

8. Hereditary angioedema

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Hereditary angioedema is an episodic swelling disorder with autosomal dominant inheritance. Attacks are characterized by brawny, self-limited, nonpruritic edema of the deep dermal layers of the skin that most often involve the hands and feet. They usually begin in childhood and become more severe after puberty. Patients also have episodic attacks of severe abdominal pain caused by edema of the gastrointestinal mucosa. Swelling attacks are life threatening when they involve the airway. Estrogens exacerbate attacks, and in some patients attacks are precipitated by trauma or psychologic stress. The disease is caused by a mutation in one of the 2 copies of the gene for the plasma protein C1 inhibitor, with the product of 1 gene unable to control generation of bradykinin. Eighty-five percent of patients have low antigenic levels of C1 inhibitor, and 15% have normal levels of poorly functioning protein. Most patients have decreased plasma complement protein C4 levels. Impeded androgens and, less frequently, ϵ -aminocaproic acid are currently the mainstays of chronic treatment. These agents or fresh frozen plasma are also used for prophylaxis. At this time, acute therapy is mostly supportive. There are currently ongoing multiple trials of new therapeutic agents. In half a century, a life-threatening disease has become one that is manageable and rarely causes death. (*J Allergy Clin Immunol* 2008;121:S398-401.)

Key words: *Hereditary angioedema, bradykinin, C1 inhibitor, C1 esterase inhibitor, complement, androgens, antifibrinolytics, danazol*

Hereditary angioedema (HAE) is an episodic swelling disorder with autosomal Mendelian dominant inheritance.

The disease is characterized by episodic peripheral swelling (edema), usually of the hands and feet but occasionally of the genitalia, trunk, face, tongue, and larynx.¹ The brawny nonpitting edema is due to leakage of plasma from postcapillary venules into the dermal layers of the skin and is often poorly circumscribed. Swelling is not associated with pain, although the swelling alone with loss of flexibility of the tissues can cause discomfort. Patients also commonly have episodic swelling of the wall of the bowel, leading to severe abdominal pain. This pain is often spasmodic rather than steady, presumably increasing with each peristaltic wave, suggesting that there is an element of bowel obstruction in the attacks. In many patients vomiting, particularly early in the attack, is a regular feature of the episode. Patients might

Abbreviations used

ACE: Angiotensin-converting enzyme

C1 Inh: C1 inhibitor

EACA: ϵ -Aminocaproic acid

HAE: Hereditary angioedema

have constipation in an attack but also might have diarrhea, usually at the end of an attack. On physical examination, the abdomen often has few bowel sounds, but this is also not constant, and rushing bowel sounds may be heard. Although there is often tenderness and at times rebound tenderness and guarding, this is not a rigid surgical abdominal examination. Attacks of abdominal angioedema, however, can lead to surgery in the patient without a diagnosis because of the severity of the pain.

In general, swelling, although uncomfortable, is not life threatening, except when it involves the airway. Nevertheless, airway swelling can lead to asphyxiation and death. In our early clinical studies we reported that about one third of untreated relatives of family members with the disease had a history of asphyxiation.²

In the average patient attacks grow more severe for about a day and a half and then clear over a similar period, but there are many exceptions to this rule. In some patients attacks last less than 24 hours, and in occasional patients abdominal pain attacks last 4 or 5 days and peripheral swelling attacks last as long as 9 days. The variability of this disease is really quite remarkable.

Angioedema attacks are often heralded by a prodrome. Usually the prodrome consists of a feeling of tingling for perhaps an hour in the area where the attack will start. Presumably, this represents the release of mediators that will induce postcapillary venule leakage and edema formation. However, there are rare patients who have no prodrome, and some patients have prodromes as long as 24 hours before attack onset. At the start of an attack, about one third of patients note the development of erythema marginatum, often described as red circles on the skin. This rash is nonpruritic and not raised, and patients often remark that they would not know they had the rash unless it was observed.

