

## LITERATURE REVIEW

# Hereditary angioedema - an otolaryngologist's perspective

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## ABSTRACT

Hereditary angioedema (HAE) is a rare autosomal dominant disease consisting of recurrent angioedema attacks, varying in severity, possibly life-threatening and with frequent involvement of the head and neck areas. The pathophysiology of HAE differs from histamine-mediated allergic angioedema. Three types of reduced quality or quantity in various complement or coagulation factors, leading to massive release of bradykinin, increase vascular permeability and produce capillary leakage. Clinical manifestations of HAE include swelling located predominantly in the head and neck area, hands, feet and urogenital area and abdominal pain caused by edema of the gastrointestinal tract mucosa. Diagnosis requires laboratory tests for complement components and genetic tests. A timely and correct diagnosis in the emergency room is of utmost importance, the medical treatment of HAE being substantially different from that of allergic angioedema. Although new therapies are available and in development, airway intervention and surgery are still life-saving procedures and the ENT surgeon is an important part of the multidisciplinary team managing an HAE attack.

**KEYWORDS:** angioedema, hereditary angioedema, surgical airway, tracheostomy

## INTRODUCTION

Angioedema is the clinical manifestation of a variety of pathophysiological processes, the end result of which being swelling of the deep dermis and subcutaneous tissue of the face, hands, feet and urogenital area, mucosal and submucosal swelling of the airways and gastrointestinal tract. Rapidly progressing angioedema of the upper airways is a life-threatening condition and should be considered a medical emergency.

Although the clinical presentation of angioedema has some similarities regardless of the pathophysiological pathway which caused it, it is of utmost importance to differentiate between types of angioedema due to their emergency, chronic and prophylactic treatment being substantially different.

Hereditary angioedema (HAE) is a rare autosomal dominant condition which manifests with recurrent angioedema attacks. As is the case with all types of angioedema, HAE attacks can vary in severity from mild to life threatening. Its treatment includes general measures, medical therapy and airway intervention as a last resort. HAE is best managed by a multidisciplinary team including otolaryngologists, allergists, emergency physicians, anaesthesiologists, pneumologists.

As stated by Moldovan D., the founder of the Romanian HAE Registry, 91 patients belonging to 43 families have been diagnosed with either type I or type II HAE in Romania. Due to the lack of awareness of both physicians and patients and the unavailability of specific medication, fatalities have been reported<sup>1</sup>.

## EPIDEMIOLOGY

The prevalence of HAE was estimated at 1 in 10,000 to 1 in 150,000 individuals, the average being considered 1 in 50,000<sup>2,3</sup>. Type I and II HAE have similar prevalence in men and women, and also in different ethnic groups. Although type III HAE can affect males, its prevalence is significantly higher in women<sup>4,5</sup>. Despite the fact that symptoms usually appear in childhood, due to the rarity of the disease, the potentially delayed symptom onset and the low awareness of the disease among the population and even among physicians determine a mean diagnosis delay of 13.1 years<sup>6</sup>.

The average HAE attack frequency in untreated patients is once every 2 weeks, but it can be as high as once every 3 days<sup>7,8</sup>. Mortality ranges from 0.3 to 1.4 % and has been in decline in the last 30 years<sup>9,10</sup>.

## **PATHOPHYSIOLOGY**

Based on pathophysiology, angioedema can be:

- Hereditary (HAE)
- Acquired
- Allergic
- ACE inhibitor-induced
- Physically induced
- Idiopathic

As opposed to histamine-mediated, autoimmune or idiopathic angioedema, hereditary angioedema does not involve IgE or non-IgE mediated mast cell activation and degranulation. HAE is a bradykinin-mediated angioedema that includes 3 types of autosomal-dominant inherited mutations. Type I is characterized by a low C1-esterase inhibitor protein (C1-INH) level; type II is characterized by a dysfunctional C1-INH. Type III HAE, more recently described, does not involve the complement system directly but the XIIth factor of coagulation. C1-INH blocks the activation of the classic complement cascade and also inhibits the coagulation, fibrinolytic and kinin-kallikrein pathways. All types of HAE present inappropriate and excessive activation of the kinin-kallikrein system of which the end result is massive release of bradykinin from high-molecular-weight kininogen. Bradykinin is an inflammatory mediator, a potent vasodilator which also increases vascular permeability and produces capillary leakage<sup>11-15</sup>.

