

Hereditary Angioedema: The Clinical Syndrome and its Management in the United States

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Hereditary angioedema (HAE) is an episodic swelling disease with autosomal Mendelian dominant inheritance. One of the oldest descriptions of the disease is from the 1840s by Graves, who clearly described patients with episodic angioedema [1]. In 1882, Quincke described a constellation of angioedema symptoms including peripheral swelling and self-limited attacks of abdominal pain; the disease is known in Europe as Quincke's disease [2]. His original description includes concern about compromise of the airway. Because the attacks he described usually lasted a matter of hours rather than days, the length of time we commonly associate with HAE today, we cannot be completely certain that the attacks described 124 years ago were hereditary angioedema. A few years later in 1888, Osler described the disease observed in each of five generations of a family and identified the autosomal dominant inheritance that we now associate with the disease [3].

Hereditary angioedema is characterized by sporadic episodic swelling, usually of the hands and feet, but occasionally of the genitalia, face, tongue, and larynx [4]. The swelling is due to edema of the dermal layers of the skin caused by leakage of plasma from capillary or more likely postcapillary venules and is often not well circumscribed. It is described as brawny, nonpitting edema. The swelling is never associated with pain, although the swelling alone with loss of flexibility of the tissues may cause some discomfort, if it involves the tissues around a joint. Patients commonly also have episodic swelling of the wall of the bowel leading to severe abdominal pain. The abdominal pain is often spasmodic rather than steady and presumably increases with each peristaltic wave; this suggests that there is an element of bowel obstruction associated with the attacks. In many patients, vomiting, particularly early in the attack, is a regular feature of the episode. Patients

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may have constipation associated with an attack, but this is not constant and diarrhea is sometimes observed. On physical exam the abdomen often has few bowel sounds at the height of an abdominal attack, but this is also not constant, and rushing bowel sounds may be heard. Although the patient usually has a protuberant abdomen with a great deal of tenderness and at times rebound tenderness and guarding, this is not a rigid surgical abdominal exam.

Many males describe episodic swelling in the genital area with swelling involving the testes and penis. In my experience the frequency of genital attacks is low, but a high proportion of males have had at least some genital attacks. In general, swelling, although at times uncomfortable, is not life threatening, except when it involves the airway. However, when the swelling does involve the airway it can lead to asphyxiation and death. In studies outlining the clinical syndrome, which we reported in 1976, we noted that about one third of untreated patients, identified by our patients as family members with the disease, had a history of asphyxiation [4]. Clearly this is a high figure, because the family members who would be remembered are the ones who had the most severe disease, but nevertheless, this is a sobering number. Attacks of abdominal angioedema, although not life threatening, cause severe pain and patients are often taken to the emergency room and operated on because of the severity of the clinical symptoms.

In the average patient, attacks grow more severe for about a day and a half and then clear over another day and a half, but there are many exceptions to this rule. There are patients whose attacks generally last less than 24 hours, and there are patients whose abdominal pain attacks last 4 or 5 days and whose peripheral swelling attacks last on average as many as 9 days. Thus, the variability of this disease is really quite remarkable.

Angioedema attacks are often heralded by a prodrome. At times the prodrome consists of a feeling of tingling in the area where the attack will start for an hour or so before the attack. Presumably this represents the release of mediators that will induce capillary or postcapillary venule leakage, ultimately leading to attacks. Nevertheless, there are rare patients who have no prodrome and some patients who have prodromes for as long as 24 hours before the onset of an attack. At the start of an attack, some patients will have erythema marginatum, which they often describe as red circles on the skin. This rash, which often occurs at the start of an attack, is nonpruritic and not raised, and patients often remark that they would not know they had the rash unless they saw it or someone pointed it out. Again, they are not an invariant feature of the disease; about one third of patients have erythema marginatum at the time of an attack.

