Hereditary Angioedema

* A Broad Review for Clinicians

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Hereditary angioedema (HAE) is an autosomal dominant disease that afflicts 1 in 10000 to 1 in 150000 persons; HAE has been reported in all races, and no sex predominance has been found. It manifests as recurrent attacks of intense, massive, localized edema without concomitant pruritus, often resulting from one of several known triggers. However, attacks can occur in the absence of any identifiable initiating event. Historically, 2 types of HAE have been described. However, a variant, possibly X-linked, inherited angioedema has recently been described, and tentatively it has been named “type 3” HAE. Signs and symptoms are identical in all types of HAE. Skin and visceral organs may be involved by the typically massive local edema. The most commonly involved visceras are the respiratory and gastrointestinal systems. Involvement of the upper airways can result in severe life-threatening symptoms, including the risk of asphyxiation, unless appropriate interventions are taken. Quantitative and functional analyses of C1 esterase inhibitor and complement components C4 and C1q should be performed when HAE is suspected. Acute exacerbations of the disease should be treated with intravenous purified C1 esterase inhibitor concentrate, where available. Intravenous administration of fresh frozen plasma is also useful in acute HAE; however, it occasionally exacerbates symptoms. Corticosteroids, antihistamines, and epinephrine can be useful adjuncts but typically are not efficacious in aborting acute attacks. Prophylactic management involves long-term use of attenuated androgens or antifibrinolytic agents. Clinicians should keep this disorder in their differential diagnosis of unexplained, episodic cutaneous angioedema or abdominal pain.

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Angioedema is an intense, usually disfiguring, temporary swelling of a localized body area. It most commonly occurs as part of an allergic response to exogenous substances and conditions. Such substances may be dietary in origin, eg, shellfish and other seafood, or may be environmental, as is the case with temperature-related angioedema. The sporadic exogenous phenomena that result in angioedema may be prevalent in up to 10% of the population. Use of some drugs prescribed for common ailments, such as angiotensin-converting enzyme (ACE) inhibitors for hypertension, renal disease, and cardiac disease, can also induce an adverse reaction in apparently healthy individuals and result in angioedema.

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In a few individuals, angioedema occurs because of an intrinsic defect that abolishes one of the body’s several safeguards against such occurrences. This defect allows a cascade of events that culminates in symptoms. This form of angioedema occurs as a result of either an inherited defect
in C1 esterase inhibitor (C1-INH) activity or an acquired deficiency of C1-INH. The inherited form of the disease, known as hereditary angioedema (HAE), is rare, although it is more common than acquired angioedema (AAE).

Traditionally, 2 types of HAE have been described. Type 1 HAE, which is estimated to occur in 80% to 85% of patients, is caused by the decreased production of C1-INH, resulting in subnormal blood and tissue inhibitor activity. In type 2 HAE, which occurs in the remaining 15% to 20% of patients, normal or elevated quantities of functionally impaired C1-INH are produced. Recently, a third type of HAE in which C1-INH levels and function are normal has been described, so far only in women.

All types of HAE have identical symptoms characterized by edema of 1 or several organ systems. The skin, gastrointestinal tract, and respiratory tract are most commonly involved. Cutaneous angioedema involves deeper layers such as the inner dermis and subcutaneous tissue, unlike urticaria, which is common in angioedema from other causes and involves the epidermis and upper dermis. The absence of pruritus, and the often-present associated visceral symptoms, makes angioedema distinguishable from urticaria.

HISTORY OF HAE

J. L. Milton first described angioedema in 1876. The subsequent article by Quincke in 1882 was the first to assign the name angioneurotic edema to the disease. A review of the literature suggests that the word neurotic was used as part of the name in an attempt to describe the observed effect of mental stress on exacerbations of this disease. In 1888, William Osler published the first article describing a hereditary form of angioneurotic edema; however, discovery of the biochemical basis for the disease did not occur until several decades later. A seminal study published in 1963 by Donaldson and Evans first described the biochemical abnormality responsible for HAE: the absence of C1-INH in patients with the disease. Since that study, the body of knowledge regarding the clinical manifestations, spectrum, pathophysiology, and genetic basis of the various forms of angioedema has broadened considerably.

CLINICAL PRESENTATION

Symptoms of HAE are usually mild or nonexistent during early childhood, typically first manifesting during the second decade of life. However, a few patients present during their first decade. Although some attacks lack an identifiable trigger, most are associated with trauma, medical procedures, emotional stress, menstruation, oral contraceptive use, infections, or the use of medications such as ACE inhibitors.

Typically, acute HAE manifests as marked diffuse edema involving all skin layers and layers of the walls of hollow visceral organs and solid organs. Most visceral organs are susceptible and can be affected singly or in any combination. Typical attacks of angioedema last approximately 2 to 5 days before resolving spontaneously. Skin edema is non-pitting, with ill-defined margins, and most commonly affects areas of the face, extremities, and genitals. Facial areas typically involved are the lips, eyelids, and tongue. More often, genital edema occurs as a result of trauma during intercourse, parturition, and even horseback riding. During acute attacks, patients may develop a rash similar to that seen in urticaria. Unlike urticaria, however, the skin lesions associated with HAE are erythematous but not warm, painful, or pruritic.

When edema occurs in the walls of the respiratory and gastrointestinal tract systems, the most obvious and distressing symptoms of HAE occur. Thus, laryngeal, nasal, and sinus edema may lead to respiratory tract compromise and death from suffocation. In such circumstances, tracheostomy can be lifesaving because the edema associated with acute episodes typically occurs at, or above, the larynx. If undiagnosed, mortality from HAE can be as high as 30% to 40%, mostly due to upper airway obstruction. Even in those with known HAE, unnecessary delay in seeking or administering appropriate medical treatment has often resulted in asphyxiation. Asphyxiation can occur at any age and has been documented in individuals as young as 4 weeks and as old as 78 years. Patients with no previous history of upper airway involvement during acute HAE exacerbations still run a risk of asphyxiation. In a recent study, 5 of 6 individuals who asphyxiated during acute HAE had never experienced upper airway involvement during previous attacks. The time from symptom onset to asphyxiation also varies, ranging from as little as 20 minutes to as long as 14 hours. Transient pleural effusions, sometimes with cough and mild pleuritic chest pain, can also occur.

