

CAS CLINIQUE / CASE REPORT

HEREDITARY ANGIOEDEMA

A Literature Review and National Management Guidelines

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ABSTRACT • Background : Hereditary angioedema, a rare and potentially life-threatening condition, is the result of a defect in the C1 esterase inhibitor. Primary care physicians should be familiar with this condition to avoid complications and improve quality of care. **Methods :** We present two cases of hereditary angioedema followed by a discussion based on a literature review of the recent guidelines and advances in this condition. **Objectives :** To highlight the clinical aspects, diagnosis and treatment of this condition and propose a practical local management based on the available medication. **Conclusion :** Hereditary angioedema management is still evolving. More efforts should be made concerning the drug therapy which is very costly and not available worldwide.

Keywords : angioedemas, hereditary

CASE 1

A 25-year-old patient, with hereditary angioedema (HAE) diagnosed in childhood, presents for dental procedure. His family history is significant for his father and his paternal grandmother having the disease. He has been well controlled on Danazol 200 every other day for five years now, with an average of one episode of peripheral edema and/or abdominal pain every two months, and normal liver enzyme tests and lipid profile. In the past, he has had three episodes of laryngeal edema: two of them occurring before 10 years of age, thought to be triggered by a facial trauma with migration of the edema and causing airway obstruction.

Blood tests done 11 years ago have shown the results below, confirming the diagnosis [NLV: normal lab values]: C1-INH: 3.66 mg/100 ml (NLV: 15-34); C1q: 73 IU/ml (NLV: 73-180) and C4: 2.28 mg/100 ml (NLV: 10-40).

The patient currently needs dental extraction (four wisdom teeth) under general anesthesia. He is admitted in a general ward, and is given 2 units of fresh frozen plasma (FFP) 12 hours before and 2 units 1 hour before the procedure. Eighty milligrams of methylprednisolone IV are also given 12 hours earlier.

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RÉSUMÉ • Introduction : L'œdème angio-neurotique héréditaire, une maladie rare mais potentiellement fatale, est le résultat d'un déficit de l'inhibiteur de la protéine C1 estérase. Les médecins devraient être familiers avec cette condition pour éviter les complications et améliorer la qualité des soins. **Méthodes :** Nous présentons deux cas d'œdème angio-neurotique héréditaire, suivis d'une discussion basée sur une revue de la littérature sur les lignes directrices et les progrès récents de cette condition. **Objectifs :** Mettre en évidence les aspects cliniques, le diagnostic et le traitement de cette maladie et proposer une conduite à tenir locale, pratique et basée sur les traitements disponibles. **Conclusion :** La gestion de l'œdème angio-neurotique héréditaire est encore en évolution. Plus d'efforts doivent être faits en ce qui concerne le traitement médical, très cher, et qui n'est pas disponible partout dans le monde.

After the operation the patient was monitored closely for laryngeal edema for 24 hours, during which he had only mild left mandible edema. He was discharged home on prednisolone 40 mg for 3 days with tapering for 12 days, with an uneventful follow-up.

CASE 2

A 40-year-old man, married with two daughters, dies of (Quincke's) laryngeal edema several hours after dental procedure, which did not respond to methylprednisolone alone in the emergency room.

No adrenalin or FFP were given because hereditary angioedema was not diagnosed earlier.

His two daughters (age 9 and 13) acknowledged having also had recurrent episodes of peripheral edema. Blood tests confirmed the diagnosis of HAE. They have been put on Stanazolol 25 mg and 50 mg per day for six months, with significant reduction of the frequency of the episodes and moderate side effects: such as facial and breast hair growth. They were advised to double the dose of Stanazolol whenever edema occurs.

DISCUSSION

Starting with these two illustrative cases of hereditary angioedema (HAE), we will discuss in this article the background, clinical characteristics, diagnosis and treatment of this life-threatening condition.

Background and clinical characteristics

Hereditary angioedema, a rare but life-threatening condition, has an incidence of approximately 1:50,000 and manifests as recurrent non-pruritic edema of skin and submucosal tissues associated with pain syndromes, nausea, vomiting, diarrhea, and life-threatening airway swellings leading to obstruction [1-2].

A prodromal serpiginous erythematous rash is sometimes seen, pruritic urticaria usually makes the diagnosis of HAE unlikely [3].

This condition is the result of a defect in the C1 esterase inhibitor (C1-INH) of the first complement system component gene that is transmitted as an autosomal dominant trait in 75% of cases. De novo mutations represent 25% of cases [4].