Although attacks are sporadic and often do not have a clear initiating cause, many patients note that pressure will often bring on an attack. Thus, a person who mows the lawn with a power lawn mower may find that the hands swell up or a woman who is a seamstress and uses a pair of scissors for a long time may note that the hand with which she used

the scissors swells up. In general, attacks are not symmetrical and often extend locally, but they may pass from one hand to a foot or one hand to the other hand, and so forth. A second precipitating cause that patients notice is emotional stress. Often they find that for unknown reasons at times of tension or high stress, their attack frequency increases. Thus, a student who has a great deal of stress surrounding an examination may have an attack before the examination. A woman confided in me that in an unhappy marriage, she had many attacks and when she got divorced and remarried to a man with whom she was more compatible, her attack frequency decreased markedly. In our initial series we noted that about one third of patients noted stress-precipitating attacks and one third noted trauma as a cause.

Attacks usually begin in childhood, but they may begin at any age. There are patients with HAE whose first attacks began at age 90. Presumably they had the biochemical abnormality all of their lives and something brought on the sudden conversion to attacks of HAE at this late age. Often initiation of use of angiotensin-converting enzyme (ACE) inhibitors is the event that activates long-standing quiescent disease [5]. ACE is important in the catabolism of bradykinin and presumably by inhibiting this enzyme, the inhibitor precipitates the bradykinin-induced attacks. In general, however, attacks start in childhood and are quite mild. Because children often have attacks of abdominal pain associated with gastrointestinal viruses and so forth, they are often not remarked upon by the patient's family or pediatrician. However, at the time of puberty, it is common for attacks to become much more severe and it is then that the full-blown syndrome develops. Presumably, the attacks are of equal severity and frequency in men and women as predicted by the autosomal dominant inheritance, but I and most physicians who have taken care of many patients over the years have noted a preponderance of women coming for care. This may represent selection bias but may be a reflection of hormonal influences on disease severity. Early on, we noted that estrogens cause attack frequency to increase and for attacks to become more severe [4,6]. These estrogens may be of many types including artificial estrogens and natural products like Premarin. Some women are exquisitely sensitive to estrogens, and very tiny amounts of estrogen taken to relieve symptoms of menopause may be enough to increase attack frequency and severity; it is occasionally true that a woman can be treated by simply taking her off 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 discussed earlier. These attacks of edema are never associated with bowel wall necrosis, but may be sufficiently severe to cause obstruction of the gastrointestinal (GI) tract. On GI series during attack, there is usually spiculation or thumb printing of the mucosa, representing edema of the rugae of the GI tract. Occasionally, repeated attacks preventing adequate biliary drainage can lead to gallbladder disease, or attacks preventing pancreatic drainage can lead to pancreatitis.

The most dangerous attacks are those that affect the airways. Often these attacks start in the mouth and extend to the larynx. Since trauma can sometimes bring on an attack, these patients learn to fear the dentist because they may have particular difficulty following injection of Novocain into the gums. Their teeth may be in poor repair. The attacks are presumed to be the same as those that affect peripheral sites, but because the airway, particularly in the region of the vocal cords, is constricted, a relatively small amount of edema may do great damage. As with peripheral attacks, these attacks usually increase in severity for about 1 and a half days and then resolve over the same period of time but again this may be variable.

HAE is often grouped with the allergic disorders, but there is no evidence that it is allergic in nature. A few of the patients have urticaria at times, but it is by no means common and one must assume that the incidence of allergies, hives, and so forth, in the HAE population is the same as in the general population. Patients can go for extended periods of time without HAE attacks and then once again become far more severe, and it is not known why the disease tends to wax and wane. Although this has not been carefully studied, one gets the impression that in certain families the pattern of attacks may be similar. For example, in my experience there are families that have mostly abdominal pain attacks and even an occasional family with an unusually high incidence of HAE affecting the throat. Patients with only abdominal attacks have been reported [7]. An interesting point that has not been studied in detail is that patients noted, before any useful therapy was available, that after a severe attack they often were attack free for a period of time. Thus, if they needed dental work done, they might wait until they had a very severe attack and then over the next several days go to the dentist, when they would find that they would be resistant to attacks and they could safely undergo extractions and other procedures. The reasons for this are unknown.

