The spectrum of chronic angioedema

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ABSTRACT

This article focuses specifically on angioedema. Chronic angioedema represents a wide range of diseases and can be categorized into several forms including hereditary, acquired, drug induced, and idiopathic. Hereditary and acquired angioedema are known to be a result of abnormalities in C1 inhibitor protein while the mechanism of drug-induced and idiopathic angioedema is less clear. Significant advances have been made in recent years with regard to diagnosis and management of these patients leading to a significant reduction in morbidity and mortality. Several novel therapies are in clinical trials and should be available in the United States within the next year. There is still a lot to learn about the pathophysiology, diagnosis, and treatment of patients with chronic angioedema. This review will hopefully provide more information to the readers who care for patients with these disorders and also stimulate further interest and research into the pathophysiology of these conditions.


Key words: ACE inhibitors, androgens, angioneurotic, bradykinin, C1 inhibitor, hereditary, idiopathic, kallikrein, swelling

Angioedema is defined as nonpruritic, nonpitting areas of swelling of cutaneous and mucosal tissues and usually affects the deeper skin layer. Urticaria, or hives, is swelling of the superficial skin layer. In the clinical setting, patients can present with angioedema alone, urticaria alone, or a combination of urticaria and angioedema. Angioedema can be categorized into several forms: hereditary, acquired, associated with allergic reactions (i.e., venom hypersensitivity, latex allergy, adverse drug reactions, and food allergy), and idiopathic.

The hereditary and acquired forms of angioedema are more chronic in nature and not associated with urticaria. This type of isolated angioedema without urticaria is frequently bradykinin mediated and, thus, not responsive to antihistamines. Angioedema associated with allergic reactions is often not chronic and is associated with urticaria that is usually responsive to antihistamine therapy. Idiopathic angioedema represents a wide spectrum of disease with varying degrees of severity and chronicity. This review focuses specifically on chronic angioedema.

HEREDITARY ANGIOEDEMA

Introduction

Hereditary angioedema (HAE) was first described in 1840.1 In 1882, the term angioneurotic edema was assigned to these patients to describe the observed effect of mental stress on exacerbations in this disease.2 The autosomal dominant nature of this disease was identified in 1888 based on observations in each of five generations of a family.3 It was not until the early 1960s that the pathophysiology of HAE was better understood when the absence of C1 inhibitor4 and the deficiency of a kallikrein5 was described in these patients.

The prevalence of HAE in the literature ranges from 1:10,000 to 1:50,000.6 HAE is categorized into types I (80–85% of cases) and II (15–20% of cases). Types I and II are reported in all races with no sex predominance, which is not surprising based on its autosomal dominant inheritance pattern. Although it is often inherited, 20–25% of cases are from new spontaneous mutations. To date, >150 mutations have been identified in the C1 inhibitor gene.7 Both types of HAE have low C4 levels (although in rare cases the C4 can be normal), but type I HAE is associated with a low C1 inhibitor level and an abnormally functioning C1 inhibitor. Type II HAE,
on the other hand, often has normal levels of C1 inhibitor with a poorly functioning C1 inhibitor (Table 1) protein. A low C2 level may be found during an acute attack of HAE.8

Pathophysiology

The pathophysiology of HAE is characterized by a deficiency in C1 inhibitor. C1 inhibitor regulates the activation of the complement system and the contact system and seems to play a smaller role in the regulation of fibrinolysis and coagulation. The first classic pathway complement component, C1, is composed of three proteins, viz., C1q, C1r, and C1s. C1 inhibitor is the only protein that can inactivate both C1r and C1s and is therefore the primary regulator of the classic pathway.7,9 C1 inhibitor also plays a role in the inhibition of the other complement pathways via inhibition of manose-binding lectin associated serine protease-1 and -2. Thus, low levels of or a poorly functioning C1 inhibitor leads to unopposed activation of the complement system via C1. Regarding the contact system, C1 inhibitor is known to inactivate plasma kallikrein, factor XIIa, and plasmin. Although α2-macroglobulin is known to inhibit the activation of these proteins, C1 inhibitor remains the major regulator. Thus, the lack of inhibition via C1 inhibitor leads to persistent activation of the contact system and increased levels of bradykinin (Fig. 1). Bradykinin is the nanopeptide known to increase vascular permeability leading to angioedema in these patients.57