Gastrointestinal tract symptoms of HAE, caused by visceral edema, result in varying degrees of intestinal obstruction. Thus, typical symptoms of gastrointestinal tract involvement are anorexia, vomiting, and crampy abdominal pain that can be severe. The abdomen is typically tender to palpation, usually without guarding. Ascites, as a result of fluid extravasation into the peritoneal cavity, occurs occasionally. In one study, ascites from acute HAE was significant enough to cause hypovolemic shock; however, the concomitant vasodilation known to occur during acute exacerbations probably played an additive role. Diarrhea can also occur, particularly as the acute episode resolves. Gastrointestinal tract HAE presenting as severe cramps, nausea, and vomiting, and unaccompanied by cutaneous symptoms, can be mistaken for an acute abdomen. This occasionally leads to unnecessary surgical abdominal exploration and the excision of otherwise normal gallbladders and appendixes. In fact, without a high index of suspicion, gastrointestinal tract HAE may be undiagnosed for decades despite patients presenting repeatedly to the emergency department with these complaints. In such circumstances, symptoms have occasionally been attributed to psychosomatization, with patients inappropriately referred for psychiatric assessment. Attacks of gastrointestinal tract angioedema generally subside within 12 to 24 hours, whereas cutaneous angioedema persists for several days.

Two case reports describe migraine-like and transient ischemic attack symptoms during acute HAE. Others have reported sei-
zures and hemiparesis. These symptoms are thought to be caused by local cerebral edema and consequent cerebral hypoperfusion, caused by the acute HAE episode.

Fever and leukocytosis are unusual in acute HAE, and their presence during an attack in a person known to have HAE should raise suspicion that another process, such as infection or intra-abdominal catastrophe, may be the inciting event for the acute exacerbation.

Pregnancy has been associated with a decrease in serum C1-INH levels, even in women with no genetic evidence of HAE, but pregnancy does not increase the risk of attacks. In fact, pregnancy has often been associated with decreased attack frequency. These counterintuitive observations may be explained by the finding that the total amount of circulating C1-INH actually increases during pregnancy; however, a decrease in the measurable level occurs as a consequence of the significant physiologic increase in plasma volume that occurs concomitantly. A study of one kindred with HAE suggested that significantly more pregnant patients with HAE (60%) experienced premature labor than did pregnant family members without HAE; however, a causal relationship has not been established. Levels of C1-INH are also decreased further in some pregnant women with preeclampsia and eclampsia, and the role of low C1-INH levels in these conditions is currently being investigated. Increased attack frequency has been reported in association with menstruation and oral contraceptive use.

**EPIDEMIOLOGIC CHARACTERISTICS**

Data on the epidemiologic characteristics of HAE are sparse. Estimates of its incidence worldwide vary, from 1 in 10,000 to 1 in 150,000 persons. Types 1 and 2 HAE have been reported in all races, and no sex predominance has been found. However, a recently described third type of inherited angioedema has been found only in women. Seventy-five percent of patients with HAE have cutaneous angioedema of an extremity as the first presenting sign of the disease. Recurrent abdominal pain and upper airway and facial edema occurred in 52% and 36%, respectively, of patients in one series. In 39% of these cases, patients could attribute their first episode to an identifiable traumatic event.

Most patients with symptomatic untreated HAE experience at least 1 acute exacerbation per month, and because each attack typically lasts a few days before spontaneously subsiding, it is estimated that individual patients can be debilitated by their symptoms for 20 to 100 days per year.

**PATHOPHYSIOLOGIC AND IMMUNOLOGIC FEATURES OF TYPES 1 AND 2 HAE**

C1 esterase inhibitor, an α2-globulin of approximately 105 kd, belongs to the serine protease inhibitor family that includes α1-antitrypsin and antithrombin. It is encoded on chromosome 11 and is synthesized mainly by hepatocytes, although peripheral blood monocytes can also synthesize significant quantities. Skin fibroblasts have also been shown to synthesize this protein, but their contribution to the body’s pool of C1-INH in physiologic circumstances in vivo is unknown. Cytokines, particularly interferon γ, can stimulate synthesis of C1-INH in these cells in vitro. Interleukin-6, an important proinflammatory cytokine, increases the release of C1-INH from HepG2 hepatoma cells in vitro. This action was potentiated by the presence of another proinflammatory cytokine, interleukin-1, which by itself has no effect on C1-INH synthesis or secretion. Thus, C1-INH synthesis in vivo can be regulated, at least in part, by these cytokines.

The major functions of C1-INH within the human body include the prevention of C1 complement autoactivation; inactivation of coagulation factors XIIa, XIIIf, and Xla; and direct inhibition of activated kallikrein. Its role in factor Xla inactivation is a minor one, however, with α1-antitrypsin being primarily responsible for inactivating this factor. In general, the direct inhibitory effect of C1-INH is achieved by the formation of irreversible covalent bonds with these substrates, forming inactive C1-INH complexes.

To facilitate a clear understanding of the role of C1-INH in the inactivation of its various substrates, brief reviews of the classical pathway of complement activation and of the contact (kallikrein/kinin) system are necessary.

**The Complement Cascade**

Nine complement components (C1-C9), and 2 pathways of complement activation (classical and alternative) have been described. C1 complement is a trimolecular heteropentameric complex composed of 1 C1q, 2 C1r, and 2 C1s components, all of which are linked through calcium molecules. In the classical pathway, interaction between the immunoglobulin Fab fragment and its target antigen results in complement activation, initiated through the binding of C1q to the constant heavy regions of the immunoglobulin Fc fragment. C1r is subsequently recruited, and complexes first with bound C1q and then with C1s. This binding activates C1s, which acquires esterase activity and cleaves C4, thereby initiating a cascade of events that generates a complex of complement fragments termed the membrane attack complex. This complex is responsible for the cell membrane damage that results in lysis of cells targeted by the specific immunoglobulins. During this cascade, C3a, C4a, and C5a are generated, cause increased capillary permeability, and contribute to edema and swelling of skin and organs that may be seen with massive complement activation, as occurs during an attack of HAE (**Figure 1**).