Patients with HAE in general do well with pregnancy. Usually their attack frequency is unchanged in the first trimester, but by the time the second trimester starts, their attack frequency is decreasing and they note that their third trimester is the best period that they have had in years. I have never seen a patient have an attack of HAE associated with the trauma of delivery, but it is not uncommon to have patients develop HAE attacks 3 to 7 days after the delivery is completed. Although we speak here of average patients, I have seen patients get worse during pregnancy more than once and when this happens, it represents a difficult management problem. In a few patients attacks have become so severe during the last trimester of pregnancy that we treated them with infusions of fresh frozen plasma three times per week to keep them relatively free of symptoms (see section on prophylaxis). I have no information that would explain why in a very few patients attacks become much more severe in late pregnancy, but I have wondered whether these patients might have an area of necrotic placenta that activates an inflammatory reaction, further catabolism of C1 Inhibitor, and an increase in attacks.

Although this has never been carefully evaluated, some investigators believe that attacks become less severe as patients age.

A question arises as to whether patients with HAE are not healthy psychologically. Clearly many patients are healthy psychologically, but many people have been struck by the fact that a subgroup of patients appears to have more psychological problems than might be expected. Patients at times have seen family members die of asphyxiation because of a disease that they themselves have, and other patients know of family members who have died. This I am sure leads to psychological difficulties. In any case, some years ago with Mary Huber, RN, we had formal psychological testing performed on a group of patients. They proved to demonstrate more impulsive behavior than a healthy patient group. Several patients have told me that they don't feel healthy psychologically at the start of an attack and I cannot but wonder whether the mediators that are responsible for attacks affect the brain.

Pathophysiology of hereditary angioedema

This topic will not be covered in detail here; see the article by Davis in this issue. In 1962 Landerman and colleagues [8] studied patients with hereditary angioedema, using what would now be considered crude technology, and suggested that kinin generation in their blood might be poorly regulated, and that the patients had an inherited defect in an inhibitor to a permeability factor, probably kallikrein. In retrospect this was an important observation. However, the great breakthrough in our understanding of angioedema came with the important work of Dr. Virginia Donaldson in 1962 [9]. Dr. Donaldson was conducting research in laboratories at Case Western Reserve Medical Center, close to those of Dr. Irwin Lepow. Dr. Lepow was investigating the properties of a newly defined protein that controlled the activation and activity of the complement protein C1. C1 is a complement system protein that circulates as an inactive precursor and is activated during certain immunologic reactions. At that time the new protein was termed C1 esterase inhibitor, because the assay in use for C1, the enzyme that was inhibited by the new protein, was cleavage of a synthetic ester substrate. Currently, the name has been shortened to C1 inhibitor. Lepow had prepared antibody to C1 inhibitor and Dr. Donaldson studied a variety of patients including patients with HAE for the level of protein in their blood. She made the seminal observation that patients with HAE have low circulating levels of C1 inhibitor, an observation that has stood the test of time [9]. This finding allowed for studies of the pathophysiology of HAE that have continued to this time (see chapter on pathophysiology). Further studies of Rosen and colleagues [10], evaluating a group of patients with HAE, demonstrated that 85% of patients (Type 1) have low levels of C1 inhibitor and 15% of patients (type 2) have normal or elevated levels of a poorly functioning protein. Presumably type 1 patients have a gene that leads to no C1

INH synthesis or failure to secrete protein and type 2 defects lead to a secreted but nonfunctioning protein.

