Hereditary angioedema (HAE) is characterized by sudden attacks of deep tissue swelling caused by C1 inhibitor deficiency. Swelling severity can vary from mild to severe, and some patients are at risk for disability and death from either asphyxiation or hypovolemic shock. Many HAE attacks are precipitated by trauma or stress. The extremities, genitalia, trunk, bowels, face, and larynx are commonly affected areas, but swelling can affect any single part of the body or multiple sites. Symptoms typically worsen over 24 to 36 hours and resolve within 48 hours. Because many symptoms of HAE overlap with those of other medical conditions, diagnosis may be delayed. A thorough family history can identify the signature symptoms of HAE, which include a family history of HAE, recurrent edema without urticaria, and symptomatic worsening during puberty. The author presents two hypothetical cases of HAE and reviews the clinical hallmarks of this condition, diagnostic tests, and available treatments.

Clinical Practice

Diagnosis and Management of Hereditary Angioedema

Douglas T. Johnston, DO

Hereditary angioedema (HAE) is a debilitating disease characterized by sudden attacks of brawny, nonpitting, and often painful edema.\(^1\) The extremities, genitalia, trunk, bowels, face, and larynx are commonly affected. Among untreated patients, death from asphyxiation during laryngeal attacks has been reported in as many as 30% of cases,\(^2\) and the possibility of asphyxiation from a first laryngeal attack is cause for concern. However, awareness of symptoms and effective interventions among physicians, patients, and families will reduce the risk of life-threatening crises.

Hereditary angioedema is an inherited autosomal dominant disorder. Offspring have a 50% chance of inheritance when 1 parent has HAE. However, 25% of cases have no family history and may arise from spontaneous mutations.\(^3\) Hereditary angioedema is caused by a deficiency or dysfunction in C1 inhibitor (C1-INH).\(^3\) Approximately 85% of cases are type 1 HAE, which is characterized by a reduced quantity of circulating C1-INH.\(^4\) Type 2 HAE, accounting for approximately 15% of cases, is characterized by dysfunctional circulating C1-INH.\(^4\)

Estimates suggest that as many as 1 in 50,000 people have HAE.\(^5\) Thus, there may be as many as 6000 HAE cases in the United States.\(^5\) Phenotypic expression in HAE may vary widely—even among family members. The frequency and severity of attacks is unpredictable, making it difficult to correlate clinical symptoms with subtype of disease.\(^4\) Mean age of symptom onset is 11.2 years.\(^6\) The diagnosis of HAE may lag considerably behind symptom onset and may not occur until 10 to 22 years after the first attack.\(^7\) This lengthy diagnostic delay places patients at increased risk of death or disability.

Research indicates that HAE is not more prevalent in patients of a given sex or race, although women tend to present with this condition more frequently than do men.\(^1\) A large percentage of affected women report more severe symptoms at puberty and while taking estrogen-containing oral contraceptives.\(^8\) By contrast, less severe symptoms have been reported by women taking progesterone-only oral contraceptives.\(^8\) These reports suggest that fluctuating estrogen levels may worsen symptoms of HAE.

In the United States, as many as 30,000 annual visits to emergency departments result from HAE.\(^9\) The presence of severe swelling can be mistaken for an allergic reaction or acute abdominal condition. Misdiagnosis can lead to ineffective therapies, unnecessary surgeries, or other inappropriate medical procedures in one-quarter of patients with HAE presenting to emergency departments.\(^10\) It is important to evaluate patients with HAE for additional medical conditions when they present to the emergency department. In patients with a diagnosis or family history of HAE who present with their first episode of severe swelling or abdominal pain, an evaluation for all potential causes will prevent misdiagnosis of other potential emergencies.

In the present article, I discuss 2 hypothetical cases of HAE and examine the clinical characteristics of this condition and the diagnostic tests and treatments that are available for patients with the disorder.

Financial Disclosures: Dr Johnston has received research support and speaker honoraria/fees from ViroPharma Inc in Exton, Pennsylvania. Dr Johnston also received an honorarium from ViroPharma for his authorship of this article.

Address correspondence to Douglas T. Johnston, DO, Allergy Partners of the Upstate, 48 Creekview Ct, Greenville, SC 29615-4800.

