

Upper airway considerations in hereditary angioedema

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Current Opinion in Allergy and Clinical Immunology 2010, 10:20–25

Purpose of review

The purpose of the present review is to outline the clinical aspects and management of the upper airway involvement in the patients suffering from hereditary angioedema.

Recent findings

Molecular mechanisms of hereditary angioedema reviewed in the literature conclude that it is an autosomal dominant disorder, characterized by the deficiency of C1 inhibitor due to mutations of its gene (SERPING). Hereditary angioedema manifests as episodes of localized swelling in any site of the body from skin, gastrointestinal tract to the upper airway, where it is severe and life-threatening. The age of onset, frequency of attacks and the factors triggering upper airway swelling in hereditary angioedema are variable among different patients. Acute laryngeal edema should be managed in emergency with monitoring of airway patency. To avoid airway obstruction, therapy should begin early either with current treatment (C1 inhibitor concentrate) or with new drugs developed recently. In patients with recurrent upper airway swelling attacks, long-term prophylaxis is recommended.

Conclusion

The use of old and new treatment in acute attacks as well as in prophylaxis (long and short-term) has changed the outcome of patients with hereditary angioedema who present upper airway swelling.

Keywords

C1 inhibitor, hereditary angioedema, swelling, upper airway

Curr Opin Allergy Clin Immunol 10:20–25
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1528-4050

Introduction

Angioedema is self-limited, localized swelling of the skin and submucosa, which results from extravasation of fluid into interstitial tissues and can be either acquired or hereditary [1,2]. Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by the deficiency of C1 inhibitor (C1-INH), due to mutations in its gene (SERPING1) [3^{••}]. C1-INH is an acute-phase reactant protein and is the primary inhibitor of the classical complement pathway as well as of the coagulation, fibrinolytic, and kinin-generating pathways. It is a member of the 'serpin' superfamily of serine protease inhibitors. In the classical complement pathway, C1-INH inhibits activated C1r and C1s as well as the early steps of the mannan-binding pathway. C1-INH also regulates the contact system activation by inactivation of plasma kallikrein and factor XIIa, preventing bradykinin release and maintains the endothelial barrier. The loss of this function, due to C1-INH deficiency, is illustrated by attacks of angioedema for which bradykinin is the primary mediator [4]. HAE results from the mutations of the C1-INH gene, located in the q12-q13.1 subregion of chromosome 11 [5,6]. The mutations of the C1-INH gene impair either protein synthesis (HAE type I, low

antigenic and functional C1-INH levels) or protein function (HAE type II, normal or elevated C1-INH levels but low C1-INH function) [1,7]. HAE with normal C1-INH was described a few years ago, mainly in women and is caused by mutations in factor's XII gene (HAE type III) [8[•]]. According to the C1-INH mutation database (HAEdb, <http://hae.enzim.hu.php>) [9] more than 250 different mutations have been described thus far, including the recent publication by Papallardo *et al.* [10], indicating the genetic heterogeneity of the disease [3^{••},11,12^{••},13]. Patients with HAE exhibit episodes of localized swelling that can affect the skin, the gastrointestinal tract, and the larynx. A prodrome of mood changes, fatigue, anxiety or trauma often precedes an attack by several hours. Attacks are always self-limited, lasting 2–4 days, and range in severity from inconvenient cutaneous swelling to life-threatening laryngeal edema [14]. Disease severity differs markedly among affected members within families, despite the presence of the same mutation [15]. Attack frequency varies considerably from 1 to 30 episodes per year [8[•]]. Manifestations of HAE vary from one patient to another in severity and frequency, ranging from 14% asymptomatic patients (identified as a result of family screening) [6] to life-threatening episodes due to the upper airway involvement.

The spectrum and management of upper airway in hereditary angioedema

Generally, HAE attacks resolve without harm; however, edema of the upper airway may result in asphyxiation. Any swelling in this area represents the most life-threatening type of attack, remaining the principal cause of life-long morbidity and mortality that should be regarded as an emergency.

Age of onset

Even today there is a long delay between the initial symptom and the diagnosis of HAE. Although the mean age at the onset of initial symptoms is 8–12 years of age, HAE can occur as early as the first year of life. Especially for laryngeal edema, it occurs usually for the first time in patients in their mid-20s. Nevertheless, it has been reported as early as age of 3 years [16].

Frequency

Laryngeal edema is rare (0.9% of all HAE attacks). It occurs in approximately one-half of all patients over their lifetimes; however, only a few percentage experience recurrent episodes [16].