The action of C1 inhibitor on C1 is twofold. It controls the rate of activation of C1 and it inactivates the active protein. C1 is the first protein component of the classical complement cascade. It circulates as an enzymatically inactive three-part molecule, C1q, C1r, and C1s, the parts held together in the presence of Ca^{++} . C1 binds via the C1q subunit to antigen-antibody complexes of the correct sort and becomes activated, that is it develops enzymatic activity. The function of activated C1 is to cleave the next two proteins in the classical complement pathway sequence, C4 and C2. It was quickly noted that patients with HAE almost always have low levels of C4 and C2, even between attacks. A rare patient has normal C4 and C2 levels between attacks. The protein that follows C2 in the sequence of steps in the complement cascade is C3 and the level of C3 is virtually always normal in these patients [4,11]. This reflects the fact that there are both circulating and cell membrane-bound proteins that regulate the level of C3 and turn off untoward activation of enzymes that would cleave C3 and lower its level in serum. Thus, in general, patients with HAE have normal C1 levels, low levels of C4 and C2, and normal levels of C3. Their level of C1 inhibitor is usually in the range of about one-third the lower limit of normal, but again, there is considerable variability in this level from patient to patient.

With the understanding that patients with HAE have constant activation of C4 and C2, attention turned to these two proteins as the possible source of the mediators causing this disease. It seemed extremely likely that a mediator was released in blood or tissue when this regulatory protein was at low levels or not properly functioning and the likeliest candidates for the source were C4 and C2. A series of papers were written that suggested that a cleavage product, C2b, could be acted upon by plasmin, another protein found to be inhibited by C1 INH, to create a peptide termed C2 kinin that mediated capillary leakage; C2 peptide became a candidate for the cause of attacks [12,13]. The question of histamine contributing to attacks was raised as well. Brickman and colleagues [14] reported that histamine concentration does not rise in the urine during attacks and appears to be normal at all times, confirming the suggestion that, unlike allergic diseases, this disease is not allergic in nature and not due to histamine release and mast cell degranulation.

Studies of the C1 inhibitor led to an understanding of the fact that this protein inhibits many of the mediator cascades in serum. These actions of C1 inhibitor are reviewed elsewhere in this issue.

There are a number of issues related to the pathophysiology of HAE that are not quite clear and may be important in the future as we sort out the various aspects of the basis of this disease: It was shown early on that the level of C1 inhibitor is not associated with the severity of disease, although all patients have low C1 inhibitor or a nonfunctioning protein [4]. In other words, patients who have a mildly decreased level may have very severe

clinical symptoms and patients who have an extremely severe depression may have a very mild case of the disease. The reasons for this are unclear. Moreover, subcutaneous injection of bradykinin into experimental animals or humans leads to severe pain, because it stimulates pain fibers. Patients with HAE have no pain associated with attacks. Injection of bradykinin into animals causes hypotension. Patients with HAE rarely become hypotensive unless they have had a severe fluid shift from the intravascular space into edematous bowel or other tissues.

Another fascinating finding is that patients with HAE have a higher than normal incidence of autoimmune diseases, although the diseases are often mild [15–17]. The type of autoimmune disease is quite variable and appears to reflect the genotype and underlying predisposition of the patient. Disease can range from systemic lupus erythematosus (SLE), to hypo or hyperthyroidism, to inflammatory bowel disease. Careful study of a large group of patients led to the finding that these patients have an elevated level of T helper cells and that the degree of elevation was inversely correlated with the plasma C4 level [18]. Complement activation is known to affect the afferent limb of the immune response and presumably constant activation of complement in this patient group leads to low C4, increased T helper cell activation, and an elevated incidence of autoimmunity.

Treatment of hereditary angioedema

For convenience, therapy of HAE is usually divided into chronic long-term therapy, short-term prophylactic therapy, and treatment of acute attacks.

Chronic long-term therapy

It is humbling to note that an approach to chronic treatment of HAE using methyltestosterone was detailed in the literature several years before any discussion of pathophysiology began and before the importance of C1 inhibitor was noted [19]. Because the reported therapy fit no reasonable theory as to why it should be effective, and because it was of a class of drug thought to be unlikely to be effective in angioedema, the observation was lost for over a decade. In 1960, Spaulding [19] described a single family with HAE treated with methyltestosterone. They reported a limited double-blind study suggesting that the drug was quite effective in this family; however, this method of therapy never came into use and even the report's existence was lost to investigators in the field. With the observation that estrogens made HAE more severe, the fact that patients with HAE improved during pregnancy and had no trouble with the trauma of delivery, and the increase in clinical symptoms at the time of puberty, my group first attempted a study of progesterone in the treatment of HAE. Although we never reported our findings, we found that patients all felt better on progesterone therapy, but in