Clinical Presentation

Angioedema can involve any part of the body, but often presents as swelling of the face, lips, tongue, abdomen, larynx, extremities, and sometimes the genitals. Angioedema may involve the gastrointestinal tract, leading to intestinal wall edema, which results in symptoms such as abdominal colic, nausea, vomiting, and diarrhea. At least 50% of HAE patients have a laryngeal attack at some point during their lifetime.10 The swelling is nonpruritic and usually lasts 3–5 days before gradual resolution. Patients do not have associated urticaria, but can have a serpiginous rash known as erythema marginatum often as a prodromal manifestation. Most patients have a prodrome and can recognize several hours in advance that an attack is starting. Common triggers can include trauma, stress, infection, menstruation, oral contraceptives, hormonal replacement therapy, and angiotensin-converting enzyme (ACE) inhibitors.

Pregnancy has been associated with a decrease in serum C1 inhibitor and can worsen symptoms. However, pregnancy can be associated with a decrease in attack frequency. This can be explained by the fact that the total amount of C1 inhibitor may actually increase during pregnancy. HAE patients have been found to experience premature labor more often than unaffected family members.11–13

Table 1 Laboratory abnormalities in hereditary angioedema (HAE), acquired angioedema (AAE), and angiotensin-converting enzyme (ACE) inhibitor-associated angioedema

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>C4</th>
<th>C1 Inhibitor Function</th>
<th>C1 Inhibitor Level</th>
<th>C1q</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAE type I</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>HAE type II</td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>AAE</td>
<td>Low</td>
<td>Low</td>
<td>Normal/low</td>
<td>Low</td>
</tr>
<tr>
<td>ACE inhibitor–associated angioedema</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Complement System (classical pathway)

- C1q
- C1r
- Prekallikrein
- Kallikrein

Contact System

- HMWK → Bradykinin

Figure 1. Role of C1 inhibitor in the complement and contact systems.

Treatment

Attenuated androgens are the main class of medications used for many years for the short- and long-term treatment of patients with HAE.14 However, the adverse effects of the attenuated androgens including hirsutism, weight gain, seborrhea, acne, deepening of the voice, decreased breast size, menstrual irregularities, decreased libido, hepatic necrosis, cholestasis, hepatic neoplasms, hypertension, and abnormal lipoprotein metabolism15 have often been of concern. Periodic monitoring of liver function tests and lipid profiles is recommended in any patient on long-term therapy with androgens. Treatment regimens in many of the
Previously published studies of attenuated androgens typically start with high doses of androgens and taper down the dose every few weeks until the lowest maintenance dose that provided symptom control is reached. Alternatively, treatment with lower doses can be initiated with a progressive increase of the dose until symptoms are controlled and adverse effects are minimized. Antihistamines and corticosteroids have not been found to be helpful in treatment symptoms. The use of fresh frozen plasma in acute HAE attacks remains controversial.

The management of HAE must address the abrogation of acute episodes of angioedema and short- and long-term prophylaxis. Purified C1 inhibitor concentrate is very effective in treating patients with HAE. Unfortunately, there are no drugs, including C1 inhibitor concentrate, approved to date in the United States for the treatment of acute episodes, although there are many in clinical trials nearing Food and Drug Administration approval. These products in phase III clinical trials for the acute treatment of HAE include icatibant, a bradykinin receptor antagonist, and DX-88, a kallikrein inhibitor, along with two purified C1 inhibitor products and a recombinant C1 inhibitor product. Each of these products plays in role in inhibiting the generation of bradykinin.

Other Types of HAE

The term type III HAE has often been used to describe a new group of patients with the classic symptoms of HAE but without any abnormalities in C4 or C1 inhibitor. It was initially described only in women and felt to be estrogen related and has led to some using the terms estrogen related or estrogen dependent. More recently, a specific mutation in factor XII has been described in some of these patients. Interestingly, estrogen has been found to up-regulate this gain of function mutation in factor XII.

