OFFICE MANAGEMENT: ALLERGY AND IMMUNOLOGY
Richard D. deShazo, MD, Specialty Editor

THE AMERICAN JOURNAL of MEDICINE®

The Spectrum and Treatment of Angioedema

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ABSTRACT

Angioedema manifests as episodes of localized swelling in the dermis and submucosa. The key to successful management is detection and avoidance of triggers, early recognition of attacks, and aggressive airway management when warranted. Review of a patient's medication list may identify drugs that include angiotensin-converting enzyme inhibitor or angiotensin receptor blockers as the cause. Initial treatment in a patient presenting with most forms of angioedema includes antihistamines and glucocorticoids if required. Epinephrine should be administered if there is concern for laryngeal edema. Patients who have a known history of hereditary angioedema should receive C1 esterase inhibitor concentrate or fresh-frozen plasma.
 • The American Journal of Medicine (2008) 121, 282-286

KEYWORDS: Acquired; Angioedema; Hereditary; Recurrent

Angioedema (AE) is defined as self-limited, localized swelling. It occurs in approximately 15% of the general population and is more common in women than men.[1] There are several different syndromes of AE, but all have the characteristic swelling that reflects release of vasoactive mediators and transient increases in the permeability of postcapillary venules of the subcutaneous and submucosal tissues (Table 1). Swelling is asymmetric, nonpitting, and nontender; however, the effects of the swelling can produce discomfort. Urticaria occurs in approximately 50% of cases (Table 2).[2] Common locations of swelling include periorbital, lips, tongue, extremities, and bowel wall. Bowel wall AE may occur without skin involvement and cause abdominal pain, nausea, and rarely bowel obstruction. The leading cause of death is airway obstruction from laryngeal edema, with a mortality of 25% to 40%.[3] Episodes typically last between 2 and 3 days and may be isolated or recurrent.

SYNDROMES OF ANGIOEDEMA

Idiopathic Angioedema

The most frequent syndrome of AE is idiopathic recurrent AE, which occurs in 38% of patients, even after a thorough evaluation for other forms.[4]

Allergic or Immunoglobin-E–Mediated Angioedema

In allergic or immunoglobulin (Ig)-E–mediated AE, an identifiable allergen triggers a Type 1 hypersensitivity reaction in which activated mast cells release histamine and other vasoactive mediators.[5] Symptoms begin minutes to 1 hour after exposure. Common triggers include foods and medications (Table 3).

Hereditary Angioedema

Hereditary angioedema (HAE) is an autosomal dominant disorder that results from C1 esterase inhibitor (C1 INH) deficiency. C1 INH regulates the activity of the complement component C1, the first step in the classic complement cascade. In addition, C1 INH has a regulatory role in the contact, fibrinolytic, and coagulation pathways. Deficiency therefore results in unregulated activity of the vasoactive mediators bradykinin, kallikrein, and plasmin.

A gene mutation results in decreased expression of C1 INH in Type 1 affecting 85% of patients with HAE.[3] In Type 2, there are normal plasma levels of C1 INH, but the protein is dysfunctional. Type 3 is believed to be a mutation in coagulation factor XII, which results in increased kinin production.[6] Type 3 also is called estrogen-dependent type, because estrogen-containing medications increase symptoms. In all 3 types, episodes occur when inflammation, trauma, or unknown factors lead to the depletion of C1 INH. Attacks are sporadic with hands and feet being commonly

This work was supported by R01-HL-069949, R01-AI 054660, and R01-AI070672.

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0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2007.09.024

Table 1 Syndromes of Angioedema

Idiopathic recurrent AE
Allergic (IgE-mediated) AE
HAE:
- Type 1: deficiency of C1 INH protein
- Type 2: dysfunctional C1 INH protein
- Type 3: coagulation Factor XII gene mutation*

AAE:
- Type 1: associated with lymphoproliferative diseases.
- Type 2: autoimmune (anti-C1 INH antibody)

Medication-induced (eg, ACE inhibitors)
Physically induced (cold, heat, vibration, trauma, emotional stress, ultraviolet light)
Cytokine-associated AE syndrome (Gleich's syndrome)
Thyroid autoimmune disease-associated AE