E-mail: djohnston@allergypartners.com

Submitted September 22, 2009; revision received March 17, 2010; accepted May 11, 2010.
rash can be distinguished from urticaria because erythema marginatum is neither raised nor pruritic.\(^7\) Erythema marginatum may appear on the trunk and appendages before or during an HAE episode (Figure 1). Prodromal symptoms, including a tingling sensation, may precede an HAE attack.\(^7\) Episodes of swelling commonly worsen over 24 to 36 hours and resolve gradually over the next 36 to 48 hours. Severe attacks may last for 5 days.\(^11\) Swelling may be isolated to a single part of the body or may affect multiple sites simultaneously (Figure 2).\(^3\)

The severity and location of HAE attacks are highly variable and unrelated to the magnitude of C1-INH dysfunction.\(^4\) The mean number of annual attacks was 26.9 in 1 survey of

**Reports of Cases**

**Case 1**

A 19-year-old man presented to the emergency department with abdominal pain that began 3 hours previously. The pain had increased in severity and progressed to cramping, nausea, and vomiting. The patient denied having diarrhea, melena, hematemesis, syncope, dyspnea, or fever. Vital signs of the patient were a blood pressure of 119/85 mm Hg, a pulse of 86 beats per minute, a respiratory rate of 34 breaths per minute, and a temperature of 98.0°F (36.7°C). The patient’s white blood cell count was within normal parameters.

Head, neck, and cardiothoracic examinations of the patient yielded normal findings. His abdomen was mildly protuberant with normal bowel sounds and diffuse tenderness with voluntary guarding. Results of rectal, genital, extremity, and neurologic examinations were all unremarkable.

A review of the patient’s medical history revealed recurrent attacks of abdominal pain or discomfort since the age of 11 years. At age 14 years, these attacks became severe enough to warrant hospitalization once or twice per year. The patient’s father had experienced similar episodes, which resolved spontaneously after several days regardless of treatment.

**Case 2**

A 27-year-old woman presented to the emergency department with dysphagia, swelling of the left side of the face, and severe swelling of the left eyelid, which impaired her vision. The patient had undergone extraction of a left upper tooth 5 hours previously. She was referred to the emergency department for the facial swelling, which began immediately after the dental procedure. Her vital signs were a blood pressure of 125/82 mm Hg, a pulse of 84 beats per minute, a respiratory rate of 36 breaths per minute, and a temperature of 98.2°F (36.8°C). Her oxygen saturation was 93% with room air. Results of laboratory tests, including white blood cell count, were normal.

Physical examination of the patient revealed edematous swelling of the left side of the face that was most pronounced in the periorbital area and the lips. The swelling was not painful on palpation, was not warm to touch, and was not red. The only evidence of intraoral inflammation was an edematous uvula. Radiographs showed no dentoalveolar abscesses. However, a computed tomographic scan showed severe swelling of the oropharynx and hypopharynx.

A review of the patient’s history revealed recurrent bouts of extremity swelling since age 14 years, rare attacks of mild facial swelling, and irritable bowel disease. There was no family history of swelling. The patient reported no previous hospitalizations for swelling.

**Clinical Presentation**

Swelling without urticaria is the hallmark of HAE. However, one-third of patients will have erythema marginatum. This

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**Figure 1.** The serpiginous, nonpruritic rash of erythema marginatum, which precedes an attack of hereditary angioedema in one-third of patients. The rash is characterized by red rings that appear on the trunk and appendages as part of a prodrome that may also include a tingling sensation in the area where swelling will occur.\(^7\) Reproduced with permission from the US Hereditary Angioedema Association.

**Figure 2.** A young woman before (left) and during (right) an episode of facial hereditary angioedema. Such attacks cause disfigurement that can reduce a patient’s quality of life and social interaction. Patients are at risk of asphyxiation from laryngeal involvement during facial attacks.\(^16\) Reproduced with permission from the US Hereditary Angioedema Association.
patients with HAE. However, weekly attacks and symptom-free periods are common in untreated patients.