Although attacks are sporadic and usually do not have a clear initiating cause, almost one third of patients note that pressure or trauma will bring on an attack. Thus use of a power lawnmower or prolonged use of scissors can cause hand swelling. In general, attacks are not symmetric and often extend locally, but they can pass from one hand to a foot or one hand to the other hand, for example. A second factor that for unknown reasons precipitates attacks in about one third of patients is emotional stress.

Attacks usually begin in childhood and become more severe at puberty, but they can begin anytime, even as late as age 70 to 80 years. Presumably, the biochemical abnormality responsible for attacks is present from birth, but something has changed to bring on attacks. At times, the first use of angiotensin-converting

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enzyme (ACE) inhibitors is the event that activates long-standing quiescent disease. ACE is important in the catabolism of bradykinin, and by inhibiting this enzyme, ACE inhibitors precipitate the bradykinin-induced attacks.³ In most patients the full-blown syndrome develops at the time of puberty. The autosomal dominant inheritance pattern would predict equal incidence and severity in men and woman, but most physicians note a preponderance of women requiring care. This might represent selection bias but could also be a reflection of hormonal influences on disease severity. Estrogens cause attack frequency and severity to increase.^{1,4} Occasionally, a patient can be treated by simply stopping estrogen-containing birth control pills. Many women note that attack frequencies are highest at the time of menstruation.

The most debilitating attacks experienced by patients are the abdominal pain attacks. These attacks are never associated with bowel wall necrosis but can be sufficiently severe to cause obstruction of the gastrointestinal tract. On gastrointestinal series during the attack, there is usually edema of the mucosa noted; however, between attacks, the gastrointestinal series is normal. Occasionally, repeated attacks preventing adequate biliary drainage can lead to gallbladder disease, or attacks preventing pancreatic drainage can lead to pancreatitis. Patients with only abdominal attacks have been reported but must be very rare.¹

The most dangerous attacks are those that affect the airways. Often these attacks start in the mouth and extend to the larynx. Because trauma can sometimes bring on an attack, these patients learn to fear the dentist. The airway, particularly in the region of the vocal cords, is constricted, and a relatively small amount of edema can do great damage. These attacks also usually increase in severity for about 1½ days and then resolve over the same period of time, but again this can be variable.

HAE is often grouped with the allergic disorders, but there is no histamine in the urine in attacks, and these patients do not appear to have more allergy than that noted in the general population.¹

Patients can go for extended periods without HAE attacks, and then once again the symptoms become far more severe; it is not known why the disease tends to wax and wane.

In general, patients with HAE do well with pregnancy, with a decrease in attack frequency starting in the second trimester. Their third trimester is often the best period that they have had in years. The trauma of delivery does not precipitate HAE attacks, but attacks can occur in the week after delivery. Occasional patients get worse during pregnancy, and when this happens, it represents a difficult management problem requiring frequent administration of C1 inhibitor (C1 Inh) or fresh frozen plasma (see section on prophylaxis). Although this has never been carefully evaluated, some investigators believe that attacks become less severe as patients age.

In caring for these patients, one can see that many are normal psychologically, but a subgroup of patients appear to have more psychological problems than might be expected.

PATHOPHYSIOLOGY OF HEREDITARY ANGIOEDEMA

In 1962, Landerman et al⁵ suggested that patients with HAE have an inherited defect in an inhibitor of a permeability factor in blood, probably kallikrein. This important observation was followed a year later by the seminal observation of Donaldson and Evans⁶ that the blood level of a protein, first termed C1 esterase inhibitor and now C1 inhibitor (C1 Inh), is abnormally low in

most patients with HAE. Further studies by Rosen et al⁷ demonstrated that 85% of patients (type 1) have low levels of C1 Inh and 15% of patients (type 2) have normal or increased levels of a nonfunctioning protein. Type 3 HAE is reported in women who have typical HAE symptoms but no clear complement or kinin system abnormality. Patients with type 1 HAE have a single gene defect that leads to no C1 Inh synthesis or failure to secrete protein, and type 2 defects lead to a secreted but nonfunctioning protein, often because of mutations that affect the active site. The C1 Inh binds covalently to the enzyme to be inhibited, and the product of one normal allele is not sufficient to prevent attacks. The C1 Inh gene has been cloned and sequenced. A large number of mutations over much of the C1 Inh molecule have been described. It is important to note that although this is an inherited disease, as many as 25% of patients have no family history and presumably have new mutations.

