HEREDITARY ANGIOEDEMA

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Abstract: *Hereditary angioedema is caused by deficiency of a protein associated with complement activation, low C1-inhibitor function. It could manifest by cutaneous swelling, life-treating upper airway obstruction and severe gastrointestinal colic. C1-inhibitor studies should be performed if there is a high index of clinical suspicion. C1-inhibitor replacement therapy represents an efficacious treatment of acute attacks.*

Cuvinte cheie: *angioedem ereditar, C1-inhibitor*

Rezumat: *Angioedemul ereditar este cauzat de deficiența unei proteine asociată activării complementului, de concentrația sau funcționalitatea scăzută a C1-inhibitor esteraza. Se poate manifesta ca tumefieri cutanate invalidante, obstructive, cu potențial letal al căilor respiratorii superioare și colică gastrointestinală severă. Determinările de C1-inhibitor esterază trebuie efectuate în cazurile de suspiciune clinică importantă. Tratamentul substitutiv cu C1-inhibitor reprezintă o alternativă terapeutică eficientă a atacurilor acute.*

Hereditary Angioedema (HAE) is a rare condition, reported to affect up to 1 in 50.000 people. HAE is characterized by unpredictable attacks of oedema in the abdomen, the extremities, the face and the larynx; it causes substantial pain and discomfort and is associated with significant morbidity and mortality. These attacks can be spontaneously produced, sometimes leading to hospitalization. In severe cases, laryngeal angioedema can compromise the respiratory function, often resulting in asphyxiation and death. Often the diagnosis is established after months or years.

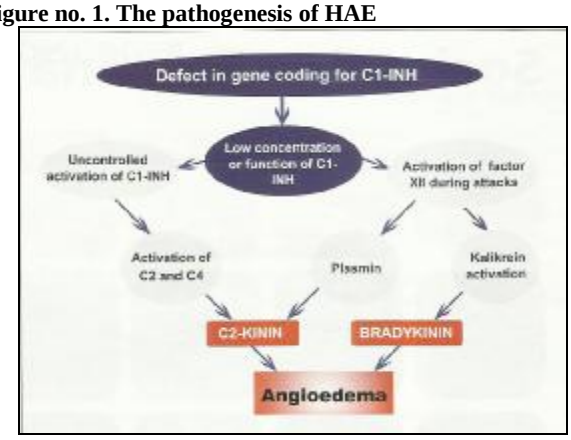
HAE is caused by a genetic defect that leads to decreased functional levels of C1 inhibitor C1-INH) (1) and is an autosomal dominant disorder. It is characterized by severe diffuse oedema in the skin of the extremities, abdominal and laryngeal swelling.(2)

The first medical documents about HAE belong to Heinrich Quincke (1882) (3) and Sir William Osler (1888). Osler was the first to fully describe its clinical features. In 1962, before any of the complement defects were known, Landerman et al. suggested that the symptoms might be due to the disturbance of the kinin system. In 1963, Donaldson and Evans demonstrated that HAE is produced by the deficiency of C1 esterase inhibitor in the plasma of patients with this disease. The gene encoding C1-INH mapping is localized in chromosome 11q12-q13.1.

Type I accounts for 85% of cases and is caused by a mutation in the C1-INH gene leading to low levels of antigenic and functional C1-INH. Type II accounts for 15% of cases and is characterized by normal levels of C1-INH, but with low activity. A third type of angioedema which does not result from C1-INH deficiency, affects women and may be estrogen dependent.(4)

Bradykinin is excessively produced when C1-INH levels is low. The oedema result from increased capillary permeability, fluid extravasation and nonvascular smooth muscle contraction.(5)

Figure no. 1. The pathogenesis of HAE



C1-INH inactivates 90% of Factor XII and 42% kallikrein causing a reduction in the production of bradykinin.

Activation of C1 complement initiates a cascade of events, one of witch is the development of oedema. C1-INH prevents activation of C1 witch interrupts this process.

The clinical characteristics of HAE are:(6)

- Recurrent attacks of diffuse oedema;
- Oedema is non-urticaric, non-pruritic and may be accompanied by rash;
- The skin and the gastrointestinal tract are the organs most often affected.

