

Angioedema

Pathogenesis, Differential Diagnosis, and Treatment

Evangelo Frigas^{1,*} and Ugochukwu C. Nzeako²

¹*Division of Allergic Diseases and Internal Medicine, and* ²*Division of Gastroenterology and Hepatology and Internal Medicine, Mayo Clinic, Rochester, MN 55905*

Abstract

Angioedema is a constellation of syndromes that present a great challenge to the clinician. The term “angioedema” describes the localized, transient, episodic edema of the deeper layers of the skin or of the mucosa of the gastrointestinal tract. Although angioedema may affect any part of the body, the skin and gastrointestinal tract are involved most commonly by far. Episodic abdominal pain arising from angioedema affecting any intra-abdominal organ may occur without skin angioedema; therefore, angioedema must be included in the differential diagnosis of intermittent, unexplained abdominal pain.

Angioedema is caused by extravasation of plasma in the affected areas, which at times is accompanied by nonspecific, minimal cellular infiltrate. The most commonly identified causes of angioedema are medications, allergens, and physical agents, but most angioedema is idiopathic. Rare forms of angioedema associated with either hereditary or acquired faulty activation of the complement and kallikrein-kinin systems have been extensively described.

Taking a comprehensive personal and family history, performing a physical examination, and compulsively monitoring the response to therapy are the most rewarding and cost-effective diagnostic and treatment tools. Diligent and knowledgeable follow-up by the attending physician spares patients costly and unnecessary tests as well as harmful treatment. The most effective treatment depends on the identification of the causative mechanism and—especially when the mechanism is not identified—on the clinician’s knowledge and experience with innovative therapeutic regimens.

*Author to whom all correspondence and reprint requests should be addressed.

Table 1
Classification of Acute, Recurrent Angioedema

A. Idiopathic (the most common variety)
B. Medication-induced
C. Allergen-induced
D. Physically induced
E. From deficiency of the inhibitor of the C1 esterase (C1 INH) of the complement and kallikrein-kinin systems
1. Hereditary angioedema (HAE) with C1 INH deficiency
a. Variant 1 HAE: 80–85% of cases of HAE
b. Variant 2 HAE: 10–15% of cases of HAE
c. Variant 3 HAE: ? percent of cases of HAE
2. Acquired angioedema (AAE) with C1 INH deficiency
a. Variant 1 AAE (associated mainly with lymphoproliferative disorders)
b. Variant 2 AAE (anti-C1 INH autoantibodies)
F. Miscellaneous causes

Index Entries: Abdominal pain; angiodema; gastrointestinal tract; skin; urticaria.

History

The term “angioneurotic edema” was established by Quincke (4) in 1882. Later, with the recognition that this disease has no neurotic component, this term was replaced with “angioedema.” Falcone (5) wrote the first published report describing a hereditary form of angioedema, and the biochemical abnormality responsible for hereditary angioedema was discovered by Donaldson and Evans (6) in 1963. Besides the hereditary form, there are many types of angioedema, with various causes (Table 1).

Clinical Presentations

Angioedema usually affects the deeper layers of the skin of the face and extremities, although any area of the skin may be involved (Fig. 1). Angioedema of the skin is nonpitting, with ill-defined margins. The skin is swollen, tender, and warm. Frequently a burning sensation is present, but pruritus is typically uncommon. Attacks of angioedema may last a few days and usually resolve spontaneously. Sometimes, physical trauma or stress may be the precipitating or triggering factors.

Any part of the gastrointestinal tract may be affected. Angioedema affecting the throat may lead to obstruction of the airway and death from asphyxiation. The mortality rate in hereditary angioedema (HAE), which can be as high as 30–40%, is mostly a result of obstruction of the upper airway (7,8). Asphyxiation from angioedema of the throat can