Ig = immunoglobulin; C1 INH = C1 esterase inhibitor; ACE = angiotensin-converting enzyme; AE = angioedema; HAE = hereditary angioedema; AAE = acquired angioedema.
*Estrogen-dependent; associated with exogenous estrogen administration, such as oral contraceptives and hormone replacement therapy.

affected sites, and urticaria is rare. Symptoms usually begin during childhood but can start at any age.[7]

Acquired Angioedema

Acquired angioedema (AAE) also results from C1 INH deficiency. There are 2 types, and both are thought to be autoimmune. Type 1 is associated with lymphoproliferative diseases, including monoclonal gammopathy of unknown significance and high-grade lymphomas, and occurs via consumption of the C1 INH protein by malignant cells.[8] Type 2 is thought to be caused by the autoantibody to the C1 INH protein. AAE usually presents after the fourth decade of life.

Angiotensin-Converting Enzyme Inhibitors

AE occurs in 0.1% to 2.2% of patients taking angiotensin-converting enzyme (ACE) inhibitors and apparently occurs from elevated levels of bradykinin.[9] The incidence is highest (25%) during the first month of taking the medication, but the first event can occur spontaneously after many years of use.[9] Common locations include the tongue, lips, and face. It is 4 to 5 times more common in African Americans than whites.[10] There have been rare reports of AE with angiotensin receptor blockers; however, these medications are generally considered safe to start in patients with a history of ACE inhibitor AE.[9,10]

Table 2 Coexistent Urticaria in Syndromes of Angioedema

Not Associated with Urticaria
- HAE Type 1
- HAE Type 2
- Acquired C1 INH deficiency
- ACE inhibitor-associated AE
- Physically induced AE
- Idiopathic recurrent AE

Associated with Urticaria
- Chronic idiopathic urticaria/AE syndrome
- Allergic (IgE-mediated) AE
- Aspirin or nonsteroidal anti-inflammatory drug-induced AE
- Physically induced AE
- ACE inhibitor-associated AE

Ig = immunoglobulin; C1 INH = C1 esterase inhibitor; ACE = angiotensin-converting enzyme; AE = angioedema.

Table 3 Common Triggers if Mast Cell-Mediated Angioedema

Medications	Food	Other
Aspirin	Nuts	Venom
NSAIDs*	Eggs	Latex
Antihypertensives	Shellfish	
Narcotics	Soy	
Oral contraceptives	Wheat	
	Milk	

*Nonsteroidal anti-inflammatory drugs

Other Causes

AE also can be induced by physical stimuli, such as cold, heat, vibration, trauma, emotional stress, and ultraviolet light. Cytokine-associated AE syndrome, also known as episodic AE with eosinophilia or Gleich's syndrome, is characterized by fever, 10% to 20% weight gain, and elevated eosinophil and IgM levels in blood. The definitive cause is unknown; however, there is an increased level of the cytokines granulocyte-macrophage colony-stimulating factor, interleukin (IL)-3, IL-5, and IL-6, which implicate CD4+ T lymphocytes in the pathophysiology of this process.

DIAGNOSIS

Evaluation begins with a detailed patient history directed at identifying potential triggers, such as allergens, medications, and trauma. A physical examination to rule out other causes of edema, such as heart failure, also is important. Family history can assist in determining whether a hereditary component exists. An algorithm for differentiating the various causes of AE is shown in Figure 1.

Laboratory investigation is directed by clinical suspicion. For IgE-mediated disease, markers of mast cell degranulation (eg, serum tryptase) will be elevated during an acute episode (Table 4). Resolution of episodes after avoidance of a suspected trigger or discontinuation of a suspected medication can be diagnostic and therapeutic. Testing for allergen-specific IgE may be useful when an allergic trigger is suspected.

In patients with a family history of HAE or with suspected C1 INH deficiency, serum markers of complement activity are assessed (Table 4). These are abnormal even when the patient is asymptomatic and do not require measurement during an acute episode for diagnosis. HAE and AAE can be differentiated from each other by the C1q level,