There are three types of HAE: • Type I HAE is defined by low plasma levels of a normal C1-INH protein. • Type II HAE is characterized by the presence of normal or elevated levels of a dysfunctional C1-INH. • Type III HAE has been recently identified as an estrogen-dependent inherited form of angioedema occurring mainly in women with normal functional and quantitative levels of C1-INH, some with mutations in the coagulation factor XII gene or other unidentified defects [1,5].

The pathophysiology of types I and II HAE has been elucidated with the candidate molecule resulting in angioedema being bradykinin. Bradykinin binds to, and activates, the bradykinin B2 receptor, causing vasodilatation, increased vascular permeability and smooth muscle contraction, all of which lead to the tissue swelling that characterizes HAE. Bradykinin secretion is not inhibited due to the defect in the C1-INH protein. Although named after its complement inhibitory activity, C1-INH also inhibits proteases of the fibrinolytic, clotting, and kinin pathways. C1-INH is the most important physiological inhibitor of plasma kallikrein, factor XIa, and factor XIIa. There is evidence for activation of a number of systems during attacks of HAE: the contact (bradykinin-forming) system being the most important for symptom mediation, the factor XII-dependent fibrinolytic cascade and the complement pathway. C1-INH is a major regulator of the complement, contact, and coagulation cascades through inhibition of several complement proteases (C1r, C1s, and mannose-binding lectin-associated serine protease 1 and 2), contact proteases (plasma kallikrein and coagulation factor XIIa), and coagulation factors (XIa and XIIa).

In HAE, a deficiency of functional C1-INH allows for uncontrolled activation of these cascades, resulting in increased bradykinin, thereby increased vascular permeability and the classic symptoms of swelling. HAE attacks are accompanied by neither inflammatory nor allergic components, and therefore generally do not respond to treatment with antihistamines, epinephrine, or corticosteroids – this clinical feature often provides an important diagnostic clue [6-8].

Precipitating factors of an attack may include stress, infections, tooth extraction, surgery, ACE-inhibitors,

minor trauma, menstruation, pregnancy, oral contraceptives but are often unidentified with attacks varying from periodic, clustering, periods of remission [1,5-6].

Some reports proposed that patients with HAE infected with *Helicobacter pylori* (HP) were more susceptible to symptoms than uninfected patients, where the eradication of the infection reduced the frequency and severity of swellings. As shown by experience from Visy *et al.* [9] and the international trial (Farkas *et al.* [10]), the eradication of *H. pylori* “may” lead to a marked reduction in disease severity. This is still not in most guidelines for the management of this condition. According to the *WAO Guideline for the management of hereditary angioedema*, published in 2012, *H. pylori* is mentioned as a “possible” trigger of HAE attacks, whereas in the “2010 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema”, the infection with *H. pylori* is not discussed. The pathophysiology is thought to be an excessive consumption of complement by antibodies directed against HP [9-10] but further studies are required to confirm these propositions.

Diagnostic pearls and tools

The differential diagnosis of angioedema without urticaria includes: HAE, secondary to ACE-inhibitors (ACEI), acquired C1-INH deficiency (AAE) and idiopathic angioedema. At least 0.2% of patients taking ACEI develop angioedema. If angioedema does not resolve after stopping the ACEI, additional analysis become necessary [6].

Acquired C1-INH deficiency (AAE) is an apparently rare condition, caused by acquired consumption of C1 inhibitor (C1-INH) [11]. It is frequently associated with B-lymphocyte disorders ranging from MGUS to B-cell malignancies [2,4,6,12]. In the presence of a defect in C1-INH protein or function, the complement 4 (C4) is low or undetectable due to the over activation of the complement pathway. Thus, if there is a clinical suspicion of C1-INH deficiency, it is recommended to evaluate C4 levels, C1-INH quantitative and qualitative (functional) [13-14].

In Lebanon, to our knowledge, the C1-INH functional assay is not available and the analysis is made abroad. A normal C4 particularly during an edema attack doubts the diagnosis of HAE [15-16]. C4 is normal between swelling events in only 2% of cases [4,12].

C1q antigenic protein is reduced in 75% of AAE but usually normal in HAE [11] and is usually necessary to differentiate between HAE type 1 and AAE when C4 and C1-INH are both low in the absence of a positive family history [1,15]

The diagnostic algorithm is illustrated in Figure 1.

Treatment

In this section we will discuss the medical management of an acute HAE attack, short- and long-term prophylaxis.