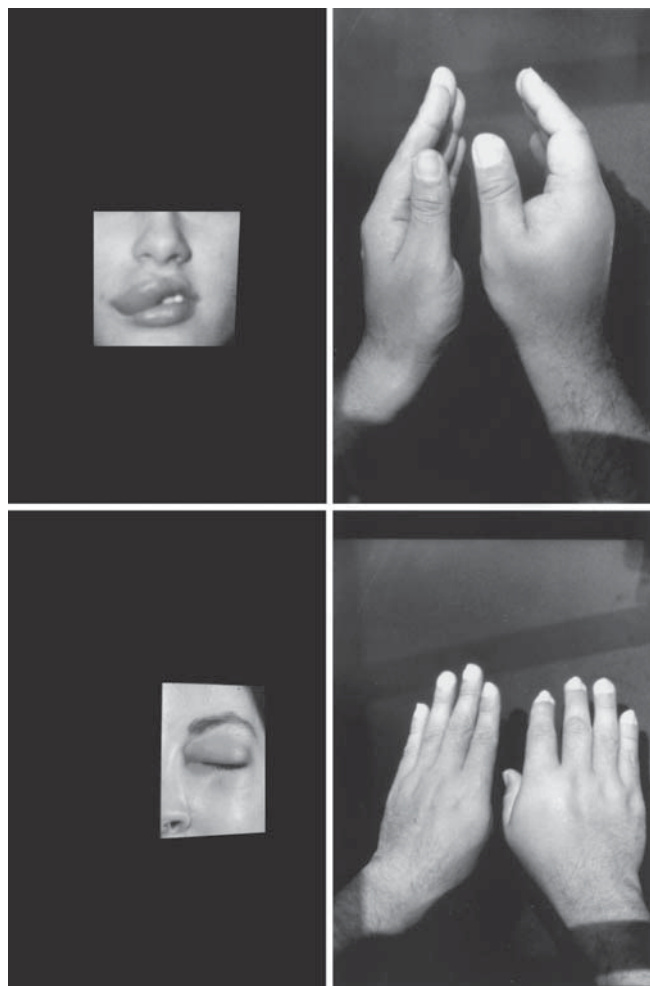


Fig. 1. Angioedema affecting the skin spares the superficial layers and involves only the subcutaneous tissues, causing nonpruritic, nonpitting localized swelling with indistinct margins. These swellings usually last a few days and usually resolve spontaneously.

occur at any age, and in patients with hereditary angioedema, asphyxiation has been documented in patients as young as 4 wk and as old as 78 yr. Death from asphyxiation caused by angioedema affecting the throat can occur as the first clinical sign of the disease (8). The time from onset of angioedema to complete obstruction of the upper airway may vary from minutes to 14 h.

Intestinal obstruction may result from angioedema of the wall of the gastrointestinal tract. The symptoms of nausea, vomiting, and abdominal pain may be severe at times, mimicking acute abdomen. For example, angioedema of the bowel wall may cause anorexia, nausea,

vomiting, diarrhea, abdominal pain, and various degrees of intestinal obstruction. These symptoms may lead to unnecessary abdominal exploration and excision of swollen but otherwise normal portions of bowel or intestinal organs, such as gallbladder or appendix. Because angioedema of the bowel or of any intra-abdominal organ may occur independently of cutaneous involvement, emergency-room physicians who evaluate patients with recurrent abdominal pain should include angioedema in the differential diagnosis (9–12). Unless there is a high degree of awareness for patients who present repeatedly in the emergency room with recurrent abdominal pain but without angioedema of the skin, the diagnosis of gastrointestinal angioedema is easily missed (2,3,9). Symptoms may be attributed to somatization, and patients may be inappropriately referred for psychiatric assessment. Attacks of gastrointestinal angioedema generally subside in 12–24 h (13).

Fever and leukocytosis are unusual in angioedema of either the skin or the bowel. Cases of cerebral angioedema, leading to migraine and transient ischemic attacks have been described (14–16).

Endoscopic and Radiographic Findings

In patients with acute angioedema that affects the oropharynx, any use of instruments in the oropharynx is contraindicated. With endoscopy under these circumstances, diffuse mucosal edema and erythema are apparent, with bulging mucosa resembling a submucosal tumor in the larynx, esophagus, or stomach (10). All mucosal lesions in the stomach resolved when endoscopy was repeated 8 wk later. Similar lesions noted with imaging studies of the small intestine are believed to cause the radiographic appearance of obstructive symptoms observed during acute attacks of intestinal angioedema (Figs. 2, 3). During attacks of angioedema, biopsy specimens of the mucosa of the stomach showed minimal nonspecific inflammatory-cell infiltration and edema of the lamina propria (10,11). Fig. 2 shows a collage, from our medical practice, of radiographic findings caused by angioedema involving intra-abdominal organs. Ascites may occur from extravasation of fluid into the peritoneal cavity (Fig. 2D).

Classification

Episodes of angioedema may be classified in two broad categories: acute angioedema (single episode) and acute recurrent angioedema (three or more episodes of angioedema within a 3- to 6-mo period). Acute recurrent angioedema is a diagnostic challenge for the clinician. A classification of its etiology is outlined in Table 1.