A recent report describes homozygous C1 inhibitor deficiency. The two homozygous patients, rather than failing to secrete C1 inhibitor, produced low levels of a poorly functioning C1 inhibitor protein. These patients had extremely low or absent levels of C1q, a finding different from the usual HAE patient with one mutant gene who has normal levels of C1q. The number and severity of angioedema attacks were very low in one patient and absent in the other patient; so, this appears to be a syndrome that may be different from the usual heterozygous HAE. In addition, their complement profile resembles a patient with acquired angioedema (AAE) rather than the usual HAE patient.

ACQUIRED ANGIOEDEMA

AAE was first described in a patient with lymphoproliferative disorder in 1972. A few years later, in 1986, the autoimmune nature of the disease was described in a patient found to have an autoreactive IgG against C1 inhibitor. The pathophysiology of this disease arises from rapid consumption of C1 inhibitor and loss of inhibition of the complement cascade leading to angioedema.

To date, there have been close to 140 cases of AAE (also known as acquired C1 inhibitor deficiency) described in the literature. Non-Hodgkin’s lymphoma was found in 20% of these patients and monoclonal gammopathy was in 35% of these patients. Other non-hematologic neoplasms, infections, and a variety of autoimmune diseases have also been found to be associated with AAE. This has led to the separation of AAE into two groups. AAE type I is associated with lymphoproliferative diseases or paraneoplastic syndromes. AAE type II is associated with autoimmune disease and these patients often have autoantibodies to C1 inhibitor.

The clinical presentation of AAE mimics that of patients with HAE and is clinically difficult to distinguish on symptoms alone. These patients differ from HAE by an absence of a family history of angioedema and a much later onset of symptoms, usually in the fourth decade of life or later. Patients with AAE have low levels (or activity) of C1 inhibitor, C4, and C1q. A low C1q along with an associated lymphoproliferative disease or autoimmune disease can help differentiate AAE from HAE.

Successful treatment of the underlying disease often leads to resolution of angioedema symptoms and biochemical abnormalities, but there are exceptions. Some patients may continue to have persistent biochemical abnormalities after treatment of the underlying disease but no clinical symptoms. In other patients, disappearance of angioedema may be temporary even without evidence of recurrent paraneoplastic disease.

DRUG-INDUCED ANGIOEDEMA

ACE inhibitors are the most common class of medications associated with isolated angioedema. However, we must also consider angiotensin receptor blockers, aspirin, NSAIDs, narcotics, antibiotics, IL-2, oral contraceptives, and interferon-α in our differential of medications associated with angioedema, although patients with adverse reactions to some of these other medications can present with a combination of urticaria and angioedema.

The incidence of angioedema from ACE inhibitors ranges in the literature from 0.1 to 2.2%. Angioedema from ACE inhibitors has a predilection for the face, tongue, and lips. Incidence of ACE inhibitor angioedema is highest in the first month of treatment, but can occur years later. There is a higher risk of angioedema in African Americans, patients with HAE,
women, smokers, and older age while diabetics seem to have a lower risk.25

The number of patients on ACE inhibitors continues to rise, leading to increasing rates of angioedema.26 In 2001, there were 35–40 million prescriptions written for ACE inhibitors worldwide,27 and in 2007, ACE inhibitors remain the most frequent class of medications prescribed for the treatment of hypertension.28 They are the most common class of medications associated with angioedema presenting to the hospital and emergency department.29 Although fatalities are exceedingly rare, patients may still need inpatient hospitalization and intensive care treatment for management of respiratory compromise and upper airway angioedema.

The mechanism of ACE inhibitor-induced angioedema remains unclear but may be related to increases in bradykinin levels.30,31 Bradykinin would normally be degraded by ACE, but its degradation by ACE is inhibited by ACE inhibitors. Other enzymes such as aminopeptidase P would degrade bradykinin in the presence of ACE inhibitors, but have also been reported to be deficient in patients with ACE inhibitor–induced angioedema, suggesting a possible cause of the angioedema.32 If elevated bradykinin levels or decreased degradation of bradykinin are the main causes of ACE inhibitor–induced angioedema, then current treatments (including antihistamines, corticosteroids, and epinephrine) will presumably not be helpful.33 Rather, newer agents such as bradykinin receptor antagonists or kallikrein inhibitors may provide novel alternatives for the treatment of ACE inhibitor–induced angioedema. These medications are currently under development for HAE and do not have Food and Drug Administration approval.34,35 Substance P accumulation as a result of low levels of dipeptidyl peptidase IV levels leading to an alternative explanation for ACE inhibitor–induced angioedema has also been proposed,36 but the exact mechanism leading to ACE inhibitor–induced angioedema is not known. Current treatment options are very limited and focus mainly on supportive care and discontinuation of the ACE inhibitor. Additional research into the exact mechanisms of ACE inhibitor–induced angioedema and development of novel treatment options are still needed.