Factors triggering upper airway swelling

Mild trauma, including dental work, tooth extraction and oral surgery are common triggers and will precipitate flares in many patients. Patients with HAE, who presented to emergency with upper airway obstruction after a routine molar extraction, are reported [17,18]. Tongue-piercing and snoring-induced local trauma of the soft palate have been implicated. Tongue swellings can occur after dental procedures or a bite on the tongue. No

recognizable triggering factor is found in many patients [8•].

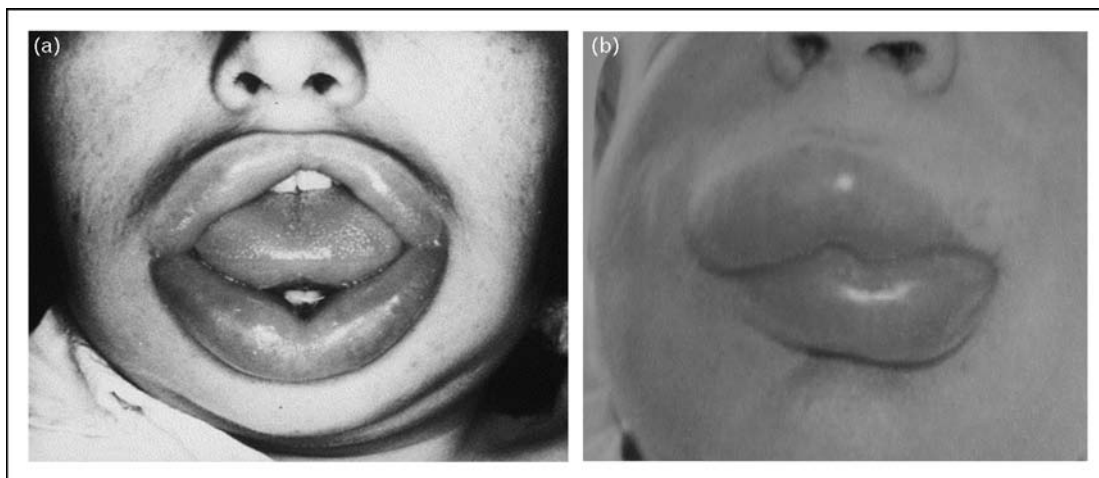
Clinical manifestations

Laryngeal swelling can occur in isolation, or in association with swelling of the lips, tongue, uvula, and soft palate (Fig. 1). Attacks involving only one site at a time, such as cutaneous attacks that spread to involve the larynx, are not uncommon. Edema formation has a propensity for the face and neck and it can progress to involve the uvula, the soft palate or the larynx. Clinical studies conclude that facial swellings are strongly associated with upper airway obstruction (608 of 2134 episodes of facial edema extended to laryngeal edema at least once) [19]. In earlier studies, 13.9–28.5% of facial swellings were complicated by laryngeal edema either simultaneously or within the subsequent 24 h [16,20]. In a recent series, among a total of 86 tongue swellings, 44 affected only the tongue, whereas the others were associated with edema of the larynx or the uvula [8•].

Obstruction generally begins slowly with voice changes (deeper voice, hoarseness, aphonia) and dysphagia. Clinical manifestations include stridor, globus sensation, and fear of asphyxiation. If untreated, the patient becomes tachypnoeic with low oxygen saturation and is referred to an emergency department with the complaint of dyspnea [16].

Laryngeal swelling usually develops over hours. However, there are disturbing reports of fulminant laryngeal attacks. Although each laryngeal attack has the potential to become life-threatening, the majority resolves before complete airway obstruction. A large series documented

Figure 1 Pictorial representation of tongue and lips edema



(a) Tongue and lips edema in HAE. (b) Facial edema involving lips in HAE. With permission from; Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1 Inhibitor activity in women. *Lancet* 2000; 356:213–217.

only three intubations in 74 episodes of laryngeal swelling [8*]. In one case intubation was impossible because of the massive swelling, and an emergency tracheotomy had to be performed [8*].

Diagnosis

Diagnostic criteria for HAE were proposed, based upon a European workshop (Table 1) [21]. A family history of recurrent angioedema with abdominal pain and/or laryngeal edema, if present (75% of patients), supports the diagnosis of HAE. Sometimes, it is not required because the patient may have a new mutation or an acquired disorder (25% of patients) [16]. The diagnosis of HAE cannot be reliably made before 1 year of age (unless using genetic typing). Diagnostic algorithms for HAE based upon international consensus have been established [22*].