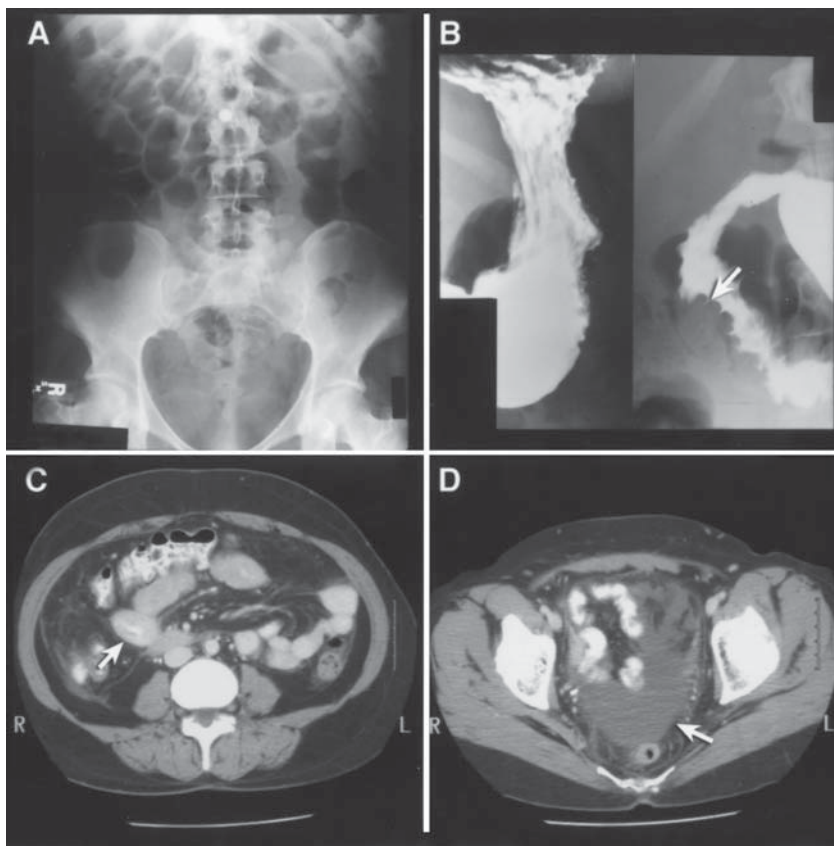


Fig. 2. Radiographic findings from angioedema affecting the gastrointestinal tract. **A**, Radiograph of the abdomen reveals dilated loops of bowel. **B**, Upper gastrointestinal series of the stomach and duodenum showing obliteration of the mucosal contour, "thumbprinting sign" (arrow), and narrowing of the lumen from angioedema affecting the submucosa while sparing the superficial layers of the mucosa. **C**, Computed tomography (CT) scan of abdomen with oral and intravenous (iv) administration of contrast material showing circumferential thickening of the bowel wall in segments of the small intestine (arrow) from angioedema. **D**, CT scan of pelvis showing ascites (arrow) from angioedema.

Pathogenesis

Medication-Induced Angioedema

Several medications have been associated with angioedema, including antibiotics, narcotics, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin II inhibitors such as losartan, and angiotensin-converting enzyme (ACE) inhibitors such as captopril. It is not known exactly how ACE inhibitors cause angioedema. Most authors postulate that the mechanism may be related to the pharmacologic action of this class of medication and that production of bradykinin causes the edema (17,18).

Angioedema develops in 1–5% of patients who use ACE inhibitors, and it is indistinguishable from any other form of angioedema (17,19,20). Although most cases of angioedema caused by ACE-inhibitor medications occur during the first week of therapy, symptoms of angioedema have occurred after the patient has used the medication for several years (17,21). Treatment involves discontinuing therapy with the ACE inhibitor. Angioedema resolves within 24–48 h after discontinuing therapy with ACE inhibitors and typically recurs if therapy is resumed with these medications. Laryngeal involvement with obstruction of the upper airway is rarely a factor in this form of angioedema.

Allergen-Induced Angioedema

Food allergens—especially fish, shellfish, nuts, preservatives, colorants, and flavor enhancers—can cause angioedema with or without urticaria. To rule out food allergy, allergy skin testing is done, but it requires considerable expertise to validate positive results (22). To rule out sensitivity to food additives, oral challenges are done, which also require special knowledge and experience to correlate the positive reactions with a patient's symptoms (23).

Physically Induced Angioedema

In susceptible individuals, physical agents such as cold, pressure, vibration, and ultraviolet radiation, can produce angioedema, which is usually associated with urticaria. The ice cube test is used to rule out a cold-induced mechanism. Cold-induced angioedema and urticaria has been reported in association with cryoglobulins, cold agglutinin disease, cryofibrinogenemia, and paroxysmal cold hemoglobinuria (24,25).

HAE With C1 Esterase-Inhibitor Deficiency

Typically, the symptoms of HAE appear in the first two decades of life, with an incidence that varies from 1 in 10,000 (26) to 1 in 150,000 (27). Three variants of HAE have been reported (Table 1), and all except the third are caused by deficiency of the C1 esterase inhibitor (C1 INH) (28). The gene encoding for C1 INH is located in chromosome 11q13.1 and has been cloned (29,30). HAE has an autosomal dominant pattern of inheritance, and it is estimated that 20–25% of cases are the result of spontaneous mutations in persons with no family history of disease (31,32). The abnormal gene is either nonfunctional and thus not transcribed (variant 1 of HAE), or it codes for the synthesis of normal quantities of an abnormally functioning C1 INH protein (variant 2 of HAE). In variant 1 of HAE, which represents 80–85% of the cases of HAE, the decreased production of C1 INH is caused by various mutations and deletions or insertions of single or multiple nucleotides in the *C1 INH* gene. However, in variant 2, which represents 10–15% of the cases of