IDIOPATHIC ANGIOEDEMA

Idiopathic angioedema is a diagnosis of exclusion after a thorough evaluation. It is often defined as three of more episodes of angioedema in a period of 6–12 months without a clear etiology.37 Idiopathic angioedema is felt to be the most common cause of chronic angioedema, but the true epidemiology is not known. Aside from what we discussed earlier in this article including HAE, AAE, and drug-induced angioedema, the differential diagnosis should also include allergic conditions such as food allergy, latex allergy, and less common conditions such as episodic (Gleich’s syndrome) and nonepisodic angioedema with eosinophilia (EAE and NEAE, respectively) and idiopathic capillary leak syndrome (Clarkson syndrome).

EAE was first described in 1984.38 Although several hypotheses have been proposed, the exact etiology remains unclear. The main hypothesis suggests a role for helper T cells leading to an increase of cytokines including granulocyte monocyte colony-stimulating factor,39 IL-3, IL-5,40 and IL-6.41 EAE is characterized by recurrent episodes of angioedema, urticaria, pruritus, fever, weight gain, elevated serum IgM,42 oliguria, and leukocytosis with peripheral blood eosinophilia and eosinophil degranulation in the dermis. Episodes usually occur every few weeks to months with complete resolution of symptoms between episodes. EAE is rare and can be difficult to diagnose but has a good prognosis with no visceral organ involvement. Low-dose oral steroids are felt to be the best initial treatment for EAE.43

NEAE was first proposed in 198844 as a separate entity from EAE because it was less severe and usually was limited to one attack. NEAE should be considered in patients, particularly women, who present with edema of bilateral upper or lower extremities and eosinophilia without urticaria. NEAE is responsive to low-dose corticosteroid or antihistamine therapy,42,44,45 but often no treatment is needed because spontaneous remission frequently occurs.46 This is in contrast to EAE, where spontaneous remission without any treatment is rarely seen.

Idiopathic capillary leak syndrome is a rare syndrome that was first described by Clarkson in 1960.47 Attacks vary in frequency, severity, and duration, but can be life-threatening with a 5-year mortality rate of 70–80%.48 This syndrome usually affects individual’s aged 30–50 years with a mean age of 46 years.49 Marked thirst is described early in the attack with subsequent muscle weakness, abdominal pain, nausea, and vomiting with generalized edema. Generally, the edema appears several hours or days before the onset of acute renal failure, pulmonary edema, and shock. This is often associated with hypoalbuminemia, rhabdomyolysis, and monoclonal gammopathy. In addition to plasma expanders and steroids, terbutaline, epoprostenol, salbutamol, loop diuretics, calcium antagonists and Gingko biloba extract have also been reported to show some success.50–52 C1 esterase inhibitor therapy has also been reported to be successful in a small number of patients and is thought to decrease symptoms via early inactivation of the complement and contact systems.53 The underlying cause is not fully understood, but this disorder is believed to be due to an alteration of endothelium permeability leading to a
rapid shift of plasma form the intravascular to the extravascular compartment.\textsuperscript{51}

Evaluation of a patient suspected of having idiopathic angioedema should include a comprehensive physical exam with a detailed personal and family history, food, or latex skin testing if appropriate, and additional labs including C4, C1Q, C1 inhibitor, CBC, serum protein electrophoresis, IgE, and erythrocyte sedimentation rate. One may want to consider a skin biopsy for further evaluation if underlying vasculitis is suspected.

There is still much to be learned about the pathophysiology, diagnosis, and treatment of patients with angioedema. Our hope is that this review will be of help to those readers who care for patients with these disorders and will stimulate interest in further research into the pathophysiology of these conditions.

REFERENCES