our small group of patients the attack frequency did not decrease. We then turned to the study of Danazol, an impeded androgen that was being developed for administration to women as a contraceptive [20]. This drug was a gonadotropin inhibitor and therefore could be expected to decrease estrogen levels in both males and females. Because it was an impeded androgen being developed as a female contraceptive, it had little androgenic activity and could be used in most women. It was for this reason that we chose to do a double-blind study of Danazol. At about the same time others were studying Stanazolol and methyltestosterone for the treatment of HAE. Our study design, developed by a brilliant statistician Dr. David Alling, was of particular interest. Patients all served as their own controls. Patients were given a 28-day course of drug or placebo. If, during the course, the patients had an attack they were considered a drug failure and went on to the next blind course. The patients were asked whether they were taking drug or placebo and the courses were sufficiently short that they could not identify the courses that included drug. The results were striking (Table 1). These were severely affected patients and almost every placebo course was attended by an attack. All but one course on drug was attack free. Thus we found that Danazol was highly effective in treatment. Similarly, all of the studies of impeded androgens confirmed the findings of Spalding [21–23]. Further work has suggested that the only androgens that are useful in therapy are methylated androgens that must be given orally. Testosterone, for example testosterone patches, do not prevent attacks of HAE. In our studies, we were surprised to find that not only was the drug, Danazol, extremely effective in treatment, but in most patients, it led to a marked increase in the blood levels of C1 inhibitor. This was associated with clinical and biochemical improvement. With the increased levels of C1 inhibitor, the C4 level tended to return to normal and the clinical symptoms disappeared. Thus, androgens appeared to be causing the synthesis of a protein known to be produced in the liver. We found the synthesis of all proteins produced in the liver is not increased; for example, the blood levels of albumin and C3 were not changed. Although some studies suggest that impeded androgens increase messenger RNA for C1 inhibitor in peripheral blood cells, this is not confirmed in other studies, and there is still no definitive study of the effect of impeded androgens on C1 inhibitor synthesis [24–26]. Nevertheless, most investigators assume that increased hepatic synthesis of C1 inhibitor is its mechanism of action. It became clear that it was impossible to predict in

Table 1
Treatment results

	Total courses	Attack-free courses	Attacks
Danazol	42	41	1
Placebo	46	3	43
Total	88	44	44

any individual patient the dose of androgen that would be required to reliably decrease or terminate attacks [27]. In the case of Danazol, there are rare individuals who do not respond to 800 mg a day and others who respond very satisfactorily to 50 mg once a week. We tend to start treatment at 200 mg three times a day, because this dose almost always prevents attacks and the patient is therefore reassured and relaxes. We then progressively lower the dosage slowly over months to determine the lowest dosage that will prevent attacks (Table 2). All impeded androgens have a number of potentially important side effects including masculinization, headaches, lack of libido or increased libido, hair gain or loss, liver function abnormalities including possible peliosis hepatic, and abnormalities in serum lipids (Table 3) [28–30]. Danazol can induce hematuria caused by low-level cystitis or bladder telangectasia [28]. These side effects have tended to be mild and in my hands the abnormalities have disappeared when the drug has been stopped. When faced with mild transaminase elevations or minimal hematuria, we have at times continued treatment, when the only other choice was resumption of attacks, and our patients have never gotten into trouble. In particular we have never had hematuria develop into hemorrhagic cystitis as sometimes occurs in patients on Cytosan therapy. Obviously, the various untoward possibilities must be discussed with patients in detail. I have had no luck in switching patients from one androgen to another to avoid side effects.

Despite the side effects, most patients are so pleased to be offered a drug that is functionally active and relieves their symptoms that they insist on facing up to the dangers and taking the drug. Androgens are not useful in terminating ongoing attacks, since it often takes at least 48 hours for the androgen to begin to have an effect.