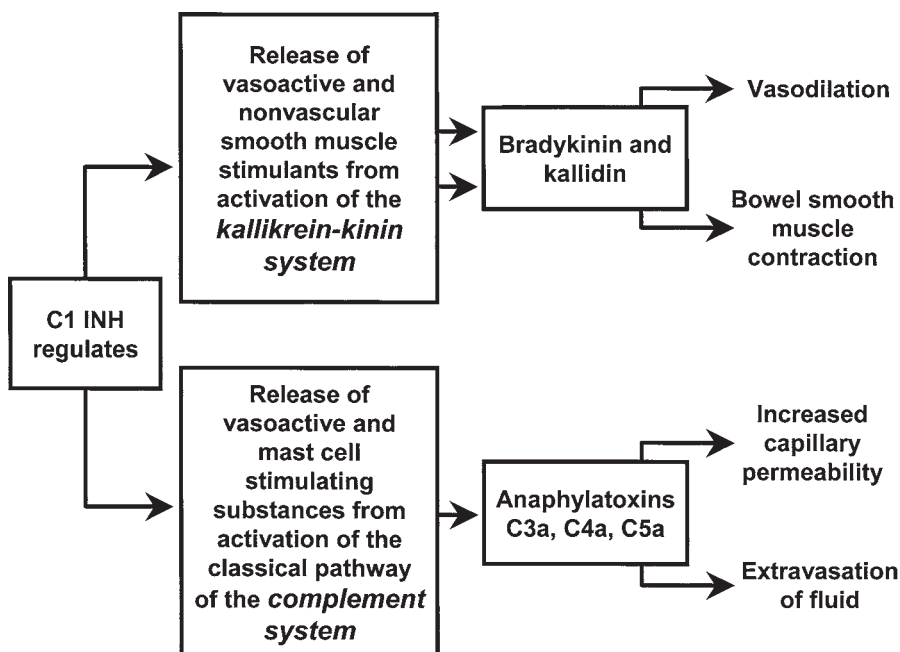


Fig. 3. Schematic representation of how the C1 esterase inhibitor (C1 INH) regulates the activation of the kallikrein-kinin and complement systems in health and disease. In hereditary angioedema or acquired angioedema, lack of or dysfunction of C1 INH causes vasoactive and nonvascular smooth-muscle stimulants to be produced in large amounts from overactivation of the kallikrein and complement systems. In turn, during attacks of angioedema, these substances cause abdominal pain and swellings of the skin and bowel wall.

HAE, the dysfunctional C1 INH is caused by point mutations in areas coding for the reactive center or hinge protein of the C1 INH protein (33,34). The exact chromosomal abnormality responsible for the recently described inherited variant 3 is unknown (28).

C1 INH is an α_2 -globulin of 105 kDa and is synthesized mainly by hepatocytes (35). It belongs to the serine protease-inhibitor family that includes α_1 -antitrypsin and antithrombin. In humans, the major functions of C1 INH include the inhibition of the autoactivation of the first component of the complement system (C1); inactivation of the coagulation factors XIIa, XII_f, and XIa; and direct inhibition of activated kallikrein (36) (Fig. 3). C1 INH prevents activation of C1 by causing dissociation of the C1q subunit and forming an inactive C1r2-C1s2-C1-INH2 complex (35,36). This complex is unable to cleave and activate the C4 and C2 components, which are essential for activation of the classical pathway. During an attack of HAE, an uninhibited activation of the classical pathway of the complement system produces anaphylatoxins C3a,

C4a, and C5a, which cause increased capillary permeability, leading to the formation of angioedema (Fig. 3). Furthermore, uninhibited activated kallikrein cleaves high-mol-wt plasma kininogens, resulting in excessive release of various kinins—especially bradykinin and kallidin—which cause increased vascular permeability (angioedema and ascites), vasodilation (vascular congestion, erythema, and hypotension), and contraction of the bowel smooth muscle (abdominal cramps and pain) (Fig. 3).

Although acute HAE may begin as a histamine-independent event, mast cells may be activated later through the formation of C3a, C4a, and C5a from activation of the classical pathway of the complement system (26). Typically, during activation of the classical pathway, levels of C4, and sometimes C2, decrease below normal levels and may return to normal in some patients between attacks of HAE (27,37,38). Conversely, levels of C3 remain normal although its turnover is increased (39). Earlier reports attributing edema to the formation of C2 kinin-like peptide from cleavage of C2 during activation of the classical pathway have been proven incorrect (40-43). Interestingly, in patients with the third variant of HAE, the levels of C1 INH and C4 were normal during symptomatic as well as asymptomatic periods.

Acquired Angioedema With C1 INH Deficiency

Typically the symptoms of acquired angioedema (AAE) occur after the fourth decade of life (2,3). Two variants of AAE associated with C1 INH deficiency have been described (Table 1). Variant 1 occurs in patients with B-cell lymphoproliferative disorders, such as chronic lymphocytic leukemia, lymphosarcoma, multiple myeloma, macroglobulinemia, and essential cryoglobulinemia. The symptoms of angioedema may antedate by several years the other symptoms of the subclinically evolving hematologic disease (2,3,36). This variant rarely occurs in association with malignancies of the rectum, stomach, and breast; rheumatoid arthritis and systemic lupus erythematosus; Churg-Strauss vasculitis; lupus anticoagulant; erythrocyte sensitization; livedo reticularis; and infections with human immunodeficiency virus, hepatitis C and B viruses, *Echinococcus granulosus*, and *Helicobacter pylori* (3,13,26,44,45).