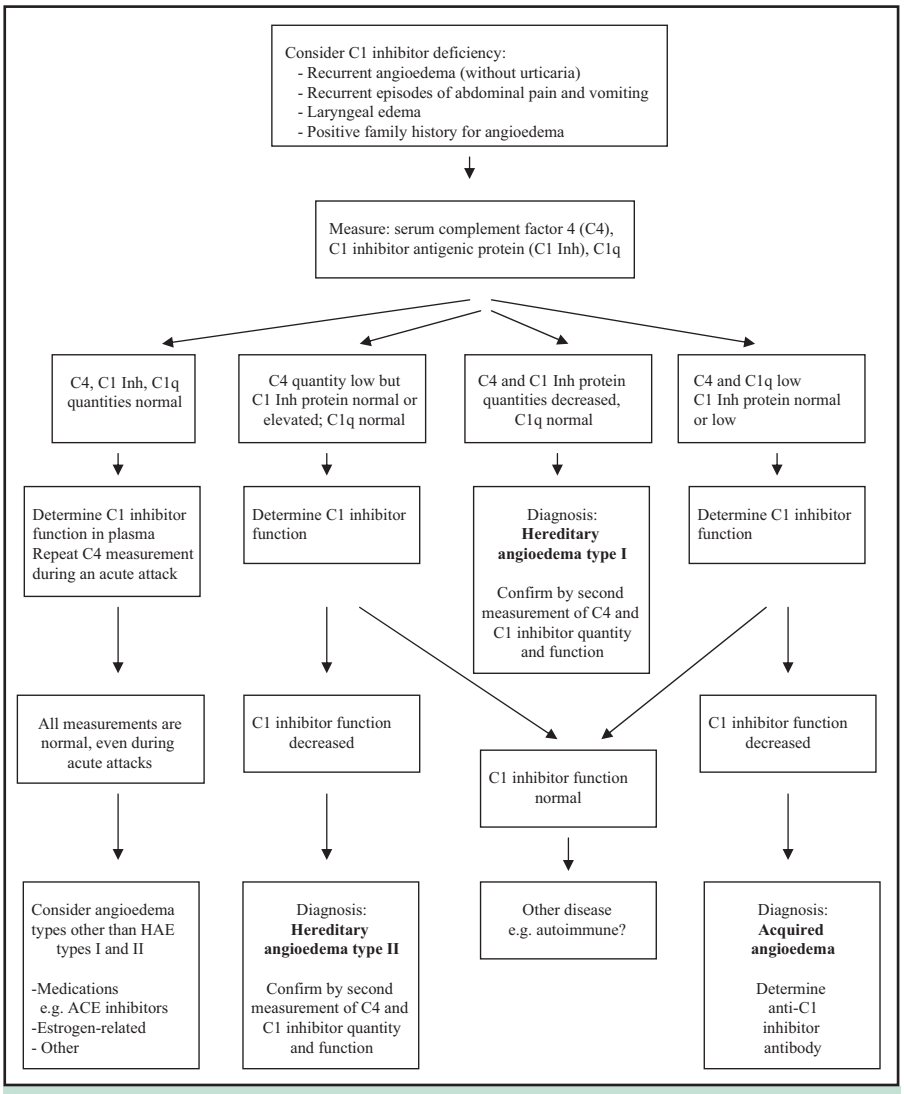

Figure 1 Diagnostic algorithm for AE. HAE = Hereditary angioedema; ACE = angiotensin-converting enzyme. Reprinted from Bowen T, Cicardi M, Farkas H, et al. Canadian 2003 International Consensus Algorithm For the Diagnosis, Therapy, and Management of Hereditary Angioedema. *J Allergy Clin Immunol.* 2004;114:629-637.

Table 4 Laboratory Evaluation in C1 Esterase Inhibitor Deficiency

	C1 INH Quantitative	C1 INH Activity	C3	C4	C1q	Urine Histamine	Tryptase
HAE Type 1	Low	Low	nl	Low	nl	nl	nl
HAE Type 2	nl or high	Low	nl	Low	nl	nl	nl
HAE Type 3	nl	nl	nl	nl	nl	nl	nl
AAE Type 1	Low	Low	nl	Low	Low	nl	nl
AAE Type 2	nl or low	Low	nl	Low	Low	nl	nl
Allergic AE	nl	nl	nl	nl	nl	high*	high*
Idiopathic	nl	nl	nl	nl	nl	nl	nl

C1 INH = C1 esterase inhibitor; HAE = hereditary angioedema; AAE = acquired angioedema; AE = angioedema; nl = normal.
*During the acute episode.

which is low in the acquired form and normal in the hereditary form. Functional and quantitative levels of C1 INH differentiate between Types 1 and 2, because the C1 INH level will be low in Type 1 and normal or high in Type 2. Patients with suspected AAE should be further evaluated for lymphoproliferative disease.