## **CLINICAL PRESENTATION**

The World Allergy Organisation suggests that HAE type I and II should be suspected when a patient presents with recurrent upper airway edema and abdominal pain, in the absence of wheals (hives), unresponsive to antihistamines, glucocorticoids or even epinephrine. A positive family history and onset of recurrent symptoms in childhood or adolescence also help the physician in differentiating HAE from other types of angioedema<sup>7,16</sup>.

A HAE attack's physical signs include:

1. Noninflammatory, nonpruritic and nonpitting swelling located predominantly in the head and neck area, hands, feet and urogenital area. Most patients have prodromal symptoms: erythema marginatum, a non-pruritic rash with raised borders may precede or develop simultaneously with edema<sup>17-19</sup>.
2. Abdominal pain caused by edema of the gastrointestinal tract mucosa, nausea and vomiting are in some cases the dominant symptoms. Up to 93% of patients with HAE experience recurrent abdominal pain and up to one third of patients with acute abdomen due to undiagnosed HAE undergo unnecessary abdominal surgery<sup>20-22</sup>.

3. Laryngeal edema, although not as common as cutaneous swelling and abdominal pain, is a potentially life-threatening manifestation of HAE. Hypoxemia, stridor, hoarseness or any other signs of respiratory arrest may be present when the upper airway is involved and may drastically change the natural course and management of the case. The cumulated lifetime incidence of laryngeal edema is 70%. Patients with HAE have a low but permanent risk of asphyxiation. Patients with undiagnosed HAE have up to 9 times the risk of asphyxiation of patients with diagnosed HAE. Some factors have been linked to an increased risk of developing laryngeal edema in HAE patients: history of dental surgery or intubation, age between 11 and 45 years, prior laryngeal or facial edema. The absence of above mentioned factors and long-term treatment with attenuated androgens (danazol, stanozolol) decrease the risk of laryngeal edema<sup>20,23,24</sup>.

## **DIAGNOSTIC**

Laboratory tests used to diagnose HAE type I or II include serum levels of C4 and C1-INH as well as antigenic and functional activity of the latter. A normal C4, particularly during an edema attack, should make one question the diagnosis of HAE<sup>25</sup>. Type I HAE is suspected when both C1-INH and C4 are low. Type II is suspected when C4 is low, C1-INH is normal or high, but its functional activity is diminished. In type III HAE, neither C4 nor C1 (both quantity and functionality) are low. Genetic testing is usually not necessary for the confirmation of type I and II HAE, but it is important in investigating mutations in the coagulation factor XII gene, the main culprit in type III HAE.

Imaging studies and histologic findings are of minor importance. Abdominal ultrasonography or CT scans may show edematous thickening of the intestinal wall and peritoneal fluid. Histologically, HAE is indistinguishable from other types of angioedema<sup>20</sup>.

## **TRIGGERING FACTORS**

A number of triggers for a HAE attack have been identified:

1. *Surgery.* Patients with HAE type I and II have a 5-30% risk of developing perioperative angioedema. Due to the unpredictability of HAE attacks, short-term prophylaxis should be considered for all HAE patients undergoing surgery. The risk of an angioedema attack does not vary significantly depending of the location of the surgery, but the site of an angioedema attack usually

corresponds with the site of the surgery, thus giving an increased risk of laryngeal edema after surgery in the head and neck region<sup>26</sup>.

2. *Diagnostic and therapeutic procedures* of the head and neck region, including dental surgery and orotracheal intubation. Along with surgery, these causes can be included in the larger category of mechanical trauma, which is the leading cause of HAE attacks. A number of cases of life-threatening or even fatal upper airway edema have been reported following routine dental extractions<sup>23,27,28</sup>.
3. *Physiologic hormonal changes* during menstruation, pregnancy (especially during the third trimester), estrogen-containing oral contraceptives and hormone replacement therapy are associated with an increase in frequency of HAE attacks. These triggers are particularly linked to HAE type 3. Pregnancy may improve or worsen the symptoms. Emotional stress also plays a significant role<sup>29-31</sup>.
4. *Angiotensin-converting enzyme inhibitors (ACEI)*. ACEI-triggered angioedema shares many clinical and pathophysiological features with hereditary angioedema (HAE). ACEI should be avoided due to their synergy with HAE resulting in excess accumulation of bradykinin<sup>32,33</sup>.
5. *Idiopathic* - in an important number of cases the triggering factor is not identified.