Attacks often occur for no apparent reason, triggers may be: trauma, surgery procedures, emotional stress, estrogen therapy, menstruation, mechanical pressure. Attacks last usually 2-4 days, afterwards resolving spontaneously. Types of severe attacks are characterized by:(7) laryngeal or upper airways oedema (rarely it may cause asphyxiation, that can occur at any age, in as little as 20 minutes) and intestinal oedema (leading to cramping, pain, nausea, vomiting, diarrohea, dehydration and occasionally hypotention). It may often be mistaken for an acute

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abdomen leading to unnecessary surgery. In type I and II of HAE, family history is present in 75% of patients, and does not respond to antihistamines, corticosteroids or epinephrine, as type III.(8)

Table no. 1. Types of HAE (9,10)

	Type I	Type II	Type III
C1-INH concentration	Low	Normal/high	Normal
C1-INH function	Low	Low	Normal
C4 concentration	low	Low	Normal
C1q concentration	Normal	Normal	Normal

Diagnosis can be established in the presence of 1 major clinical and laboratory criterion.(11)

Table no. 2. Laboratory and clinical diagnosis of HAE

CLINICAL	
	Self-limiting cutaneous angioedema without urticaria, often recurrent and often lasting> 12 hours
Major	Self-remitting abdominal colic without clear etiology often recurrent and often lasting > 6 hours
	Recurrent laryngeal edema
Minor	Family history of recurrent angioedema and/or abdominal pain and/or laryngeal edema
LABORATORY	
	C1-INH antigenic level <50% of normal at 2 separate determinations with patient in basal condition and after the first year of age
	C1-INH functional levels of <50% normal at 2 separate determinations with patient in basal condition and after the first tear of age
	Mutation in C1-INH gene altering protein synthesis and/or function

Differential diagnosis is made with: allergic angioedema, associated with food, venom, latex on environment allergens and responding to antihistamines, corticosteroids and epinephrine.

Idiopathic angioedema may occur daily, it often responds to antihistamines and corticosteroids.(12) Angioedema with urticarial vasculitis is usually accompanied by urticaria.(13) Drug-induced angioedema can be caused by angiotensin-converting enzyme inhibitors or nonsteroidal anti-inflammatory drugs, typically accompanied by urticaria.(14)

Long-term preventive treatment with tranexamic acid, androgens or C1-INH concentrate is considered if the patient experiences more that one severe event per month or is disabled more that 5 days per month.(5)

Tranexamic acid is mostly used when prophylaxis is indicated before puberty, in dose of 1-1,5 g , two or three times a day, depending on disease severity, reducing to 0.5g once or twice a day as the attacks remit. Diarrhea may appear as a side effect.(11,15)

Attenuated androgens, more effective than antifibrinolitic agents, are contraindicated in pregnancy, lactation, cancer and childhood. The side effects are dose dependent and are: virilisation, headaches, depression, menstrual irregularities, masculinization of the female fetus, decreased growth rate in children, cholestatic jaundice and hepatocellular adenoma.(16) Danazol is daily administered 400-600mg for one month, with a slow tapering to 50mg/day 5 day per week (17) and increase or decrease of the dose afterward, depending on the response obtained.

Short term preventive treatment is indicated in mild interventions up to 24 h before the procedure with 500 to 1500 U C1-INH concentrate. If the C1-INH concentrate is not available antifibrinolytics or attenuated androgens could be administered, starting 5 days before the procedure and the following 2 days thereafter: danazol 10mg/kg/day or tranexamic acid 75mg/kg/day split in 2 or 3 times per day.(18) Less safe alternative options are fresh frozen plasma.

Treatment of acute attacks is necessary in laryngeal and abdominal attack or total airway obstruction and C1-INH concentrate shortens the duration of attacks by about a third.(19,20) If symptoms persist at a high intensity 2 h after infusion, additional C1-INH concentrated should be given. If C1-INH concentrate is not available, danazol or tranexamic acid could be administrated. Use of frozen plasma can worsen the attacks.(19)

In pregnancy, we may use in predelivery 500-1000U C1-INH concentrate and the postpartum period is one of higher risk of acute attacks.(17,20)

In children, the use of antifibrinolytics and androgens is not recommended because of the serious side effects. Prophylaxis is required in cases of frequent attacks of laryngeal edema or recurrent attacks of abdominal pain.

For a HAE patient, it is very important to keep a patient infocard and to have a travel insurance that will cover HAE.

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