Differential diagnosis

The differential diagnosis of laryngeal edema includes tonsillitis, peritonsillar abscess, pharyngeal foreign body, and allergic reaction. Historical information should differentiate these entities from angioedema, as infectious causes should have accompanying fever and other signs of illness. The diagnosis of a pharyngeal foreign body, based upon the history, occasionally can be difficult, particularly in the preverbal infant. Allergic reactions and anaphylaxis can involve laryngeal swelling. There are often associated symptoms affecting multiple organ systems simultaneously, such as urticaria, wheezing, vomiting, diarrhoea, and hypotension. The onset of allergic reactions is rapidly progressive or even explosive, and the patient can often identify a precipitating event, such as a meal, an insect sting, or administration of a new medication.

Current treatment

The management of acute attacks of upper airway swelling in HAE is based upon airway management.

Airway management in laryngeal attacks

Assessment and protection of the upper airway are the first and most important management issues in the patient with an acute attack involving any part of the airway. Intubation should be performed immediately

if stridor or signs of respiratory arrest are present. Edema may distort upper airway anatomy and make intubation problematic. A physician trained in difficult airway management should be summoned if possible, because failed attempts can lead to fatal obstruction. Emergent cricothyroidotomy may be required in rare cases. Direct visualization of the airway is discouraged if immediate airway support is not available. Such patients require hospitalization for careful monitoring of airway patency [14]. This is important particularly for the children who manifest rapid obstruction because of the small diameter of their upper airway. Laryngeal edema in children is a medical emergency and is an indication for admission to an ICU with ready access to endotracheal intubation, tracheostomy if needed, and airway management. Emergency therapy, potentially C1-INH concentrate, should be administered at home if the conditions are reliable, as early as possible and the patient should be sent to an emergency department for further surveillance [16].

Emergency therapy

There is no evidence of efficacy for corticosteroids and antihistamines in the treatment of acute HAE [8*]. Fresh frozen plasma as acute therapy was supported in the literature but its use remains controversial as it could theoretically worsen attacks, though this had not been observed in several series of such treated individuals [22*,23].

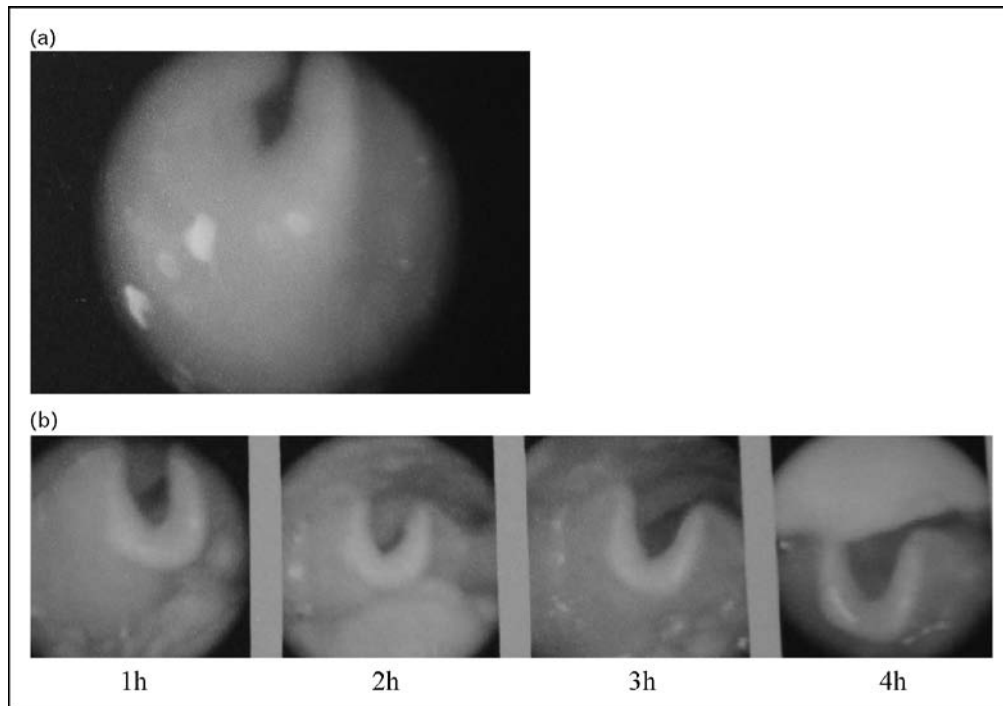
The treatment of choice of acute attacks is replacement therapy with C1-INH concentrate [8*,14]. C1-INH concentrates have been used in humans for intravenous use. The C1-INH products are those plasma derived: Berinert and Cinryze [20,24] and the recombinant human C1-INH: Rhucin. For this product, the human gene for C1-INH has been introduced into rabbits, under the gene regulatory control of a bovine α S1-casein promoter; the human protein is secreted in the milk of the rabbit where can be isolated [23,25].