Several therapies have been approved during the last decade for the management of HAE acute attacks and

prophylaxis [17-19]. Several therapeutic phase III trials are underway. HAE management is still evolving [1,20].

Corticosteroids and antihistamines have no proven efficacy in HAE attack. Epinephrine has a modest and transient effect [1].

a. Management of an acute HAE attack

It is recommended to treat as early as possible. Plasma derived C1-INH (concentrate of C1-INH protein) has been the first line therapy for an acute HAE attack for several decades in Europe and the United States of America [1, 21-22]. A pharmaceutical grade C1-inhibitor was approved for the use of HAE in 2008. It was the first C1-inhibitor approved for use in the United States. A recombinant C1-inhibitor obtained from the milk of transgenic rabbits, conestat alfa, is approved for the treatment of acute HAE attacks in adults. Several other first line therapies were also approved recently: Icatibant, a bradykinin receptor blocker (approved in 2008) and Ecallantide, a kallikrein inhibitor (approved in 2009). Icatibant inhibits the bradykinin by blocking its receptor and Ecallantide acts mainly on the kinin pathway to inhibit the production of bradykinin.

If first line therapies are not available, which is the case in Lebanon, then FFP should be considered. FFP seems to be safe and effective for acute attacks of HAE [21].

One must note that some patients on anabolic androgen prophylaxis therapy can abort attacks by doubling their dose at the first signs or prodromes of an attack [23-24].

b. Short-term prophylaxis

Short-term prophylaxis is indicated when a patient known to have HAE will undergo a traumatizing manipulation that could activate the contact (bradykinin-forming) system leading to bradykinin excess and an acute attack of angioedema. Manipulations are classified as minor (any superficial manipulation not involving the airway) or major (surgery requiring intubation). To note that dental procedures are considered as major manipulations since they can compromise the airway if an angioedema attack occurred.

Since pdC1-INH on demand is not available in Lebanon to be used if an induced angioedema attack occurred, Danazol at a dose of 600 mg or Stanozolol at a dose of 6 mg for a couple of days prior to the manipulation and 2-5 days after the manipulation can be safely used.

FFP is used for major risk manipulations; there are no randomized controlled trials to validate the use of FFP in prophylaxis but its benefit is shown through case reports and experts opinion, the dose used is 10-15 mL/Kg administered 3 to 6 hours before the procedure and a second dose is given during the procedure.