A variety of impeded androgens are now available in the United States. This author has most experience with Danazol. However, others have used other impeded androgens and there clearly are patients who prefer one impeded androgen over another. Oxandrolone has been recommended, especially in children [31]. We have tried to switch from one impeded androgen to another and have never been able to decrease drug toxicity by this method.

Table 2
Effective therapeutic dose of danazol^a

Danazol dose	% with clinical response
600 mg	95
400 mg	88
300 mg	58
200 mg	11

^a At the lowest effective therapeutic dose there may be no evidence of a biochemical response.

Table 3
Side effects of danazol therapy

Side effect	No.	%
Abnormal liver function tests	9	16
Hematuria	9	16
Myopathy	21	38
Myalgias, cramps	17	30
Elevated CPK	11	20
Headache	7	16
Abnormal menses requiring Rx	5	13
Decreased libido	5	9
Hair loss	7	13
Anxiety reactions	18	32

Abbreviation: CPK, creative phosphokinase

Following the observation of Spaulding, but before the other impeded androgens were found to be effective in the treatment of HAE, it was noted that epsilon aminocaproic acid (EACA) is effective in the treatment of the disease [32–34]. Because it was believed that plasmin acting on C2 might generate the angioedema causing peptides, it was decided to use this plasmin inhibitor. In an empiric noncontrolled study it was found that symptoms of angioedema were improved. This was confirmed in a limited number of patients, first in Sweden and then in England [33,34] (Table 4). We performed the first double-blind study that confirmed the activity of epsilon aminocaproic acid in the treatment of this disease [35]. Similar to the Danazol study, patients were treated with drug or placebo for 1-month courses and each patient served as his or her own control. There were two attacks in 21 courses of EACA and each of 24 courses on placebo ended in an attack. There was no change in C1 inhibitor or C4 titer during drug treatment. Thus, the drug proved to be very effective. A dose-finding study suggested that most patients respond to about 8 g EACA per day. Others showed that tranexamic acid, a circularized relative of EACA, is far more effective on a per milligram basis [36]. It was interesting that in our studies, patients on EACA noted the prodrome of HAE attack, but the attack spread slowly. This

Table 4
Treatment of hereditary angioedema with epsilon aminocaproic acid

Case (Sex)	Age, y	Courses with EACA		Courses with placebo	
		Without attacks	With attacks	Without attacks	With attacks
1 (M)	22	2	2	0	4
2 (F)	30	5	0	0	5
3 (F)	47	5	0	0	5
4 (M)	57	4	0	0	5
5 (F)	22	3	0	0	5

Data from Frank MM, Sergeant JS, Kane MA, et al. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema: a double-blind study. *N Engl J Med* 1972;286(15):808–12.

was quite different from the situation with the impeded androgens, where the patient noted no prodrome and no attack. In our hands, EACA has proven to be a very difficult drug to use. We found early on that patients sometimes develop severe muscle toxicity on EACA. One of our early patients had to be carried to the phone because she had severe weakness from EACA, although she was having relief from her HAE. Work-up showed a markedly elevated CPK (creatine phosphokinase) and aldolase. The weakness and biochemical abnormalities cleared when the EACA was discontinued. The reason for the severe muscle toxicity noted with these drugs is unknown. It is interesting that even on androgens, some patients will detect muscle toxicity and I think it quite likely that patients with HAE have a muscle problem as well as an angioedema problem, although its nature has never been clearly defined. As with impeded androgens, there is a considerable time lag (probably 48 hours) before the effect of EACA in controlling angioedema is manifest. Since over 90% of the drug is excreted in the urine in 6 hours the reasons for this are unclear. Since the drug treatment does not lead to an increase in the level of C4, I do not believe that the mechanism of action of this agent is to act as a C1 inhibitor.

Chronic disease treatment for HAE is satisfactory for most patients, but it requires daily treatment. However, both androgens and plasmin inhibitors are not useful in some patients. The treatments available are not proven to be safe in pregnant women where masculinization of the fetus on androgens can occur. In some women the side effects are intolerable. Finally some patients do not respond to therapy.