Relief of symptoms can occur from as early as 10 min after administration of Berinert and complete resolution of symptoms has been reported from approximately 1 h after treatment, especially when treated early [26]. Most of the patients started to find relief of symptoms within

Table 1 Diagnostic criteria for hereditary angioedema

Clinical criteria	Laboratory criteria
Self-limiting, noninflammatory subcutaneous angioedema without urticaria, recurrent, and lasting >12 h	*C1 inhibitor antigenic levels <50% of the lower limit of normal
Self-remitting abdominal pain without clear organic etiology, recurrent, and lasting >6 h	*C1 inhibitor function <50% of normal
Recurrent laryngeal edema	Mutation in C1 inhibitor gene altering protein synthesis and/or function. This is the only laboratory criterion that can be used to make the diagnosis in patients younger than 1 year of age.

* At two separate determinations (at least 1 month apart) with the patient in basal condition and after the first year of life. The diagnosis is established in patients with one clinical and one laboratory criterion.

Figure 2 Endoscopic and laryngoscopic images of acute laryngeal edema before and after treatment

(a) Endoscopic image of acute laryngeal edema in HAE before treatment. (b) Laryngoscopy after treatment with icatibant. Previously published by Bas M, Bier H, Greve J, *et al.* Novel pharmacotherapy of acute hereditary angioedema with bradykinin B₂-receptor antagonist icatibant. *Allergy* 2006; 61: 1490–1492. h, hours. Adapted with permission from [34].

30–60 min. A repeat dose may be required, if the symptoms do not recede within 1 h or progress furthermore [27]. Since their introduction, plasma derived products have dramatically improved the outcome of laryngeal attacks in HAE patients [23]. Estimated risk of death from asphyxiation if the attack is left untreated is fairly high (15–33%) [6]. No transmission of infections in the pasteurized products has been referred [28]. Several authors have demonstrated home therapy as a potential option that causes rapid initiation of symptom relief and early complete resolution of attacks [25,29^{*}]. Certainly, in the case of laryngeal edema, a patient should first call the emergency before attempting a home infusion [30].

Two new compounds, the kallikrein inhibitor (Ecallantide) and the bradykinin receptor antagonist (Icatiban), are currently in use [31]. Both are foreign peptides. Ecallantide (DX88) is a recombinant 60-amino acid peptide produced in the *Pichia Pastoris* strain of yeast [32,33]. Given that bioavailability of the drug was found to be similar for both intravenous and subcutaneous routes of administration, it is now exclusively administered by subcutaneous injection. Early trials suggested that significant improvement in symptoms occurred within 4 h of receiving the drug and that the median time to initial improvement was less than 30 min [23]. Icatiban is a synthetic decapeptide that is structurally similar to

bradykinin, for subcutaneous use. Icatiban reduces angioedema in HAE patients by antagonizing bradykinin binding to bradykinin B₂ receptor. The mean time to onset of symptoms release is 45 min (Fig. 2) [34]. The initiation of subcutaneous drugs must be done early from the first signs of upper airway involvement in the HAE patients. Their great advantages are that they are free of human or animal contaminants and are ideal for home administration. There is no experience in children [5].

It should be mentioned that all facial swellings must be treated to inhibit the progression to laryngeal edema. As described in a recent study [20], none of the 483-treated facial swellings was complicated by laryngeal edema. In the opposite, 51 out of 628 untreated facial swellings extended to laryngeal swellings. The treatment of acute attacks of HAE is outlined in Table 2.