These patients do not have the genetic mutations described for HAE. Variant 1 of AAE is a hypercatabolization of C1 INH. In these patients, immunocomplexes are continuously formed between anti-idiotypic antibodies and abnormal immunoglobulins on the cell surface of their lymphocytes, which in turn activate the classical pathway of the complement system through activation of its first component, C1. In preventing activation of the complement system, C1 INH is consumed as it inactivates the continuously activated C1. When the synthesis of C1

Table 2
Differential Diagnosis Between HAE and AAE With C1 INH Deficiency^a

	HAE	AAE
Pathogenesis	Inherited (autosomal dominant) genetic abnormality of C1 INH	Acquired abnormality of C1 INH most commonly caused by lymphoproliferative disorders
Age at onset	Early, usually within the first 2 decades of life	Later, usually after the fourth decade of life
Complement abnormalities ^b	Present	Present
C1q complement	Normal	Decreased
C4 complement	Decreased ^c	Decreased ^c
C1 INH (Q) assay	Decreased or normal	Decreased or normal
C1 INH (F) assay	Decreased	Decreased
Response to therapy	Good	Variable

^aAAE, acquired angioedema; C1 INH, C1 esterase inhibitor; HAE, hereditary angioedema.

^bA newly reported variant 3 of HAE occurs with no complement abnormalities (28).

^cMay be normal when asymptomatic.

INH cannot keep up with its consumption, its inhibitory capability falls below a critical level, which allows for an uninhibited activation of the complement and kallikrein systems and leads to angioedema.

In variant 2 of AAE, autoantibodies (immunoglobulin IgG and sometimes IgM) directed against the C1 INH molecule are produced and lead to inactivation of C1 INH (40,46). An inactivated, 96-kDa C1 INH fragment is cleaved and circulates in the patient's blood, where it can be measured. After the 96-kDa fragment is cleaved, the autoantibody dissociates from the C1 INH remnant to which it was bound and then binds with a fresh C1 INH molecule. In this way, small concentrations of autoantibody can inactivate large quantities of C1 INH (10). Analysis of autoantibodies to C1 INH recognizes different epitopes within the C1 INH molecule; consequently, variant 2 of AAE has a heterogeneous population of autoantibodies. The fractional catabolic rate of C1 INH in patients with AAE is over twice that of unaffected individuals and approximately 1.5 times that of individuals with HAE (47). Profound depletion of C1 INH leads to the production of large amounts of bradykinin and other vasoactive previously mentioned substances which cause angioedema.

Patients with AAE have significantly decreased serum levels of C1q, C4, and C2. In particular, decreased serum levels of C1q help

distinguish AAE from HAE, in which the levels of C1q are usually normal (Table 2). The decreased levels of C1q present in AAE but not in HAE reflect the central role of consumption of C1 autoactivation in driving the symptoms of AAE through depletion of C1 INH.

Interestingly, a 12% prevalence of autoantibodies to C1 INH has been reported in patients with liver cirrhosis (43). Although these patients have significantly lower levels of C1 INH than those without autoantibodies, they do not develop acute angioedema. Causes of cirrhosis in these patients included infection with hepatitis C virus (HCV), infection with hepatitis B virus, and alcoholism.

Initial Work-up

All patients with acute recurrent angioedema (i.e., three or more episodes within 3–6 mo) or with unexplained abdominal pain should have an initial work-up. The main parts of this work-up are a comprehensive physical examination; detailed personal and family history; measurements of C4, C1q, and C1 INH by functional and quantitative assay; a complete blood count (CBC); and a blood chemistry group. If the initial work-up provides no clues, no additional tests should be done, and the patient should be reevaluated during office visits every 3–4 mo, for as long as symptoms persist, to determine whether any new symptoms or clues warrant further testing or rechecking of the complement measurements mentioned here.

Further Evaluation and Follow-up

After a low concentration of C1q and C4 and a decrease in C1 INH function are confirmed, work-up for an underlying malignant condition should proceed. This work-up should include a peripheral blood smear, protein electrophoresis, immunoelectrophoresis, and immunophenotyping of peripheral-blood lymphocytes to rule out underlying dysproteinemia and circulating abnormal lymphocytes. Computed tomography of the chest, abdomen, and pelvis and endoscopy of the upper and lower gastrointestinal tract should be done to rule out lymphoma and malignancies of the gastrointestinal tract. When concern is high for an underlying hematologic disorder, a bone-marrow biopsy may be helpful. If this work-up is negative for disease, the patient should be checked periodically for as long as the episodes of angioedema persist. The complement studies described here should be performed every 3–6 mo. These tests must be conducted in reliable laboratories in which the personnel are experienced in performing these tests. If any doubt exists about the laboratory, at the first discovery of a complement abnormality, these tests should be repeated in a more reliable laboratory before embarking on an extensive and costly work-up.