The article in this issue by Davis discusses C1 inhibitor, the characteristics of the protein, and its mechanism of action and this material will not be reviewed here. The C1 inhibitor gene has eight exons, four of them preceded by ALU sequences. It is believed that one reason for large deletions in the gene is improper alignment of the gene on chromosomes during meiosis. This would lead to a truncated protein ultimately leading to no product. A large number of mutations over much of the C1 inhibitor molecule have been described in patients. It has been found that those patients with type 2 HAE for the most part have single point mutations near the active site, thus preventing the formation of a C1 inhibitor enzyme complex. Treatment of acute attacks with C1 inhibitor is discussed below, but there is at least one report that suggests that weekly C1 inhibitor infusions are effective as chronic prophylactic therapy [37].

Short-term prophylaxis to prevent attacks

There are times when patients with HAE require short-term prophylaxis to prevent attacks. For example, if a patient is to undergo dental surgery, it is essential that attacks be prevented. Similarly, if a patient is in an automobile accident and is not having an attack, it may be prudent to prevent attacks from occurring. In these situations in which prophylaxis is

important, fresh frozen plasma has been used successfully to prevent attacks [38–40]. Two units of fresh frozen plasma given the night before surgery or even in many cases on the day of surgery have prevented attacks, and it has been possible to treat patients as if they did not have HAE.

Presumably, the fresh frozen plasma replaces the missing C1 inhibitor, which acts to control attacks. As discussed in section on therapy of acute attacks, substrates that can be acted on to release mediators such as high-molecular-weight kininogen may be present in the infused plasma and may exacerbate an ongoing attack, but if the patient has no signs of an attack at the time of the infusion, this is not a problem. In our published studies we infused the plasma the night before surgery to be certain that the molecule had sufficient time to leave the circulation and enter the extracellular space, but recent experience suggests that this is not necessary. Since the half-life of C1 inhibitor in the circulation of patients is about 40 to 60 hours, it is not reasonable to expect the effectiveness to last more than about 3 days, although experience suggests that the effect of the protein may actually last longer.

There are reports in the literature of using androgen or plasmin inhibitors as prophylaxis in these situations [41,42]. Androgen as noted in the section on chronic therapy is useful as chronic therapy in preventing attacks of HAE and is not useful for acute attacks. We have elected not to use attenuated androgens for the most part in prophylaxis of attacks. An occasional patient will have an attack on adequate chronic prophylactic therapy. For example, I have seen a patient develop complete respiratory obstruction on chronic Danazol, 600 mg per day. I therefore am uneasy about using chronic androgen therapy to prevent attacks in potentially life-threatening situations, when there is no adequate back-up therapy. Nevertheless, there are those who have used it successfully. In a similar vein, I do not use plasmin inhibitors as prophylaxis for procedures, although others have reported success with this treatment. There is no question that patients can have attacks on plasmin inhibitor therapy and again at this time there is no adequate therapy. Once C1 inhibitor or other agents that reliably terminate attacks is available, it may be reasonable to use attenuated androgens or plasmin inhibitors with the understanding that if an attack starts, the patient will be treated rapidly with one of these other agents.

Therapy of acute attacks

In the United States, therapy of acute attacks is the area that has received the least attention and is most unsatisfactory. In the United States, patients receive supportive therapy. They are treated with epinephrine, which in this investigator's opinion often has a mild, but not dependable, effect in limiting attacks, being beneficial particularly early in attacks. Patients are also given antihistamines for sedation and are usually given glucocorticoids, although there is no evidence that glucocorticoids have efficacy. I treat patients with