Prophylaxis

Patients who present frequent attacks involving the upper airway (more than one severe event per month) or are disabled more than 5 days per month or have a history of previous airway compromise should be treated prophylactically [16,24]. In the case of no accessibility to effective therapies for acute attacks (such as C1 inhibitor replacement) or access to emergency care, or travelling to

Table 2 Emerging drugs for upper airway attacks of hereditary angioedema

Agent	Company	Action	Dose	Route	Safety	Half- life
Berinert	CSL Behring (Marburg, Germany)	Plasma derived-pasteurized C1-INH	Adults: 1000 U Children: 500 U	IV	Potential transmission of viral infections, anaphylaxis	36–48 h
Cinryze	Lev Pharmaceutical (New York, USA)	Plasma derived-nanofiltered C1-INH	1000 U	IV	Potential transmission of viral infections, anaphylaxis	36–48 h
Rhucin	Pharming (Leiden, Netherlands)	Recombinant human C1-INH	100 U/kg	IV	Contraindicated if rabbit allergy	3 h
Icatibant	Jerini (Berlin, Germany)	Bradykinin-2 receptor antagonist	30 mg	SC	Local discomfort	2–4 h
DX88 Ecallantide	Dyax (Cambridge, UK)	Kallikrein inhibitor	30 mg	SC	Prolonged partial thromboplastin time, antidrug antibodies, anaphylaxis	2–4 h

C1-INH, C1 inhibitor; IV, intravenously; SC, subcutaneously; U, unit.

remote areas or countries in which there is no healthcare readily available, maintenance therapy is strongly indicated [12**].

Maintenance therapy

It is a long-term prophylaxis. Three preventing therapies can be used.

Attenuated androgens

Synthetic 17- α -alkylated androgens such as danazol, stanozolol, and oxandralone were observed to have a therapeutic benefit with minor side effects [14]. Contraindications include pregnancy, lactation, prostate cancer and childhood (until finished growing) [22*]. The adverse reactions are dose related, with the most important being hepatotoxicity and virilization [14]. When initiating treatment, the physician can start with a high dose (danazol 400–600 mg daily) and taper down or with a low dose (50–200 mg/daily) and increase as required. Patients should be treated with the lowest dose needed to maintain symptom control, usually 50–200 mg of danazol daily or every other day [14,35]. In children who fail to achieve satisfactory control with other agents, the lowest dose of danazol (2.5 mg/kg) per day or every other day or at 3-day intervals can be used with caution. Regular monitoring of liver function and lipid profiles is critical [16].

Antifibrinolytics

The antifibrinolytic drugs ϵ -aminocaproic acid (EACA) and tranexamic acid are considered to be less effective than attenuated androgens. Because their safety profile is more favorable, they are often reserved for the cases of intolerance to androgens. The typical therapeutic dose of EACA is 1 g orally three or four times daily and of tranexamic acid 50–75 mg/kg/day. In pediatric patients tranexamic acid at a dosage of 20–40 mg/kg per day split two or three times is better tolerated than EACA (0.17–0.43 g/kg per day), which often causes gastrointestinal discomfort [14,16].

C1-INH concentrate

Levi *et al.* [36] demonstrated a significant reduction in attack frequency in patients with C1-INH concentrate

self-infusions at home every 5–7 days at a dose of 1000 UI. Kreuz *et al.* [37*] conclude that patients refractory to danazol prophylaxis abolish the incidence of laryngeal edema and reduce the incidence of acute attacks, when treated with self-infusion of 500–1000 IU of C1-INH concentrate up to twice a week. Patients should be vaccinated against hepatitis B in case they require blood-derived C1-INH concentrate. C1-INH prophylaxis is the safest prophylactic agent during pregnancy [22*].

Trigger avoidance

Patients should be educated regarding avoidance of known triggers: facial trauma, stress, medications including angiotensin-converting enzyme inhibitors, estrogens (oral contraceptives, hormone replacement therapy) [23].

Short-term prophylaxis

It is indicated in particular circumstances.

Minor manipulations

In the case of mild dental work, no prophylaxis is needed if C1-INH concentrate is available. If not, prophylaxis with danazol (2.5–10 mg/kg/day, maximum 600 mg daily) for 5 days before and 2 days post event is required [22*]. It is emphasized the need to refer the HAE patients for all dental and oral surgical treatment within a hospital framework [18].

Intubation or major procedures

In the case of surgery where intubation is used, C1-INH concentrate must be given 1 h before surgery at a dosage: 500 U if less than 50 kg, 1000 U if more than 50 kg, 1500 U if more than 100 kg. Two doses of C1-INH concentrate should be available.

All patients with HAE should be equipped with a medical information bracelet or necklace identifying the condition and a written plan for treatment of acute airway attacks for use in emergency department care [12**].

Conclusion

HAE is considered a rare disease with variable prognosis and unpredictable course. Prior to the introduction of effective therapies, up to one-third of patients died of asphyxiation. However, despite effective therapies, deaths secondary to laryngeal attacks still occur. The development of new drugs, self administration programs, patient organizations, the awareness of doctors and public on HAE could change the outcome of the disease in the future.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 87–88).

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