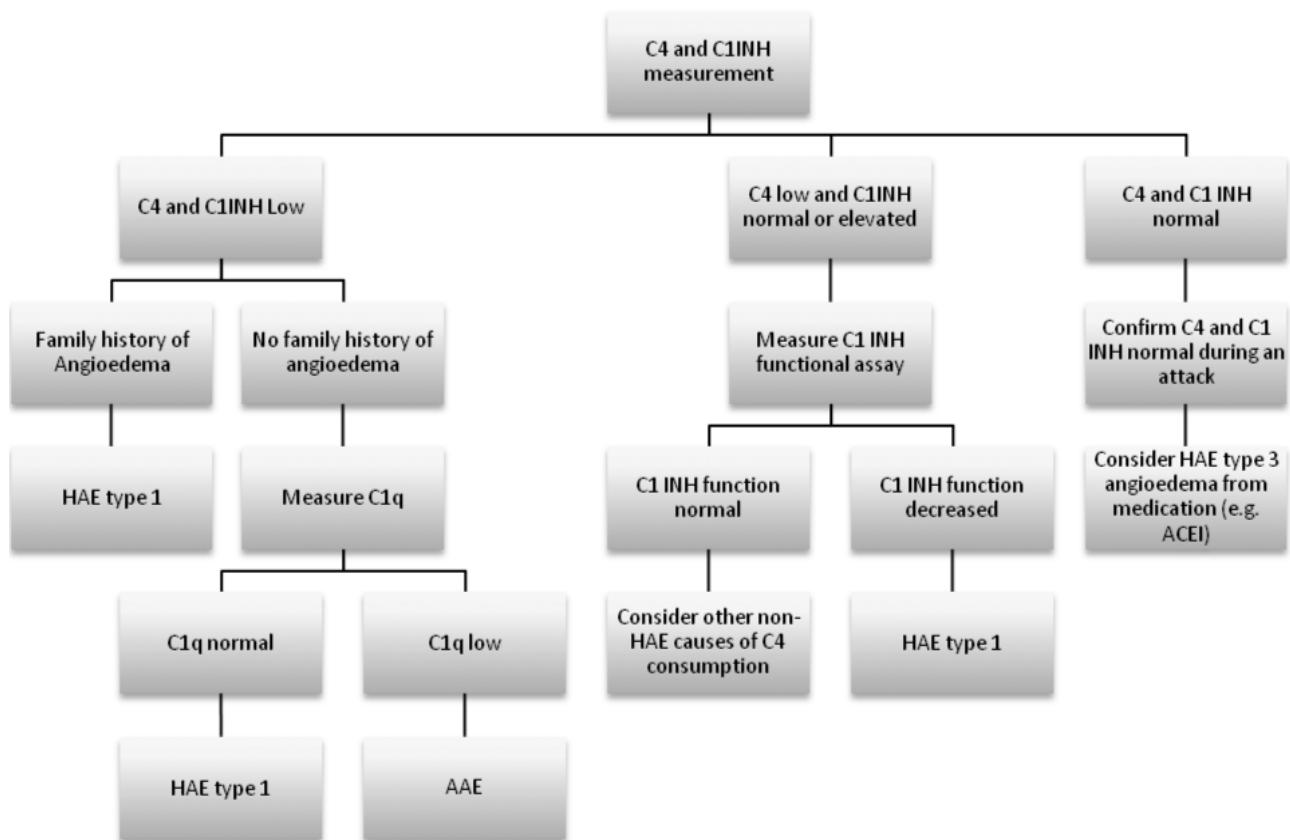


FIGURE 1. Diagnostic algorithm of hereditary angioedema

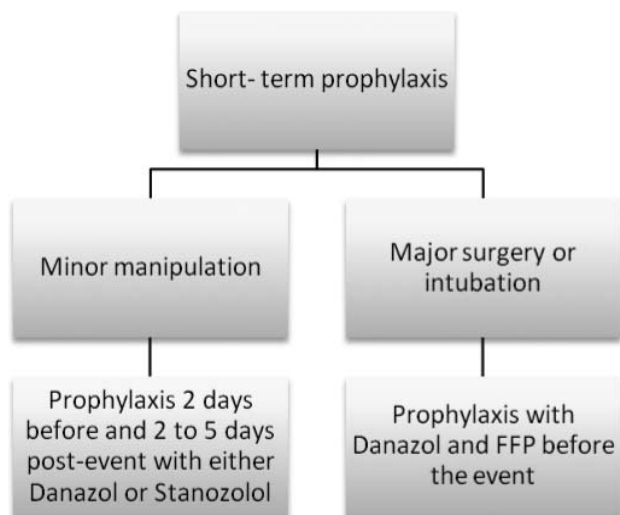


FIGURE 2

Short-term prophylaxis of hereditary angioedema guidelines.

Figure 2 [1,4,13,16,18-25] illustrates a diagram proposed as a practical local management of HAE short-term prophylaxis in Lebanon.

c. Long-term prophylaxis

Long-term prophylaxis should be considered in every patient who suffers from more than one severe HAE attack per month and if the treatment for acute attacks is not sufficient or available.

Long-term prophylaxis should be made with antifibrinolytics, attenuated androgens, or pdC1-INH [1,26].

Traxenamic acid (TA) being the most effective antifibrinolytic [19] is less effective in preventing HAE attacks than attenuated androgens such as Danazol or Stanozolol [1,24].

PdC1-INH subcutaneous self-infusion therapy is the

most effective and should be offered to patients [26-27]. It is a very costly therapy exceeding 350,000\$ per year [28] and does not carry the side-effects of Danazol such as virilization and a risk of liver tumors [29].

In Lebanon, since antifibrinolytics and pdC1-INH are not available, long-term prophylaxis is mainly made by androgens with either Danazol or Stanozolol with the lowest effective dose (Figure 3). Notably, androgens are also unavailable in Lebanon, but patients often manage to import them with relatively acceptable yearly cost.

CONCLUSION

Hereditary angioedema, a rare but potentially life-threatening condition, is the result of a defect in the C1-INH. This condition should be suspected in case of non-pruritic recurrent angioedema in the absence of associated urticaria. HAE medical management is still evolving and is not available worldwide; therefore, local guidelines are important to assist physicians in treating patients with HAE.

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Androgens	
Danazol 200 mg	Stanozolol 2 mg
↓	
Induction	
Danazol up to 600 mg/day for a couple of days	Stanozolol up to 6 mg/day for a couple of days
↓	
Long-term dosage	
Danazol ≤ 200 mg/day	Stanozolol ≤ 2 mg

FIGURE 3. Androgens long-term prophylaxis.

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