Many HAE attacks are triggered by trauma or stress, but they can also be spontaneous, occurring without an obvious trigger. Known causes of attacks include physical trauma; surgical, medical, or dental procedures; mechanical pressure during daily activities (eg, typing, hammering, standing for a long period); infection; emotional stress; and certain medications, such as angiotensin-converting enzyme (ACE) inhibitors and estrogen-containing oral contraceptives. Trauma or emotional stress may be responsible for half of HAE attacks.

Nonemergency Cases
Among all patients with HAE, 96% will be affected by angioedema in 1 or more extremities. Such cases are the most common type of HAE attack and often leave patients unable to perform daily activities, such as walking, writing, or typing. In addition, swollen joints may lead to discomfort and immobility. These episodes rarely lead to hospitalization, but they may greatly reduce the patient’s ability to work, to attend school, or to participate in recreational activities.

Urogenital attacks can be triggered by sexual intercourse, childbirth, or other activities that place pressure on the pelvic area. These episodes are common among patients with HAE and usually lead to swelling and discomfort. They rarely require urgent intervention, but treatment for symptomatic relief may be necessary.

Emergency Cases
Abdominal angioedema may affect 93% of patients with HAE, making it the second most common form of HAE attack. Abdominal attacks range from mild to severe, and pain is spasmodic with increasing intensity. Vomiting, constipation, diarrhea, and intestinal obstruction can occur. The most feared complication during abdominal attacks is hypovolemic shock resulting from extravasation of fluids. The abdomen during such episodes is typically protuberant and tender. Rebound tenderness and guarding may also be present. Bowel sounds may be either reduced or hyperactive.

The symptoms of an abdominal HAE attack can mimic those of surgical emergencies. Patients may present with severe cramps, nausea, and vomiting in the absence of cutaneous symptoms—the same hallmarks of appendicitis or cholecystitis. Patients may need emergency consultation for pain control. Patients who experience hypotension from an abdominal HAE episode may require aggressive rehydration to prevent hypovolemic shock. It is important to approach each abdominal attack as a potential emergency, especially if hypotension is present, because imaging studies may be needed to differentiate between emergency and nonemergency cases.

Severe swelling may cause temporary disfigurement, which contributes to decreased quality of life and impaired social interaction for patients. Approximately half of patients with HAE will have at least 1 laryngeal attack in their lifetime. Laryngeal attacks are associated with statistically significant mortality and frequently necessitate intubation or tracheotomy to prevent asphyxiation. Therefore, patients with laryngeal swelling will require an emergency department visit and, if the attack does not dissipate, hospitalization. To prevent asphyxiation from laryngeal involvement, it is imperative that all patients with facial HAE episodes be treated as emergency cases.

Pathophysiologic Mechanisms
Overproduction of bradykinin in the contact system pathway is the primary pathologic mechanism responsible for swelling during episodes of HAE. Bradykinin is a potent vasodilatory peptide regulated by factor XII and plasma kallikrein. Kallikrein cleaves bonds in high-molecular-weight kininogen, releasing bradykinin (Figure 3). Binding of bradykinin to its B1 receptor on endothelial cells leads to increased vascular permeability and edema. C1-INH is the primary regulator of both the contact system pathway and the classical complement pathway. It prevents overproduction of bradykinin by inhibiting several steps in the contact system pathway that lead to the activation of kallikrein (Figure 3).

Patients with HAE have C1-INH levels that are 5% to 30% of normal levels. Because C1-INH is a suicide inhibitor, proteins that are consumed cannot be readily regenerated. C1-INH depletion results in unchecked production of bradykinin and consequent swelling episodes. It is important to note that HAE attacks are not caused by histamine- or immunoglobulin E-mediated allergic inflammation.

Differential Diagnosis
Hereditary angioedema can be characterized by nonpitted, nonpruritic subcutaneous or submucosal edema, with possible nonpruritic serpiginous erythematous rash. Symptoms overlap with those of other disorders that feature angioedema. Therefore, an appropriate management strategy cannot be determined until the root cause of the attacks is identified. Figure 4 depicts an algorithm to guide diagnosis of HAE. Because of the complexity of this disease, the diagnosis should be confirmed by an allergy and immunology specialist who has experience with HAE. Initial management decisions can be made in conjunction with the specialist, and the patient with HAE should see the specialist for periodic follow-up to ensure optimum control of symptoms.