## INITIAL MANAGEMENT

The World Allergy Organisation recommends that all attacks resulting in debilitation/dysfunction and/or involve the face, neck or abdomen should be considered for on-demand treatment and treatment of attacks affecting the upper airways is mandatory. Securing airway permeability should be prioritized regardless of the cause of angioedema. Oxygen should be given in case of head and neck edema or hypoxia. Fluids should be administered intravenously. Pain management and supportive care are essential but do not affect the outcome of an attack; specific therapies should be used without delay. Continuous pulse oximetry and electrocardiogram monitoring is indicated<sup>16,25,34</sup>.

## MEDICATION SUMMARY

### I. DURING AN ATTACK

HAE is generally refractory to histamine blockers, steroids and epinephrine. Plasma-derived C1-INH - PdC1INH is considered the first line therapy in a HAE attack. Dosage depends on the product [Berinert®

(CSL Behring), Ceter® (Sanquin)], on average 20 units/kg being administered intravenously. Being a blood product, hemovigilance is important. PdC1INH has shown efficiency in treating some Type III HAE attacks<sup>25,35</sup>. Icatibant (Firazyr® - Jerini/Shire), a selective B2 bradykinin receptor antagonist, is a new, safe and effective treatment for acute attacks of HAE. Administered subcutaneously, it provides relief from laryngeal symptoms, and most attacks can be self-treated successfully with one icatibant injection<sup>36,37</sup>. Ecallantide (Kalbitor®), a recombinant plasma kallikrein inhibitor, is another newly developed drug with promising results in managing acute HAE<sup>38,39</sup>. Androgens and antifibrinolytics may be used if previously mentioned therapies are not available.

### II. PROPHYLAXY

- a. *Short-term prophylaxis*, in situations that might trigger an attack. These situations include iatrogenic trauma such as surgery, especially dental, maxillofacial or head and neck surgery. Danazol was the first drug used as short-term prophylaxis. When administered 4 days prior and 4 days after surgery, at a dose of 600mg/day it is considered an effective preventive measure<sup>40</sup>. C1-INH concentrate is significantly superior to orally administered drugs in reducing the instances of post-procedural edema<sup>41</sup>. For pre-procedure prophylaxis before medical, dental, or surgical interventions, 1,000 U nanofiltered, human C1-INH concentrate (Cinryze® -ViroPharma Inc., Exton, PA, USA) is given within 24 hours before the procedure<sup>42</sup>. Fresh frozen plasma received one day before surgery is also a safe and effective method of prophylaxis<sup>43</sup>. Antifibrinolytic agents, such as tranexamic acid and aminocaproic acid, replace attenuated androgens in children and pregnant women due to their adverse effects<sup>4,44</sup>.
- b. *Long-term prophylaxis*. Not all patients with HAE require long-term medication, and therapy recommendations should be individualized. General indications for prophylaxis based on expert decision are: more than 1 attack per month, rapid attack progression, limited access to health-care, more than 10 days per year absence from school/work, previous laryngeal swelling, more than 3 emergency department visits or at least 1 hospitalization per year, previous intubation, prior ICU care, significant decrease in the quality of life<sup>45</sup>. Until recently, androgen derivatives were regarded as standard in the long-term prophylaxis of swelling attacks in patients with HAE. The treatment is not without side effects, and requires close patient monitoring<sup>46</sup>. Antifibrinolytic agents are considered to be less effective than androgens. Plasma-derived C1-INH every 3

to 4 days is another effective treatment in preventing or reducing the frequency of HAE attacks<sup>47</sup>.

## AIRWAY INTERVENTION AND SURGICAL MANAGEMENT

The World Allergy Organisation strongly recommends physicians to consider intubation or tracheotomy early in progressive upper airway edema<sup>16</sup>. When airway obstruction is present or imminent, the airway should be secured using intubation or surgical techniques.