C1 is a complement system protein that circulates in inactive form and is activated during immunologic reactions. It functions to cleave the next 2 proteins in the classical complement pathway sequence, C4 and C2, and patients with HAE without normal inhibitor function almost always have low levels of C4 and C2, even between attacks. C1 Inh and C4 measurements are the usual diagnostic tests. The protein that follows C2 in the complement cascade is C3, and the level of C3, which has its own control proteins, is virtually always normal.

C1 Inh inhibits many of the mediator cascades in serum, including the complement, kinin-generating, clotting, and fibrinolytic systems, and recent studies have indicated that the major mediator of the angioedema attacks is bradykinin, which is released during activation of the kinin-generating system.⁸

Another fascinating finding is that patients with HAE have a higher than normal incidence of autoimmune diseases, although the diseases are often mild.⁹ The type of autoimmune disease is quite variable and appears to reflect the genotype and underlying predisposition of the patient.

TREATMENT OF HAE

Chronic long-term therapy

In 1960, Spaulding¹⁰ reported a limited double-blind study in one family showing that methyltestosterone provides effective therapy. This therapy never came into use, and the finding was lost to investigators in the field. With the observations that estrogens made HAE more severe, that patients with HAE improved during pregnancy and had no attacks associated with the trauma of delivery, and the increase in clinical symptoms at the time of puberty, attention turned to hormonal therapy. We reported that danazol, an impeded androgen and gonadotropin inhibitor that was developed as an oral contraceptive, provided highly effective treatment and tended to normalize C1 Inh and C4 levels.¹¹ At about that time, others showed that stanazolol and methyltestosterone provided effective treatment.¹ The only androgens that are useful in therapy are methylated substituted androgens that must be administered orally. The synthesis of all proteins produced in the liver is not increased, and their mechanism of action is still uncertain.

It became clear that it was impossible to predict in any individual patient the dose of androgen required for prophylaxis (Table I). We tend to start danazol treatment at 200 mg 3 times daily because this dose almost always prevents attacks, and the patient is therefore reassured and relaxes. We then progressively

TABLE I. Effective therapeutic dose of danazol

Danazol dose (mg/d)	Percentage with clinical response
600	95
400	88
300	58
200	11

At the lowest effective clinical dose, there might be no evidence of a biochemical response.

decrease the dosage slowly over months to determine the lowest dosage that will prevent attacks.

All impeded androgens have many potentially important side effects, including masculinization, headaches, lack of libido or increased libido, hair gain or loss, liver function abnormalities (including possible peliosis hepatis), and abnormalities in serum lipid levels (Table II). Danazol can induce hematuria caused by low-level cystitis or bladder telangiectasia. Side effects have tended to be mild, and abnormalities have usually disappeared when the drug is stopped.

Oxandrolone has been recommended, especially in children.¹ Switching from one impeded androgen to another does not appear to decrease drug toxicity.

It was also shown in double-blind studies that ε-aminocaproic acid (EACA), a fibrinolysis inhibitor, is effective in chronic therapy.¹² Tranexamic acid, a circularized relative of EACA that is not available in oral form in the United States, is far more effective on a per-milligram basis.¹ Side effects of EACA include severe muscle toxicity with at times a markedly increased creatine phosphokinase and aldolase level. Neither impeded androgens nor antifibrinolytics are useful in acute attacks in that they require about 48 hours of treatment before the onset of action.