In humans, it is believed that circulating C1 can undergo autoactivation and that it does so in increasing quantities when C1-INH is insufficient or absent. A discussion of evidence for such autoactivation is beyond the scope of this review; however, several detailed articles have been written on the subject. C1 esterase inhibitor prevents this autoactivation of C1.
complement by causing dissociation of the C1q subunit and by forming an inactive C1r2-C1s/(C1-INH)2 complex.22,23 This complex is unable to cleave and activate complement components C4 and C2, the usual substrates of activated C1, thus keeping the classic complement pathway quiescent.22

Results of quantitative kinetic experiments32,33 suggest that C1-INH activity, approximately 90% of factor XIIa and its metabolite factor XIIIf (Figure 2). Approximately 42% of plasma kallikrein is inactivated by C1-INH activity, approximately 50% is inactivated by α2-macroglobulin, and the remaining 8% is inactivated by other minor inhibitors.

Inactive precursor components of the contact system include high-molecular-weight kininogen and prekallikrein. Factor XII is technically not a component of the contact system, but it plays a significant role in its activation. It is hypothesized that in healthy individuals, small quantities of factor XII are constantly autoactivated to factor XIIa, possibly by a multitude of contacts between circulating factor XII and negatively charged initiator surfaces within the body.24 Factor XIIa is cleaved during its metabolism to another active molecule, termed factor XIII. Unopposed activation of even small quantities of factor XII to factors XIf and XIIIf result in an increasing positive feedback loop, with factor XIfa cleaving and activating further molecules of factor XII. Because C1-INH is the major inhibitor of factor XIIa, a decrease in its level and activity allows generation of significantly increased quantities of factors XIfa and XIIIf. Trauma, such as that seen during surgery and dental manipulation, also exposes large areas of negatively charged tissue and endothelial surfaces, which also results in activation of circulating factor XII.9

Factor XIfa also cleaves prekallikrein to the active enzyme kallikrein. Kallikrein in turn cleaves high-molecular-weight plasma kininogens, resulting in excessive release of various kinins, especially bradykinin and kallidin. Subnormal C1-INH activity also results in loss of its direct inhibitory effect on kallikrein activity, thus further promoting bradykinin generation. The large quantity of bradykinin released during acute attacks of HAE or AAE is thought to be responsible for most symptoms by directly causing increased vascular permeability (edema, swelling, and ascites), vasodilation (congestion, erythema, and hypotension), and contraction of nonvascular smooth muscle (cramps, spasms, and pain). By increasing capillary permeability, C3a, C4a, and C5a may also contribute to local edema of skin and visceral organs, ascites, and intra-vascular volume depletion.

Kallikrein also cleaves plasminogen to the active enzyme plasmin. In addition to its better-known role of fibrin breakdown, plasmin also activates factor XIII, cleaves prekallikrein to produce even more kallikrein, and activates C1 (Figure 3). At the tissue level, plasmin activity may play a role in acute exacerbations of HAE; however, its role in plasma is probably short-lived because of its rapid inactivation by α2-antiplasmin and α2-macroglobulin, its major inhibitors in plasma.22

Factor XIIIa activates complement component C1, thus initiating the classic pathway. Together with the constant autoactivation of complement component C1 that occurs unchecked when C1-INH activity is subnormal, activation and consumption of C4 and C2 occur during acute HAE attacks, resulting in profoundly decreased serum levels. Levels of C4, and sometimes C2, are typically less than normal during symptomatic quiescence, showing ongoing low-grade consumption between attacks; however, these levels may return to normal in some patients between attacks.9,24,34

Recent studies35-38 have shown that bradykinin, not a C2 kininlike peptide, is responsible for most of the symptoms of acute HAE (Figure 2). Supporting data include the following: (1) large amounts of activated kallikrein are present in induced blister fluids of patients with HAE;39, (2) levels of prekallikrein and high-molecular-weight kininogen are decreased during acute HAE exacerbations;40, (3) plasma bradykinin levels increase significantly in persons with acute HAE and in those experiencing ACE inhibitor therapy—
related angioedema, and (4) venous blood bradykinin levels were significantly higher in samples taken from the affected vs unaffected arm of patients with localized HAE exacerbation.

Typical HAE attacks usually subside spontaneously after 2 to 5 days. However, the risk of death from a vicious cycle of bradykinin and complement fragment production exists during every acute episode until appropriate therapy is administered to raise serum levels of active C1-INH or until spontaneous remission occurs. Spontaneous remission may occur because the rapid consumption of various substrates during the acute attack rapidly outstrips the body’s ability to manufacture them.

In patients with angioedema from causes other than heredity, urticaria is a frequent accompanying symptom. Urticaria seems to be primarily a histamine-mediated event, whereas angioedema seems to be mediated primarily by bradykinin. This explains why patients with acute HAE typically have no urticaria. However, urinary histamine excretion is increased in 18% of patients with acute HAE, suggesting increased systemic histamine release during this process. Complement fragments C3a, C4a, and C5a, and small fragments of C2 and bradykinin, all of which are produced in large quantities during acute HAE attacks, can cause mast cell degranulation. Although total levels of complement component C3 usually remain normal during attacks, its turnover is increased (Figure 3).

ASSOCIATED DISEASES

Patients with HAE have an increased incidence of autoimmune diseases. An estimated 2% of patients also have systemic lupus erythematosus. This association has a strong female preponderance and, although patients seem to have less severe manifestations of systemic lupus erythematosus overall, skin lesions are prominent. In one study, approximately 12% of patients with HAE had an associated autoimmune disorder. This high proportion mainly comprises arthritides, thyroiditis, glomerulonephritis, and inflammatory bowel disease, all of which have been reported to occur at a greater incidence in these patients. Rarely, Sjogren syndrome, drug-induced lupus, pernicious anemia, scleroderma, and autoimmune aortitis have also been associated with the disease.