Idiopathic recurrent AE is diagnosed if 3 or more episodes occur within 6 to 12 months without an identifiable cause. Referral to an allergist-immunologist is helpful in patients with C1 INH deficiency and in patients with severe or recurrent episodes.

TREATMENT

Emergent Treatment: All Types

The first priority of acute management is airway protection. Providers must have a low threshold for intubation with the first signs of airway compromise. Laryngeal edema is typically progressive, and once it occurs it can make endotracheal intubation difficult, necessitating tracheostomy.

Allergic Angioedema

Allergen avoidance is the standard of treatment; however, antihistamines and glucocorticoids improve symptoms during an acute episode. Laryngeal edema responds well to epinephrine, which can be given intramuscularly or via an endotracheal tube. Daily antihistamines may decrease the severity of symptoms but often fail to prevent attacks.

Hereditary Angioedema

Patients with HAE should avoid taking ACE inhibitors and estrogen contraceptives. The treatment of choice for acute episodes of HAE is plasma-derived C1 INH concentrate. Used in Europe and Canada with success, plasma-derived C1 INH concentrate is not approved by the Food and Drug Administration for use in the United States.[11] Symptoms typically improve within 30 to 60 minutes of the infusion. Treatment with fresh-frozen plasma, which contains C1 INH, has been shown to be as effective as C1 INH concentrate.[9]

Attenuated androgens, such as danazol, have been used for many years for chronic prophylaxis of HAE. Androgens work by increasing the hepatic production of C1 INH. The lowest effective dose should be used, with a maximum dose of 600 mg daily.[4] Side effects include virilization, weight gain, and liver dysfunction. Patients receiving androgens should have a complete blood count, hepatic function panel, lipid profile, and urinalysis obtained every 6 months. A hepatic ultrasound should be obtained yearly to monitor for the possible development of hepatocellular carcinoma.

Antifibrinolytics, such as tranexamic acid and epsilon aminocaproic acid, have many side effects, are less effective, and are used only in patients who cannot take androgens.

C1 INH replacement also has been shown to be beneficial for short-term prophylaxis in patients undergoing elective procedures, such as surgery and dental extractions (Table 5).[12] One to 4 units of fresh-frozen plasma given the day before surgery significantly decreased the risk of having an episode of AE.[11] Alternatively, 10 mg/kg/d of danazol (maximum 600 mg daily) given for 4 days before and 4 days after the procedure also can be used.[4] Fresh-frozen plasma is safe to use in pregnancy and labor and delivery.

Table 5 Indications for Administration of Prophylactic Medications in Hereditary Angioedema

Long term
Severe episode >1 per mo
Disabled for >5 d/mo
History of laryngeal edema
Lack of acute treatment immediately available
Short term
Dental work
Surgery
Intubation
If risk of the procedure is uncertain
Lack of acute treatment immediately available

Acquired Angioedema

C1 INH concentrate and fresh-frozen plasma are the treatments of choice for acute episodes of AAE. These are less efficacious in AAE than in HAE because of the presence of autoantibody to the protein. Treatment of underlying lymphoproliferative disease is often curative in AAE Type 1.

Medications currently undergoing clinical trial include nanofiltered pasteurized C1 INH concentrate and recombinant human C1 INH protein.[12] These formulations replace but do not carry the risk of viral transmission.

Angiotensin-Converting Enzyme Inhibitor-Induced Angioedema

Definitive treatment is discontinuation of the agent because it is a class effect; patients should avoid all ACE inhibitors.

Idiopathic Recurrent Angioedema

Glucocorticoids have been shown to be of some benefit in the treatment of idiopathic episodes, but the risks of chronic therapy usually outweigh the benefits. Therefore, a daily antihistamine is the initial prophylactic therapy. Patients should be reevaluated every 3 to 4 months to determine whether any new symptoms or identifiable triggers have developed in the interim.

Other potential therapies, including bradykinin receptor antagonist (icatibant) and plasma kallikrein inhibitor (DX 88), are currently undergoing phase 2 trials in the United States. These medications work at the receptor level to block the response to elevated bradykinin and kallikrein levels found in patients with AE.

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