Intubation options include fiberoptic bronchoscope intubation and videolaryngoscopic intubation. Hypoxemia, stridor, hoarseness or any other signs of respiratory arrest require immediate intubation. Until recently, awake fiberoptic intubation in a spontaneous breathing patient with anaesthetist and ENT involvement was considered gold standard. More recent studies show the same effectiveness of fiberoptic and videolaryngoscopic methods with a more time efficient way of securing the airway in videolaryngoscopic intubation. The size and anatomical location of the upper airway edema may deem intubation impossible and may require surgical intervention<sup>48-50</sup>.

Surgical options for upper airway edema caused by HAE include cricothyroidotomy, percutaneous tracheostomy and surgical tracheostomy. Cricothyroidotomy is a relatively fast and easy to perform emergency procedure. The average speed of the procedure is 83 seconds<sup>51</sup>. Should no cricothyroidotomy set be available, acceptable gas exchange results can also be obtained using an intravenous catheter with a minimum inner diameter of 3 mm<sup>52</sup>. Although no specific study has been conducted regarding the use of percutaneous tracheostomy in HAE attacks, individual case-reports suggest that emergency percutaneous tracheostomy is feasible in experienced hands<sup>53,54</sup>. Percutaneous dilational tracheostomy is, on average, 10 minutes quicker than open surgery tracheostomy<sup>55</sup>. When neither the extreme swelling of the neck nor the life-threatening impaired respiratory status contraindicates it, a proper surgical tracheostomy should be performed. Up to 10% of patients suffering from HAE have at least one form of surgical airway intervention in their history. A permanent tracheostomy may even be preferred by some patients who fear future attacks and improper emergency care<sup>52,56</sup>.

A few studies have attempted to predict the risk of airway compromise and the need for airway intervention in angioedema. Even fewer studies have focused specifically on HAE predictors for airway intervention.

Kieu et al. have concluded that, regarding patients with angiotensin-converting enzyme inhibitor-induced

angioedema, a higher acuity level of care is required when drooling or respiratory distress are present, when the tongue, soft palate or larynx are involved or when the presentation is within 4 hours of symptom onset<sup>57</sup>.

Ishoo et al. have concluded that voice change, hoarseness and dyspnea are correlated significantly with ICU stay. Voice change, hoarseness, dyspnea and stridor were also present in patients requiring airway intervention. The authors proposed a staging system according to the anatomic location of the edema, linking it with the need for airway intervention: no patient presenting with face, lip and/or soft palate edema required neither ICU admission nor airway intervention; two thirds of patients with tongue edema had to be admitted in the ICU and 7% required airway intervention; edema of the larynx was associated with 100% ICU treatment out of which 24% required airway intervention<sup>34,58</sup>.

Bentsianov et al. have concluded that stridor, hoarseness and dysphagia correlate with disease severity. These symptoms, when confirmed with fiberoptic visualisation of pharyngeal and laryngeal edema, should determine the physician to consider immediate intervention<sup>59</sup>.

## CONCLUSIONS

When faced with an edema in the head and neck region, physicians should consider both allergic (histamine-mediated) angioedema and non-allergic angioedema. A brief history of the patient may guide the clinician's ulterior diagnostic and therapeutic decisions.

Although there are clinical similarities, the treatment of histamine-mediated angioedema and bradykinin-mediated angioedema like HAE differs significantly. C1-INH is the first-line treatment in a HAE attack, as opposed to antihistamines and corticoids in allergic angioedema.

The physician should always consider obtaining a surgical airway as the next possible step in managing a severe or progressing angioedema of the head and neck. Anatomical locations, like the base of the tongue and the larynx, have a higher risk of requiring airway intervention.

HAE is best managed by a multidisciplinary team on physicians. The head and neck surgeons' role is obtaining a surgical airway or providing a fiberoptic/laryngoscopic view needed for intubation when initial medical treatment fails.

Although no 100% efficient prophylactic medication is available, procedures with a risk of triggering a HAE attack like head and neck surgery, dental surgery, orotracheal intubation can be relatively safely per-

formed using currently available prophylactic treatments.

An otolaryngologist should be aware of the risk of triggering an attack in patients with hereditary angioedema during surgery in the head and neck region, but also by performing basic manoeuvres on the patient during diagnostic or therapeutic procedures.

**Conflict of interest:** The authors have no conflict of interest.

**Contribution of authors:** All authors have equally contributed to this work.

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