EACA as well (16 g a day for the first day, falling back to 8 g a day), not because the EACA terminates attacks but because the physician can be assured that 48 hours later the attack will begin to resolve. Since EACA is available in intravenous form in most hospital pharmacies and has very little toxicity in this acute setting, there is little reason for not adding it to therapy, unless there is a contraindication. Contraindications would include advanced age, previous thrombosis, or procoagulant state. Clearly, airway management is the most important aspect of treatment of acute attacks of HAE and patients are given nasotracheal intubation if possible, before there is complete airway obstruction, or a tracheotomy. Inability to swallow secretions, or a change in the tone of the voice, often are indicators of impending airway obstruction. Acute attacks of abdominal pain are usually treated with narcotics. The latter are the only agents that relieve the acute pain. Patients with HAE are particularly prone to develop narcotic addiction, and care must be taken to prevent the overuse of narcotics in this patient group. We particularly try to avoid the use of Demerol, a favorite of the addicted patients. As mentioned, epinephrine sometimes has an effect and we use it for abdominal as well as peripheral attacks. Narcotics given very early in an attack for unknown reasons may terminate the attack.

In 1969 Pickering and his colleagues [43] published a report of treatment of acute angioedema attacks with fresh frozen plasma and many patients will recount successful treatment of attacks with fresh frozen plasma. Those of us who have taken care of many patients with HAE in acute, sometimes life-threatening situations have noted that a few patients get worse following fresh frozen plasma. Presumably, as discussed above, substrate for the various active enzymes is present in fresh frozen plasma and the replacement of fresh frozen plasma replaces substrate as well as the inhibitor. Depending on ratio of substrate and inhibitor, the edema formation may get worse before it gets better. Since in this country we do not have a satisfactory treatment for acute attacks of HAE, many of those who have taken care of many patients feel that it is undesirable to treat a patient with fresh frozen plasma at the time of a possible acute life-threatening attack.

When it became apparent that patients with HAE have low levels of C1 inhibitor, the idea of using C1 inhibitor to terminate attacks was advanced. In the United States, our group working with the American Red Cross developed a C1 inhibitor preparation, which we studied in a group of patients with HAE [44]. We reported in 1980 that the preparation successfully terminated attacks in a non-double-blind study. Similarly, groups in Europe studied a Dutch Red Cross preparation and presented evidence in an open-label study that this material could be used to terminate attacks [45]. Behring Germany prepared C1 inhibitor as a commercial product for treatment of these patients. This material has been on the market for over 25 years and is used extensively in many European countries. The experience of all investigators is that such material terminates attacks [46]. It was essential that efficacy be shown in a double-blind study, since psychological

factors clearly play a role in attack frequency and severity. In 1996, Waytes and colleagues, using a preparation prepared by the Austrian company Immuno, in a double-blind placebo-controlled trial, demonstrated that purified C1 inhibitor terminates attacks and that attack termination is prompt [47]. Thus, it is clear from the weight of experience and evidence that purified C1 inhibitor can be used to terminate attacks of HAE.

The approach to treatment of HAE in various countries has recently been outlined in a number of reports. [48–50].

Purified C1 inhibitor, made available by each of two pharmaceutical companies, Lev and ZLB Behring, is currently in clinical trials in the United States as a drug for terminating attacks. As discussed in other chapters, currently there are several other therapies under study. The Dutch company, Pharming, is testing the usefulness of a recombinant human C1 inhibitor made by introducing the human gene into rabbits in such a way that it is secreted into the milk. Attacks of HAE appear to principally involve the kinin generating system and a peptide that inhibits kallikrein, the enzyme that generates bradykinin from high-molecular-weight kininogen (DX88) and a bradykinin receptor type 2 antagonist (Icatibant) are both in clinical trials. Early 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 a description of the gene defect, the characterization of the gene, the understanding of the molecular defects that lead to HAE, and to a great extent an understanding of the pathophysiology of this disease. We have gone from no therapy, to the development of very effective empiric therapy, to the development of much more specific therapy based on pathophysiologic understanding. Although experiments to replace or correct the gene defect in patients with HAE have not been attempted, that is the only step left in developing a complete cure of this illness. Patients have gone from a life-threatening situation to a situation where they can be assured that in the future, their lives will be far more comfortable and productive.

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