Diagnosis and Differential Diagnosis

The criteria for the diagnosis and differential diagnosis of HAE and AAE associated with C1 INH are summarized in Table 2. During an acute attack of angioedema, the concentration of C4 markedly decreases, sometimes to undetectable levels. The level of C4 may remain abnormal in most patients, but not all (27,37,38). Therefore, the authors recommend measurement of C4 as the first test for screening for AAE or HAE (2,3). To distinguish between AAE and HAE after a low level of C4 is found, the C1q level should be measured. The concentration of C1q is low in AAE and normal in HAE. Confirmatory laboratory retesting must include measurement of C1 INH by quantitative and functional assays (2,3). Because treatment with heparin can increase the activity of C1 INH, the C1 INH functional assay should be repeated after discontinuation of heparin therapy (48). Besides distinguishing between HAE and AAE, diagnoses for all patients who present with recurrent attacks of angioedema should distinguish between angioedema caused by medications, food allergens, or other environmental or physical agents (Table 1).

When the diagnosis of HAE is made, the parents, siblings, and offspring of the patient should receive detailed and comprehensive genetic counseling, and their levels of C4 and C1 INH should be measured by functional assay. For unknown reasons, some individuals with detectable biochemical findings consistent with HAE never develop symptoms, and others do not manifest symptoms until 70 yr of age (12,47). In 20–25% of patients with HAE, no family history exists of the disease or of family members with symptoms of HAE (12,16,31,32). Therefore, when typical symptoms are present, a family history that is positive for HAE should not be a prerequisite for consideration of HAE in the differential diagnosis.

Treatment and Follow-up

Treatment and follow-up of angioedema depend on the diagnosis. Angioedema caused by medications, allergens, or physical agents is treated by eliminating the causative agents. HAE, which requires lifelong treatment and careful monitoring, is best treated by referral to a specialist who is skilled in the management of this disease. Also, all the relatives of these patients should be genetically counseled, tested, and periodically rechecked.

Androgens

Androgens with impeded androgenic action (17 α -alkylated androgens), such as danazol and stanozolol, are the most successful and commonly used medications in the prevention and treatment of symptoms

of angioedema in patients with either HAE or AAE. Androgen therapy benefits patients with variant 1 of AAE more than patients with variant 2 of AAE. The androgens increase the serum concentration of C1 INH, C4, and C2 (49,50). Treatment should be modified according to symptoms. Some patients may not require therapy, and others may need prolonged or lifelong therapy (2,3,32,51). Criteria for starting long-term therapy must be carefully weighed; after therapy is started, the patient should be monitored closely with appropriate blood tests and with physical examinations for the duration of the treatment. In a recent case report of a patient with recurrent HAE attacks, *Helicobacter pylori* infection resolved with 800 mg of danazol daily, resulting in the absence of further attacks and permitting a decrease in the daily maintenance dose of danazol to 400 mg (52).

For an adult patient with symptoms, a typical regimen using the less expensive agent, stanozolol, begins with 4 mg 3× a day for 1–2 mo and then tapers to the lowest maintenance dose that provides symptomatic relief. The typical maintenance dose of stanozolol is between 2 and 6 mg a day. Androgens also appear to be efficacious for prophylaxis of angioedema of the central nervous system (CNS) (15).

The major contraindications of treatment with androgens are pregnancy and lactation, prostate cancer, and childhood. Potential adverse effects from prolonged treatment with androgens include hirsutism, weight gain, acne, deepening of the voice, menstrual irregularities, decreased or increased libido, liver-function abnormalities, hepatic necrosis or cholestasis, hepatic neoplasms, hypertension, and possibly an increase in the concentration of serum cholesterol. Hepatocellular adenomas have been reported in patients who have taken danazol for 10 or more yr (53,54). Abnormal concentrations of liver enzymes from chronic hepatitis do not change during therapy with these agents and, therefore, should not be considered an absolute contraindication to their use (51). The use of antiandrogens for treatment of prostate cancer may decrease the efficacy of androgen therapy.

C1 INH Concentrate

Whenever possible, severe or life-threatening attacks of HAE should be treated with iv administration of purified, vapor-heated C1 INH concentrate, which is not available in the United States (55). C1 INH concentrate, although very successful in the treatment of severe attacks of HAE, is not consistently effective in the treatment of AAE (56). For the newly described variant 3 of HAE (Table 1), the use of C1 INH concentrate is ineffective (28). For variant 1 of AAE, treatment of the underlying disease (usually a hematologic malignancy) is the treatment of choice (3,9,13). When the underlying disease cannot be immediately identified, patients diagnosed with AAE should be promptly

referred and managed by a specialist in the etiology and natural history of this illness.

Fresh Frozen Plasma

The iv administration of fresh frozen plasma (FFP) that contains C1 INH has been used for therapy of acute attacks of either HAE or AAE. Exacerbation of symptoms may occur because the FFP includes C4, which acts as a substrate for continuing activation of the complement system. Therefore, FFP is not recommended for the acute phase of either HAE or AAE. However, prophylactic use of FFP before surgical procedures or dental extraction may be useful. The typical dose of FFP is 2 U, administered 12–24 h before the procedure.

Other Medications

During life-threatening exacerbations of either HAE or AAE, antihistamines, epinephrine, or glucocorticoids are widely used; however, whether these medications offer any additional benefit to the patient remains a subject of controversy among authors (3,26).

