not effective in hereditary angio-oedema) unfortunately died of asphyxiation.[42,60] In another patient who died, oedema of the tongue developed four hours after images had been taken; intubation was impossible because of intense swelling, and the patient died of asphyxiation.[42]

Before any dental procedure patients must be questioned about any previous swelling, and prophylaxis must be given in patients with a diagnosis of HAO. The guidelines published by WAO / EAACI in 2017 suggested that a C1-INH concentrate should be given as prophylaxis before the procedure in patients with HAO.[48] Because the C1-INH concentrate has such a long half-life, it is expected to provide preservation up to one or two days after the procedure.[62] It is recommended that the prophylaxis be given as near as possible to the start of the procedure, and the dose of pdC1-INH has been calculated as 1000 units or 20 units/kg.

Fresh frozen plasma can also be used for short-term prophylaxis but is not as safe as a C1-INH concentrate because of its high risk of contamination and allosensitisation.[7,26,37,63–65] For short-term prophylaxis, attenuated androgen (danazol) may be used but, when given too frequently, there may be side effects as there are after long-term use.[37,48] Androgen is used for short term prophylaxis five days before and two days after the procedure, but the use of tranexamic acid for prophylaxis before the procedure is no longer recommended.[37,66] In patients with HAO, prophylaxis before the procedure does not guarantee that attacks will not develop after it, so the patient must be kept under surveillance after the procedure and the measures needed in case of an attack should be kept ready.[42,62,66]

The use of C-1INH was proposed as first-line treatment, and the use of androgens was proposed as second-line treatment, in the long-term prophylaxis of patients with HAO.[48] Androgens have side effects such as weight gain, muscle cramps and pain, virilisation, myalgia, depression, acne, menstrual disorders, and alterations in liver enzymes and lipids.[67–69] It should be noted that despite long-term prophylaxis, an attack may occur.

Dental and oral and maxillofacial procedures

Patients with HAO are among those who require a special procedure by dentists and oral and maxillofacial surgeons, and if the practitioners do not have sufficient knowledge about the disease and cannot manage the treatment correctly, they may face serious complications. Consultation should be requested from the patient's allergy specialist/immunologist before starting treatment. The patient should be informed in detail about the risks and possible complications of the procedure. Emotional stress is one of the most important factors that initiate attacks, so management of stress during the procedure is vital.

Dental procedures and conscious sedation to be given during oral and maxillofacial surgery are the first choice in the prevention of acute attacks.[70] Even small interventions such as pulpal extirpation and taking a dental impression may cause the onset of the attack.[71–73] Patients with HAO should therefore have no intervention without prophylaxis and without consultation with their physicians. Invasive procedures should be avoided as much as possible, and the decision about extraction should be made after considering the patient's condition. Because intubation can trigger a laryngeal attack, sedation may be preferred rather than operating under general anaesthesia.[74,75]

Table 1

Management of hereditary angio-oedema according to the World Allergy Organization (WAO) and the European Academy of Allergy and Clinical Immunology (EAACI).[49]

	First-line treatment	Second-line treatment	Alternatives
Treatment of acute attack	C1-INH concentrate Ecallantide İcatibant	Solvent detergent-treated plasma	Fresh frozen plasma
Short-term prophylaxis	C1-INH concentrate	Fresh frozen plasma	Attenuated androgen
Long-term prophylaxis	C1-INH	Androgen	–

Because epinephrine and even phenylpressin can induce an attack, it is recommended to use a local anaesthetic without vasoconstrictors for anaesthesia.[74] Long-term follow up of the patient is important, because the laryngeal oedema may develop after 24–48 hours following an asymptomatic latent period.[40,62,76,77] Because infection can trigger an attack of HAO, care should be taken to treat any oral infections, and antibiotics should always be given when necessary.[78] Oral and maxillofacial surgery can be done successfully in patients with HAO when the necessary precautions are taken and correct procedure is followed. Christensen et al did double-jaw orthognathic surgery for a 16-year-old patient who had been given prophylaxis with C1-INH, and did not experience any oedema or breathing difficulties other than swelling as a result of the operation and one week later.[79] Moraes et al enucleated a dentigerous cyst for an 8-year-old girl with HAO under general anaesthesia after prophylaxis with danazol.[80] The patient was operated on, again under general anaesthesia, because of a recurrence of the cyst nine months after the first operation, and this time prophylaxis was given in the form of fresh frozen plasma. These operations were successful without life-threatening complications.

Conclusion

HAO is a serious, life-threatening disease and requires special procedures. Dentists and oral and maxillofacial surgeons should therefore take maximum care in the treatment of patients with HAO, consult with the patient's doctor, ensure that prophylaxis is given before the procedure, should work as atraumatically as possible, and should minimise stress.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

No ethics permission or patients' permission required.

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