VARIANT (“TYPE 3”) HAE

A recent German study described recurrent angioedema in 10 female probands and 26 of their female relatives in the setting of normal C1-INH level and function. These patients all manifested symptoms indistinguishable from types 1 and 2 HAE, such as recurring skin le-
sions, abdominal cramps, and laryngeal edema. Eighteen (50%) of these women had experienced at least 1 episode of laryngeal edema, whereas 15 had experienced multiple episodes (range, 2-200 episodes). Three of the women died of asphyxiation. Age at onset varied widely, but most patients developed initial symptoms in their second decade of life, as in the better-known types 1 and 2 HAE. Twenty-two (61%) of patients developed initial symptoms between ages 10 and 23 years, and 7 (19%) developed symptoms between 1 and 10 years of age. Like HAE, acute exacerbations of this variant have been linked to oral contraceptive use (10 patients [28%]).

In patients with this variant, C1-INH level and function and C4 levels are normal during active angioedema and when asymptomatic. This variant most likely represents a congenital deficiency of enzymes such as ACE, carboxypeptidase N, and α2-macroglobulin or a phenotypic decrease in the function of these enzymes. Another possibility is that these individuals produce an as yet unknown substance that is not regulated by C1-INH and that is capable of cleaving large quantities of high-molecular-weight kininogen to produce bradykinin. Because C1-INH exerts inhibitory actions on kallikrein and factors XIIa and XIIIf and because C1-INH levels are normal in these patients, the physiologic defect responsible for angioedema in these patients is probably downstream of kallikrein (Figure 3).

The absence of detectable abnormalities in C1-INH level or function, or in C4 levels, even during acute exacerbations of angioedema, makes it likely that this entity will receive its own unique nomenclature. So far, the defect has been found only in women, suggesting an X-linked–dominant pattern of inheritance, and X-linked angioedema may be an appropriate name.

GENETICS OF HAE

The gene encoding C1-INH has been cloned. It is located on chromosome 11q11-q13.1, possesses 7 exons and approximately 7 introns, and contains multiple Alu repeat sequences.47,48 Hereditary angioedema has an autosomal dominant pattern of inheritance, although it is estimated that 20% to 25% of cases are the result of spontaneous mutations in persons with no family history of the disease.49,50 All patients described in the literature have been heterozygotes. Thus, by mendelian inheritance, affected individuals inherit one normal gene and one abnormal gene, and a child of an affected patient has a 50% chance of acquiring the abnormal allele. The abnormal gene is either nonfunctional and thus is not transcribed (type 1 HAE) or codes for the synthesis of normal quantities of an abnormal C1-INH protein (type 2 HAE).

Type 1 HAE is caused by a variety of mutations with deletions or insertions of single or multiple nucleotides in the C1INH gene, whereas type 2 HAE results from the synthesis of a dysfunctional C1-INH protein, usually caused by point mutations in the areas coding for the “reactive center” or “hinge region” of the C1-INH protein.51,52 The reactive center of C1-INH is the site that binds and cleaves target molecules. It is located at the Arg444-Thr445 site of the C1-INH molecule and requires an intact peptide bond between these 2 amino acids for proper function.23 Some mutations in the C1INH gene result in substitutions at Arg444 of the C1-INH protein, and such mutations have been estimated to account for up to 70% of those with type 2 HAE.51-53 Such mutations result in an amino acid change, from arginine to others such as cysteine or histidine at position 444. Other mutations within the reactive loop, but distant from the reactive center, have been described. One such mutation in a patient with type 2 HAE resulted in the substitution of threonine for alanine at position 436 of the C1-INH molecule.54 To date, more than 100 different C1-INH mutations have been identified in patients with HAE, and their varied effects on C1-INH protein synthesis and function may explain the observed clinical differences in disease severity in affected individuals.51,55 Homozygous C1-INH deficiency has not been described.

The exact chromosomal abnormality responsible for the recently described inherited variant, in which recurrent angioedema occurs in females with normal C1-INH and C4 levels and function, is unknown.2 No affected males were identified, and these women came from 10 different families, with 2 to 7 members affected in each family. Findings from pedigree studies2 of these families suggest an X-linked–dominant pattern of transmission; on occasion, the disease would skip one generation of females and affect the subsequent generation. Thus, the asymptomatic daughter of an affected woman may give birth to female offspring who ultimately manifest the disease.

Phenotypically, type 1 HAE manifests as subnormal C1-INH levels, as low as 5% to 30% of normal, with resultant decreased activity.22 Type 2 HAE results in synthesis of normal and mutant protein. The C1-INH functional activity of the mutant protein is impaired despite the presence of normal or supranormal serum levels. Because patients with type 2 HAE possess one normal and one abnormal allele, theoretically their pool of C1-INH should consist of 50% normal protein and 50% mutant protein. However, it has been found that levels of normal C1-INH protein in these patients are typically far below 50% (range, 5%-30%), despite evidence that synthesis of this normal protein in these patients occurs at approximately half the rate seen in individuals without HAE.56 Such low levels are thought to occur because the single normal allele cannot increase synthesis of normal C1-INH to a rate necessary to keep pace with its consumption.22 The finding that the fractional catabolic rate of normal C1-INH is increased by approximately 29% in patients with HAE lends support to this hypothesis.56,57

ACQUIRED ANGIOEDEMA

Acute attacks of angioedema can also occur because of the acquired form of the disease. Acquired angioedema results from increased destruction or metabolism of C1-INH. Patients with AAE do not have the genetic mutations of HAE. Typi-
cally, the first exacerbations of HAE occur during the second decade of life or earlier, whereas AAE usually becomes symptomatic during or after the fourth decade.