Antifibrinolytic agents such as plasmin inhibitors including tranexamic acid and ϵ -aminocaproic acid, have been used for prophylaxis against attacks of angioedema. These agents do not appear to be as efficacious as the androgens. In children, antifibrinolytic agents have been used as the first line of therapy because the side effects of androgens may make them less desirable in these patients (57). Also, some patients with AAE who fail to respond to androgen therapy may respond to antifibrinolytic therapy (26). The mechanism by which the antifibrinolytic agents prevent the frequency of the attacks of angioedema is unknown.

Cytotoxic and immunosuppressive medications, such as cyclophosphamide, and glucocorticoids with or without plasmapheresis are beneficial in decreasing the autoantibody production in variant 2 of AAE (10). Nafamostat mesylate, a serine protease inhibitor with inhibitory activity on enzymes in the kallikrein-kinin system, has been used to treat HAE in Japan (58,59), but its therapeutic merit remains undefined.

Use of ACE inhibitors, estrogen replacement therapy, and oral contraceptives should be avoided in patients with either HAE or AAE.

Prophylaxis

Before surgical procedures or dental extraction, preparation of the patient with androgen therapy, FFP (if angioedema symptoms are absent), or C1 INH concentrate (when available) is required to prevent exacerbations of either HAE or AAE. For the same purpose, prophylactic administration of androgens, FFP, or C1 INH concentrate should be considered before administration of an iv contrast material, streptokinase,

or tissue plasminogen activator, because studies have suggested that these agents may decrease the levels of C1 INH in these patients (60–62).

Acknowledgments

The authors thank Ms. LaDonna G. Mourning for secretarial assistance with rough drafts, typing, and retyping countless revisions. This work was supported by educational and research grant ZZ0551 from Mayo Clinic and Mayo Foundation.

References

1. Warin, R.P. and Champion, R.H. (1974), *Major Probl. Dermatol.* **1**,1–164.
2. Frigas, E. (1989), *Mayo Clin. Proc.* **64**,1269–1275.
3. Markovic, S.N., Inwards, D.J., Frigas, E.A., et al. (2000), *Ann. Intern. Med.* **132**,144–150.
4. Quincke, H. (1882), *Monatshefte für Praktische Dermatologie* **1**,129–131.
5. Falcone, T. (1886), *Gazetta Degli Ospedali e delle Cliniche* **7**,125.
6. Donaldson, V.H. and Evans, R.R. (1963), *Am. J. Med.* **35**,37–44.
7. Sofia, S., Casali, A., and Bolondi, L. (1999), *J. Clin. Ultrasound* **27**,537–540.
8. Bork, K., Siedlecki, K., Bosch, S., et al. (2000), *Mayo Clin. Proc.* **75**,349–354.
9. Nzeako, U.C., Frigas, E., and Tremaine, W.J. (2002), *J. Clin. Gastroenterol.* **34**,57–61.
10. Hara, T., Shiotani, A., Matsunaka, H., et al. (1999), *Endoscopy* **31**,322–324.
11. Molina, C., Brun, J., Coulet, M., et al. (1977), *Clin. Allergy* **7**,127–135.
12. Shinzato, T., Nakamura, H., Kuniyoshi, T., et al. (1992), *Intern. Med.* **31**,633–635.
13. Heymann, W.R. (1997), *J. Am. Acad. Dermatol.* **36**,611–615.
14. Krause, K.H., Rentrop, U., and Mehregan, U. (1979), *J. Neurol. Sci.* **42**,429–435.
15. Brettell, R.P., Dunmow, R.E., Milne, L.A., et al. (1982), *Scott Med. J.* **27**,309–311.
16. Thorvaldsson, S.E., Sedlack, R.E., Gleich, G.J., et al. (1969), *Ann. Intern. Med.* **71**,353–357.
17. Hedner, T., Samuelsson, O., Lunde, H., et al. (1992), *Br. Med. J.* **304**,941–946.
18. Slater, E.E., Merrill, D.D., Guess, H.A., et al. (1988), *JAMA* **260**,967–970.
19. Israili, Z.H. and Hall, W.D. (1992), *Ann. Intern. Med.* **117**,234–242.
20. Inman, W.H., Rawson, N.S., Wilton, L.V., et al. (1988), *Br. Med. J.* **297**,826–829.
21. Byrne, T.J., Douglas, D.D., Landis, M.E., et al. (2000), *Mayo Clin. Proc.* **75**,1201–1204.
22. Ten, R.M., Klein, J.S., and Frigas, E. (1995), *Mayo Clin. Proc.* **70**,783–784.
23. Giehlbrock, K.R., Flynn, S.M., Andrist, D.T., et al. (1999), *J. Allergy Clin. Immunol.* **103**,S6.
24. Horton, B.T., Brown, G.E., and Roth, G.M. (1936), *JAMA* **107**,1263–1269.
25. Gorevic, P.D. Cryopathies: Cryoglobulins and cryofibrinogenemia, in Frank, M.M., Austen, K.F., Claman, H.N., et al., eds., *Samter's Immunologic Diseases*, 5th ed., vol. 2, Boston, Little, Brown, and Company, 1995, pp. 951–974.
26. Frank, M.M. Urticaria and angioedema, in Goldman, L. and Bennett, J.C., eds., *Cecil Textbook of Medicine*, 21st ed., Philadelphia, W.B. Saunders Company, 2000, pp. 1440–1445.
27. Talavera, A., Larraona, J.L., Ramos, J.L., et al. (1995), *Am. J. Gastroenterol.* **90**,471–474.
28. Bork, K., Barnstedt, S.E., Koch, P., et al. (2000), *Lancet* **356**,213–217.
29. Theriault, A., Whaley, K., McPhaden, A.R., et al. (1990), *Hum. Genet.* **84**,477–479.
30. Carter, P.E., Dunbar, B., and Fothergill, J.E. (1988), *Eur. J. Biochem.* **173**,163–169.