Chronic disease treatment for HAE is satisfactory for most patients; however, both androgens and plasmin inhibitors are not always useful. These treatments are not proved safe in pregnancy, in some patients the side effects might be intolerable, and some patients do not respond to this therapy.

Short-term prophylaxis to prevent attacks

Prophylaxis to prevent HAE attacks might be required for surgery or after trauma. Administration of 2 units of fresh frozen plasma to replace the missing C1 Inh the night before or the day of surgery has been found to prevent attacks.¹

Androgens or plasmin inhibitors have also been used for prophylaxis. We have elected not to use these agents in prophylaxis because an occasional patient has an attack during adequate chronic prophylactic therapy, and at present, there is no adequate back-up therapy available. Once C1 Inh or another agent that reliably terminates attacks is available, attenuated androgens or plasmin inhibitors will be preferred.

Therapy of acute attacks

Therapy of acute attacks is the area that is currently most unsatisfactory.¹ In the United States patients are treated with epinephrine, which often has a mild, but not dependable, effect in limiting attacks; antihistamines for sedation; and glucocorticoids, although there is no evidence that glucocorticoids have efficacy. I treat patients also with intravenous EACA, which is available in most hospital pharmacies (16 g/d for the first

TABLE II. Side effects of danazol therapy

	No.	%
Abnormal liver function test results	9	16
Hematuria	9	16
Myopathy	21	38
Myalgias, cramps	17	30
Increased CPK level	11	20
Headache	7	16
Abnormal menses requiring therapy	5	13
Decreased libido	5	9
Hair loss	7	13
Anxiety reactions	18	32

CPK, Creatine phosphokinase.

day and decreasing to 8 g/d), not because the EACA terminates attacks but because I can be assured that 48 hours later, the attack will begin to resolve. Contraindications to its use include advanced age, previous thrombosis, or procoagulant state. Patients with airway difficulty, as suggested by inability to swallow secretions or a change in voice tone, are treated with nasotracheal intubation, if possible, before there is complete airway obstruction or tracheotomy.

Acute attacks of abdominal pain are treated with judicious use of narcotics, recognizing that these patients are prone to narcotic addiction. Narcotics administered very early in an attack for unknown reasons might terminate attacks. Fresh frozen plasma to replace C1 Inh will often terminate attacks, but some patients become acutely worse from the infused kinin substrates.

We reported in 1980 that purified C1 Inh successfully terminated attacks in a non-double-blind study.¹³ Similarly, groups in Europe presented evidence that this material terminates attacks.¹ C1 Inh has now been on the market in Europe for more than 25 years. Because psychologic factors play a role in attack frequency and severity, it was essential that efficacy be shown in a double-blind study. Such a study was reported by Waytes et al¹⁴ in 1996. It is interesting that one recent report suggests that weekly C1 Inh infusions are effective as chronic prophylactic therapy.¹⁵

The approach to treatment of HAE in several countries has recently been outlined.¹⁶⁻¹⁸

Purified C1 Inh, made available by each of 2 pharmaceutical companies, Lev and CSL Behring, is in clinical trials in the United States. Currently, there are several other therapies under study. The Dutch company, Pharming is testing a recombinant human C1 Inh made by introducing the human gene into animals in such a way that it is secreted and can be purified from their milk. Because attacks of HAE principally involve the kinin-generating system, a peptide that inhibits kallikrein, the enzyme that generates bradykinin from high-molecular-weight kininogen (DX88), and a bradykinin receptor type 2 antagonist (Icatibant; Jerini AG, Berlin, Germany) are both in clinical trials. Word from all of the manufacturers suggests that these therapies are successful.

In one generation we have gone from the complete clinical description of HAE to defining and characterizing the gene defects to understanding the molecular consequences of the defect and the pathophysiology of this disease. We have gone from no therapy for HAE to the development of effective empiric therapy and are now developing more specific therapy based on our understanding of its pathophysiology.

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