Two types of AAE have been described. Type 1 AAE typically occurs in patients with rheumatologic disorders and B-cell lymphoproliferative diseases, including leukemia (chronic lymphocytic leukemia), lymphosarcoma, multiple myeloma, macroglobulinemia, and essential cryoglobulinemia.22 Rarely, it has been reported in association with carcinomas (rectal, gastric, and breast), lupus anticoagulant, Churg-Strauss vasculitis, erythrocyte sensitization, livedo reticularis, infections (human immunodeficiency virus, hepatitis C virus, hepatitis B virus, Echinococcus granulosus, and Helicobacter pylori), and, in one instance, T-cell lymphoma.13,38-60 These patients have circulating antidiotopic antibodies against specific immunoglobulins expressed on the surface of B cells. Thus, immune complexes are continually being formed between antidiotopic antibodies and surface immunoglobulins on the cell surface, and these complexes in turn are thought to continuously activate complement component C1. C1 esterase inhibitor is consumed as it activates these large quantities of C1, and, ultimately, because C1-INH synthesis cannot keep up with its consumption, levels decline below normal, setting the stage for acute attacks of angioedema.

In type 2 AAE, autoantibodies (typically IgG and sometimes IgA or IgM) directed against the C1-INH molecule are produced and released into the patient’s circulation. These bind the active site of the C1-INH molecule, leading to its inactivation.35,61,62 After inactivation of the normal 105-kd C1-INH molecule through binding with autoantibody, an inactive 96-kd C1-INH fragment is cleaved from the bound C1-INH molecule and circulates in the patient’s blood, where it can be measured. This fragment can lead to the finding of “normal” C1-INH levels on some laboratory assays, in the setting of markedly attenuated C1-INH activity. Once the 96-kd fragment is cleaved, the autoantibody dissociates from the C1-INH remnant to which it was bound and proceeds to bind with a fresh 105-kd C1-INH molecule. Thus, low levels of autoantibody can result in inactivation of large quantities of C1-INH.13 Analysis of autoantibodies to C1-INH has shown that patients produce antibodies that recognize different epitopes within the C1-INH molecule.

As described earlier in the section “The Complement Cascade,” small amounts of C1 component autoactivate on a continuous basis in humans. In unaffected individuals, normal levels of C1-INH inactivate these molecules and prevent full activation of the classic complement pathway. However, in patients with AAE, in whom C1-INH levels are already significantly decreased via consumption or inactivation, C1-INH is further consumed as it performs its housekeeping functions, including inactivation of autoactivated C1. In fact, the fractional catabolic rate of C1-INH in patients with AAE is more than twice that seen in unaffected individuals and approximately 1½ times that in individuals with HAE.37 Patients with AAE have significantly decreased serum levels of classic complement components, particularly C1q, C4, and C2. In particular, decreased serum C1q levels help distinguish AAE from HAE, in which C1q levels are usually normal. The decreased C1q levels seen in AAE but not in HAE reflect the central role of C1 autoactivation and consumption in driving the symptoms of AAE via C1-INH depletion and consequent contact system autoactivation.

A 12% prevalence of autoantibodies to C1-INH has also been reported in patients with liver cirrhosis.63 Although these patients had significantly lower quantitative C1-INH levels than those without autoantibodies, they did not develop acute angioedema.

**ACE INHIBITOR THERAPY–INDUCED ANGIOEDEMA**

A variety of commonly prescribed medications have been associated with the occurrence of angioedema in healthy individuals, including antibiotics, narcotic and nonsteroidal analgesics, angiotensin II inhibitors (losartan potassium), and ACE inhibitors. Allergic phenomena seem to play a major role in all except ACE inhibitor therapy–related angioedema. Although allergic and immunologic mechanisms, such as the “hapten hypothesis” in the case of captopril, have been proposed to explain ACE inhibitor therapy–related angioedema, they do not explain the constellation of manifestations and laboratory findings seen in this condition. Urticaria, which sometimes occurs concomitantly in ACE inhibitor therapy–related angioedema, is more aptly explained by the hapten hypothesis than is angioedema.

Most of the structurally diverse ACE inhibitors on the market have been reported to cause angioedema (Table 1).1 Angiotensin-converting enzyme has 2 main substrates in the human body, angiotensin I and bradykinin, which it cleaves into smaller molecules. In the case of bradykinin, this cleavage inactivates the molecule.72 Because bradykinin excess has been implicated at the tissue level in HAE, ACE inhibitors may induce angioedema in susceptible individuals by causing bradykinin accumulation with resultant vasodilation, capillary leakage, and edema.

Angiotensin-converting enzyme, also called kininase II, is widely distributed in the human body. It is still unclear why only a few individuals develop angioedema from ACE inhibitor therapy, whereas most do not. Patients who develop angioedema while taking an ACE inhibitor may be those with a congenital or acquired impairment in carboxypeptidase N activity (also called kininase I, which degrades bradykinin), which would lead to significant accumulation of bradykinin once ACE activity is blocked.74 Use of ACE inhibitors has been associated with angioedema in approximately 0.1% to 0.5% of cases.1,75-76 No sex predominance has been noted in patients without gastrointestinal tract involvement. In contrast, all patients described in the literature of ACE inhibitor therapy–associated angioedema in whom gas-
trointestinal tract involvement has occurred have been women.44 This has led to speculation about a possible sex-linked susceptibility to gastrointestinal tract involvement.

Although the onset of angioedema typically occurs during the first week of therapy with these agents, symptoms have occurred as long as 2 to 3 years after the first medication use.1,65 Symptoms resolve within 24 to 48 hours of discontinuing the drug therapy and typically recur on rechallenge with the same, or another, ACE inhibitor. Upper airway obstruction rarely occurs in patients with angioedema secondary to ACE inhibitor use. One study77 has proposed that previous upper airway trauma, instrumentation, or manipulation may represent a risk factor for developing such upper airway obstruction secondary to ACE inhibitor therapy–related angioedema.

Findings on physical examination and radiologic testing are similar to those seen in HAE. However, unlike in HAE, a mild to moderate leukocytosis has been noted in some studies48,66,68 of ACE inhibitor therapy–related angioedema.