31. Eck, S.L., Morse, J.H., Janssen, D.A., et al. (1993), *Am. J. Gastroenterol.* **88**,436–439.
32. Agostoni, A. and Cicardi, M. (1992), *Medicine* (Baltimore) **71**,206–215.
33. Zuraw, B.L. and Herschbach, J. (2000), *J. Allergy Clin. Immunol.* **105**,541–546.
34. Aulak, K.S., Pemberton, P.A., Rosen, F.S., et al. (1988), *Biochem. J.* **253**,615–618.
35. Oltvai, Z.N., Wong, E.C., Atkinson, J.P., et al. (1991), *Lab. Invest.* **65**,381–388.
36. Davis, A.E. (1988), *Annu. Rev. Immunol.* **6**,595–628.
37. Grunewald, T. (2000), *Ann. Intern. Med.* **133**,837.
38. Frank, M.M., Gelfand, J.A., and Atkinson, J.P. (1976), *Ann. Intern. Med.* **84**,580–593.
39. Carpenter, C.B., Ruddy, S., Shehadeh, I.H., et al. (1969), *J. Clin. Invest.* **48**,1495–1505.
40. Nussberger, J., Cugno, M., Amstutz, C., et al. (1998), *Lancet* **351**,1693–1697.
41. Nussberger, J., Cugno, M., Cicardi, M., et al. (1999), *J. Allergy Clin. Immunol.* **104**,1321–1322.
42. Cugno, M., Cicardi, M., Bottasso, B., et al. (1997), *Blood* **89**,3213–3218.
43. Shoemaker, L.R., Schurman, S.J., Donaldson, V.H., et al. (1994), *Clin. Exp. Immunol.* **95**,22–28.
44. Farkas, H., Csepregi, A., Nemesanszky, E., et al. (1999), *J. Allergy Clin. Immunol.* **103**,711–712.
45. Quastel, M., Harrison, R., Cicardi, M., et al. (1983), *J. Clin. Investig.* **71**,1041–1046.
46. Jackson, J., Sim, R.B., Whelan, A., et al. (1986), *Nature* **323**,722–724.
47. Melamed, J., Alper, C.A., Cicardi, M., et al. (1986), *J. Allergy Clin. Immunol.* **77**,322–326.
48. Nielsen, E.W., Johansen, H.T., Straume, B., et al. (1994), *J. Immunol. Methods* **173**,245–251.
49. Sheffer, A.L., Fearon, D.T., and Austen, K.F. (1981), *J. Allergy Clin. Immunol.* **68**,181–187.
50. Gelfand, J.A., Sherins, R.J., Alling, D.W., et al. (1976), *N. Engl. J. Med.* **295**,1444–1448.
51. Cicardi, M., Castelli, R., Zingale, L.C., et al. (1997), *J. Allergy Clin. Immunol.* **99**,194–196.
52. Rais, M., Unzeitig, J., and Grant, J.A. (1999), *J. Allergy Clin. Immunol.* **103**,713–714.
53. Bork, K., Pitton, M., Harten, P., et al. (1999), *Lancet* **353**,1066–1067.
54. Crampon, D., Barnoud R., Durand, M., et al. (1998), *J. Hepatol.* **29**,1035–1036.
55. Waytes, A.T., Rosen, F.S., and Frank, M.M. (1996), *N. Engl. J. Med.* **334**,1630–1634.
56. Alsenz, J., Lambris, J.D., Bork, K., et al. (1989), *J. Clin. Investig.* **83**,1794–1799.
57. Borum, M.L. and Howard, D.E. (1998), *Postgrad. Med.* **103**,251,255–256.
58. Matsumura, M., Haruki, K., Kajinami, K., et al. (1993), *Intern. Med.* **32**,424–426.
59. Nomura, H., Tsugawa, Y., Koni, I., et al. (1992), *Intern. Med.* **31**,94–97.
60. Ewald, G.A. and Eisenberg, P.R. (1995), *Circulation* **91**,28–36.
61. Lynch, M., Pentecost, B.L., Littler, W.A., et al. (1993), *Clin. Exp. Immunol.* **94**,279–285.
62. Francis, C.W., Brenner, B., Leddy, J.P., et al. (1991), *Br. J. Haematol.* **77**,562–563.