Angioedema resulting from ACE inhibitor use can be distinguished from HAE and AAE only by history, C1-INH levels, and complement assays. Most patients who develop ACE inhibitor use–related angioedema have normal C1-INH levels and function. However, ACE inhibitors trigger attacks when taken by individuals with HAE.

Table 1. Cases of Gastrointestinal Tract Angioedema Related to Angiotensin-Converting Enzyme (ACE) Inhibitor Therapy in the English-Language Literature*

<table>
<thead>
<tr>
<th>Study</th>
<th>ACE Inhibitor</th>
<th>Duration of ACE Inhibitor Use Before Symptom Onset</th>
<th>Method of Diagnosis</th>
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<tbody>
<tr>
<td>Chase et al44</td>
<td>Lisinopril</td>
<td>1 mo</td>
<td>Abdominal CT scan</td>
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<tr>
<td>Byrne et al45</td>
<td>Fosinopril sodium</td>
<td>3 d</td>
<td>Clinical examination</td>
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<td>Not specified</td>
<td>Small-bowel radiography and laparotomy</td>
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<td>Abdelmalek and Douglas48</td>
<td>Lisinopril</td>
<td>48 h</td>
<td>Small-bowel radiography, abdominal CT scan, and US</td>
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<tr>
<td>Matsumura et al49</td>
<td>Captopril</td>
<td>2 d</td>
<td>Abdominal US</td>
</tr>
<tr>
<td>Jacobs et al50</td>
<td>Enalapril maleate</td>
<td>9 wk</td>
<td>Small-bowel radiography</td>
</tr>
<tr>
<td>Guy et al51</td>
<td>Lisinopril</td>
<td>4 mo</td>
<td>Laparoscopy and US</td>
</tr>
<tr>
<td>Gregory and Davis52</td>
<td>Lisinopril</td>
<td>Not specified</td>
<td>Abdominal CT scan</td>
</tr>
</tbody>
</table>

*CT indicates computed tomographic; US, ultrasonography.

Chronic urticaria occurs with angioedema but are ineffective if use of the ACE inhibitor is continued.67 Subcutaneous (1:1000 mixture) and nebulized epinephrine should be administered in cases in which the airway is threatened, as outlined in the “Management” section.

CHRONIC IDIOPATHIC ANGIOEDEMA

In some instances, chronic recurrent angioedema cannot be attributed to HAE, AAE, or any of the known drug-induced and physical causes. Patients with such symptoms have been deemed to have chronic idiopathic angioedema (CIA). This is an important differential diagnosis for such patients, because its management differs from that for HAE. In most instances, chronic urticaria is also present. The clinical presentations of CIA and HAE are similar, but pruritus typically accompanies CIA and laryngeal edema is rare.

Antihistamines and, in severe or refractory cases, corticosteroids are the mainstay of therapy. Histamine, receptor antagonists provide symptomatic relief in most instances, but the addition of histamine, receptor antagonists seems to provide additional relief in a few patients. If use of antihistamines does not provide symptomatic control, corticosteroids may be administered. The details of management of CIA are well documented23,78 but are beyond the scope of this review.

Patients with CIA, particularly those with frequent and persistent episodes, should undergo annual general medical evaluation to investigate for any underlying occult disease.

DIAGNOSIS

Hereditary angioedema is transmitted in an autosomal dominant pattern, and the parents, siblings, and offspring of patients with HAE should be tested and receive genetic counseling. Some individuals with biochemical findings consistent with HAE never experience an acute exacerbation of the disease.78

We80 described a patient with HAE whose 53-year-old father was asymptomatic despite having decreased C1-INH function (37%) in the setting of normal serum levels. Other patients do not manifest symptoms of the disease until as old as 70 years.23 In 20% to 25% of patients with HAE, there is no family history of the disease.10,49,50,79 Therefore, a positive family history of HAE is not a prerequisite for consideration of HAE in the differential diagnosis when typical symptoms are present.

In the patient with suspected HAE who is currently asymptomatic, serum C1-INH activity should be measured. If this is subnormal, then quantitation of C1-INH and C1q levels will help distinguish between HAE and AAE.3 Patients with HAE will have markedly decreased C1-INH activity and normal C1q levels, with decreased (type 1), normal, or supranormal (type 2) levels of C1-INH. Those with AAE will also show a marked decrease in C1-INH activity; however, C1q levels are concomitantly decreased below normal (Table 2).

During an acute presentation of symptoms consistent with HAE, C4 and C2 levels are markedly decreased, sometimes to undetectable levels, and therefore are useful.
confirmatory tests. Complement is chronically consumed in patients with HAE even between exacerbations, albeit at a much slower rate than that seen in acute exacerbations. The C4 level is persistently low in most, but not all, patients, whereas the C2 level may remain decreased in a smaller proportion of patients. In a few patients, C4 and C2 levels normalize in the absence of symptoms. There is no correlation between the magnitude of decrease in C1-INH level or activity and the severity of frequency of acute HAE attacks. In newly symptomatic middle-aged or older patients with biochemical findings of HAE, C1q quantitation should be performed to rule out AAE.

Heparinization, such as that attained during management of cardiac ischemia or cardiac bypass surgery, has been associated with spurious elevated C1-INH activity. Thus, if C1-INH function is normal in a heparinized patient when the index of suspicion for HAE is high, the C1-INH functional assay should be repeated a week after the discontinuation of heparin therapy.

Diagnosis of the recently described HAE variant in the setting of recurrent angioedema requires a detailed personal and family history, pedigree analysis, and biochemical evidence of normal C4, C1q, and C1-INH levels and function during symptomatic and asymptomatic periods. The personal history must rule out all other causes of isolated angioedema, including drugs, food allergens, and environmental and topical allergens.

Patients with acute gastrointestinal tract HAE have been inadvertently subjected to endoscopy when the diagnosis is unknown. Any instrumentation of the oropharynx is relatively contraindicated when acute HAE is considered the leading differential diagnosis in a patient with acute abdominal pain because of the risk of inducing life-threatening laryngeal edema. If there are compelling reasons why upper endoscopy should be done in this circumstance, appropriate prophylaxis, as described in the “Management” section, is necessary. Nonetheless, the endoscopic appearance of gastrointestinal tract HAE has been described, with findings of diffuse mucosal edema and erythema, with bulging masses of gastric mucosa resembling a submucosal tumor. All the gastric lesions had resolved at second endoscopy weeks later. Similar lesions noted along the small intestine on imaging studies are thought to be responsible for the radiographic appearance and obstructive symptoms seen during acute attacks.

Stomach mucosal biopsy samples taken during attacks of HAE show moderate nonspecific inflammatory cell infiltration and edema of the lamina propria. Plain radiographs and computed tomographic scans of the abdomen typically show varying degrees of ileus (sometimes with air-fluid levels) and small-bowel thickening, respectively. "Thumbprinting" and a stacked coin appearance, also signs of mucosal edema, may also be seen on radiographs. Mild or moderate ascites, which resolves after the acute attack, may also be seen on ultrasound. Patients typically are afebrile and have normal liver enzyme, bilirubin, amylase, and lipase levels during acute episodes. White blood cell counts may be normal or slightly elevated.

Ultrastructurally, gaps in the postcapillary venule endothelial cells, as are typically seen with the actions of vasoactive substances, are seen in tissue from affected areas. The resulting edema has minimal cellularity.

**MANAGEMENT**

Although approximately a quarter of HAE cases occur as a result of spontaneous mutations, most patients inherit the responsible mutation in an autosomal dominant pattern. Thus, genetic counseling of affected individuals, as well as their parents and siblings, is an important part of their overall treatment. These relatives of the proband, as well as their offspring, should be tested after genetic counseling is completed.

Where available, the treatment of choice for acute attacks of HAE or AAE is intravenous purified, vapor-heated C1 esterase inhibitor concentrate. If this is unavailable, then attenuated androgen administration (below) should be started immedi-

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**Table 2. Classification and Distinguishing Features of Hereditary and Acquired Angioedema**

<table>
<thead>
<tr>
<th></th>
<th>Hereditary Angioedema</th>
<th>Acquired Angioedema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Type 2</td>
<td>New Variant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Type 3”</td>
</tr>
<tr>
<td>Typical age at presentation</td>
<td>Infancy to second decade of life</td>
<td>Infancy to second decade of life</td>
</tr>
<tr>
<td>C1-INH level</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>C1-INH activity</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Serum C4 level</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Serum C1q level</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Mode of transmission</td>
<td>AD</td>
<td>AD</td>
</tr>
<tr>
<td>Sex predominance</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Efficacy of C1-INH concentrate</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Efficacy of attenuated androgens</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Efficacy of antifibrinolytic agents</td>
<td>Yes (all)</td>
<td>Yes (all)</td>
</tr>
</tbody>
</table>

*C1-INH indicates C1 esterase inhibitor; ↓, decreased; ↑, increased; AD, autosomal dominant; NA, not applicable; and all, e-aminocaproic acid and tranexamic acid.
ately, particularly when there is upper airway involvement. After an infusion of C1 esterase inhibitor concentrate, serum levels of C1-INH increase immediately, followed 2 to 24 hours later by a slower increase in levels of C4. A randomized, placebo-controlled trial of therapy with C1 esterase inhibitor for acute attacks of HAE found that approximately 69% of acute attacks treated with the concentrate responded completely within 30 minutes of the infusion, and up to 95% of attacks responded within 4 hours. In comparison, only 12% of those who received placebo had their attacks subside by 4 hours. Patients who received C1 esterase inhibitor concentrate were monitored for 4 years after completion of the study, and none developed seroconversion for any blood-borne viral infection (human immunodeficiency virus and hepatitis B and C). Also, none developed autoantibodies to C1-INH as a result of the infusion of concentrate. Therapy with C1 esterase inhibitor concentrate is thus considered safe and effective for the management of acute HAE attacks. Currently, C1 esterase inhibitor concentrate is not available in the United States.

C1 esterase inhibitor concentrate, although recommended as the first line of therapy for acute AAE exacerbations, is not as effective for this condition as it is for HAE. The presence of large amounts of anti-C1-INH autoantibodies, which rapidly inactivate infused C1 esterase inhibitor concentrate in the serum of patients with type 2 AAE, is thought to be responsible for this decreased efficacy. For type 1 AAE, treatment of the underlying malignancy, lymphoproliferative or hematologic, disorder may result in resolution of clinical and laboratory abnormalities. C1 esterase inhibitor concentrate was ineffective in treating patients with the variant inherited angioedema.

Intubation and ventilator support may be necessary for episodes associated with severe respiratory tract compromise from laryngeal edema. Most reports suggest that acute exacerbations of HAE or AAE typically do not respond to administration of antihistamines, glucocorticoids, or epinephrine. However, some researchers have reported success in the acute management of AAE using these agents, probably owing to control of the mast cell degranulation and histamine release. Proponents of this therapy suggest administration of nebulized racemic epinephrine (1:1000 mixture) and subcutaneous epinephrine (0.2-0.3 mL of 1:1000 concentration administered every 20-30 minutes up to a maximum of 3 doses). Administration of epinephrine early in an attack seems to produce better results. Symptomatic improvement has been reported for type 2 AAE using intravenous methylprednisolone, 500 to 1000 mg daily.

Use of attenuated androgens (17-α alkylated androgens), such as danazol and stanozolol, can prevent symptomatic attacks in patients with HAE. Some patients with AAE, particularly type 1 disease, also respond to administration of these agents. Patients with type 2 AAE typically derive little benefit from androgen therapy. Androgens increase serum C1-INH, C4, and C2 levels.

Methyltestosterone therapy is effective in men. In an anecdotal study, oxandrolone, a potent androgen, was used successfully as prophylaxis in a 13-year-old girl who had failed prophylactic therapy with high-dose danazol and e-aminocaproic acid. The patient’s symptoms were controlled with a daily dose approaching 7 mg.

Some authors suggest that long-term prophylaxis should be offered to patients with 1 or more acute exacerbations monthly. However, in a recent study, of 6 patients with HAE who asphyxiated, 2 with danazol therapy did not have increased C4 and C2 levels. Methyltestosterone therapy is effective in men. In an anecdotal study, oxandrolone, a potent androgen, was used successfully as prophylaxis in a 13-year-old girl who had failed prophylactic therapy with high-dose danazol and e-aminocaproic acid. The patient’s symptoms were controlled with a daily dose approaching 7 mg.

Attenuated androgens are used in the long-term prophylactic treatment of male and female patients because they are effective and have relatively mild adverse effects. Dosage ranges for danazol, stanozolol, and methyltestosterone are 200 to 800 mg/d, 2 to 12 mg/d, and 10 to 30 mg/d, respectively. A typical treatment regimen using the less expensive agent, stanozolol, is to start adult patients at a dosage of 4 mg 3 times daily for the initial 12 weeks, then tapering the dosage by 2 mg every 12 weeks until the lowest maintenance dose that provides symptomatic relief is reached (typically 2-6 mg/d). An alternative approach is to reduce the dosage as soon as symptomatic control is achieved. Maintenance using alternate-day administration of stanozolol is also effective. The lowest effective dose should be used for maintenance. Attenuated androgens are efficacious in the prophylaxis of central nervous system angioedema. Danazol doses as low as 200 mg every 2 or 3 days have been used successfully to reduce attack frequency.

When surgery, dental manipulation, or another source of trauma is planned, prophylactic treatment is necessary using danazol, 600 mg, daily for 10 days before surgery, or equivalent doses of another androgenic agent.

The major contraindications to therapy with attenuated androgens are pregnancy and lactation, prostate cancer, and childhood. Potential adverse effects include increased hair growth, weight gain, seborrhea, acne, deepening of the voice, vasmotor symptoms, decreased breast size, menstrual irregularities, decreased libido, hepatic necrosis or cholestasis, hepatic neoplasms, hypertension, and possibly increased atherogenesis resulting from abnormal lipoprotein metabolism. Hepatocellular adenomas, and in one instance hepatocellular carcinoma, have been reported in patients taking danazol for 10 or more years. Abnormal liver enzyme levels, from chronic hepatitis, have been shown not to change significantly after initiation of therapy with these agents and should therefore not be considered an absolute contraindication to their use. Stanozolol therapy seems to have fewer adverse effects than does danazol therapy. Antiandrogens used in the treatment of prostate cancer may decrease the efficacy of these therapies.
Intravenous administration of fresh frozen plasma (FFP), which contains C1-esterase inhibitor, may help abort most episodes of acute HAE. However, a paradoxical exacerbation of symptoms occasionally occurs presumably because the excess C4 supplied in FFP acts as a substrate that fuels further tissue damage. Consequently, FFP infusion is not recommended as therapy for severe exacerbations, particularly for those already manifesting symptoms of laryngeal edema. Prophylactic FFP infusion before surgery and dental extraction may be useful in patients not receiving chronic prophylactic therapy with attenuated androgens. Such infusions result in a small and transient increase in C1-INH and C4 levels above baseline levels; however, this seems to be sufficient in preventing acute attacks. Levels typically return to baseline in 1 to 12 days. A typical regimen is to infuse 2 U of FFP 12 to 24 hours before the procedure begins.

Antifibrinolytic agents (plasmin inhibitors), such as tranexamic acid and ε-aminocaproic acid, are also used for prophylaxis against attacks; however, these do not seem to be as effective as attenuated androgens in the management of HAE. In children, antifibrinolytics have been used as first-line drugs because of the adverse effects of attenuated androgens. These agents produce better results than do attenuated androgens when used for long-term prophylaxis in AAE and may be used as first-line prophylactic agents in patients with this condition. Some patients with AAE who did not respond or responded suboptimally to androgen therapy may respond to administration of antifibrinolytic agents. After an initial oral loading dose of 5 g, typical dosages effective for management of HAE have ranged from 7 to 10 g/d. Myalgia, with or without elevated serum creatine phosphokinase or aldolase levels secondary to rhabdomyolysis, is a potential adverse effect of therapy with this class of agents. Muscle weakness, hypotension, and fatigue may also occur with the use of high doses.

The use of antihistamines and epinephrine was ineffective in the treatment of the variant angioedema. One patient responded to danazol therapy, whereas another did not. Use of antifibrinolytic agents was also ineffective.

Cytoxic and immunosuppressive therapy (typically with cyclophosphamide) and glucocorticoid therapy, with or without plasmapheresis, are beneficial in decreasing autoantibody production in type 2 AAE, thereby alleviating symptomatic attacks.

Nafamostat mesylate, a serine protease inhibitor shown to exert inhibitory activity on enzymes in the kallikrein-kinin system, has been used rarely to treat HAE in Japan. However, its efficacy for this purpose has not been convincing.

Prophylactic administration of FFP, C1 esterase inhibitor concentrate, or oral 17-α alkylated androgens before any major surgical or dental procedure is necessary to prevent an acute episode of HAE.

Angiotensin-converting enzyme inhibitors are contraindicated in patients known to have HAE because they increase the half-life of bradykinin and can thus precipitate symptoms. Oral contraceptive agents should also be avoided because it can precipitate attacks in some individuals with HAE. Prophylactic administration of C1 esterase inhibitor concentrate, FFP, or androgens should also be considered for affected individuals before administration of intravenous radiologic contrast, stertopokinese, or tissue plasminogen activator because previous studies have suggested that these agents may decrease levels of C1-INH in these patients.

On occasion, acute attacks may recur frequently despite maximal maintenance doses of attenuated androgens. In such instances, a search for ongoing environmental triggers and chronic infections may be prudent. In a recent case report, eradication of H pylori infection in a patient with recurrent acute HAE attacks unresponsive to 800 mg of danazol daily resulted in no further acute attacks and permitted a decrease in the daily maintenance dose of danazol to 400 mg.

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