Laboratory testing of patients suspected of having HAE will aid in accurate diagnosis. Testing for C4 complement protein serves as a useful initial screening tool. Patients with HAE typically have low levels of C4 complement protein and normal levels of C1 and C3 complement proteins. In rare cases, C4 complement protein levels may be normal in patients between HAE attacks. Follow-up laboratory tests will be needed to verify the diagnosis and to distinguish among possible sub-
It is important to remember that as many as 25% of HAE cases result from spontaneous genetic mutations.7 Spontaneous cases of HAE are initially indistinguishable from acquired, idiopathic, or medication-induced angioedema or Gleich syndrome—especially when the patient has no family history of HAE. Acquired angioedema typically appears in the fifth decade of life20 and can be distinguished from HAE by 2 clinical factors: (1) HAE typically emerges in childhood or adolescence and (2) the patient has no family history of angioedema.21 Acquired angioedema is often associated with autoimmunity, malignancy, or lymphoproliferative disorders. Although HAE and acquired angioedema can share the same clinical features, a low C1q complement protein level is characteristic of only acquired angioedema. The C1q complement protein level would be normal in individuals with HAE. Therefore, C1q level can help to distinguish between the 2 diseases.2

Recurrent angioedema of 3 or more episodes in a single year with no apparent cause suggests idiopathic angioedema.22 As many as 20% of people worldwide have idiopathic angioedema, the most common type of recurrent angioedema. More women than men may have this condition.22 Half of patients may experience urticaria with episodes of idiopathic angioedema.22 The presence of urticaria may help distinguish idiopathic angioedema from angioedema of other etiologic mechanisms.22 Complement protein levels will typically be normal in patients with idiopathic angioedema.22 Recent research suggests that many cases of idiopathic angioedema are autoimmune conditions.23 In patients with chronic autoimmune urticaria and angioedema, autoantibodies against IgE receptors on the surface of mast cells and basophils trigger degranulation without the presence of an allergen. Autoantibodies against IgE have also been described.23 Angiotensin-converting enzyme inhibitors may be the second most common cause of angioedema, based on the large number of patients who are prescribed these medications. The manifestation of this condition closely resembles that of HAE. The reported incidence of ACE inhibitor–induced angioedema varies widely, from 0.1% to 6% of patients treated with these agents.24 The lips, tongue, and face are the most common sites of ACE inhibitor–induced angioedema, although the bowel wall may be involved in rare cases.24 These adverse events of ACE inhibitors typically occur in the first month of treatment.24 In some cases, the adverse events may not emerge

Figure 3. Hereditary angioedema (HAE) attacks involve the activation of the contact, complement, and fibrinolytic plasma proteolytic cascades. C1 inhibitor (C1-INH) is irreversibly consumed in each activated pathway. Because patients with HAE have inadequate stores of C1-INH, they cannot replace it as it is consumed in proteolytic pathways. Bradykinin is a vasodilatory peptide regulated by factor XII and plasma kallikrein. Kallikrein cleaves bonds in high-molecular-weight kininogen, resulting in the unimpeded production of bradykinin in the contact pathway. Binding of bradykinin to its B2 receptors on endothelial cells leads to increased vascular permeability and edema. Ecallantide is a kallikrein inhibitor approved by the US Food and Drug Administration for treatment of patients with acute HAE attacks. Icatibant is an antagonist of bradykinin B2 receptors that is currently under investigation for use in patients with acute HAE attacks. C1, C2, C3, and C4 are complement proteins. Reproduced with permission from Zuraw.7

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Types of HAE.7 Low levels of circulating C1-INH and low levels of functional C1-INH suggest type 1 HAE, whereas normal levels of circulating C1-INH and low levels of functional C1-INH suggest type 2 HAE.7

Commercial laboratories may offer C1-INH and C4 panels as separate tests, and more specialized laboratories may offer an angioedema-specific panel. Figure 5 summarizes clinical characteristics and laboratory markers that can be used to distinguish among HAE subtypes and other conditions with similar symptoms.
for months or years, and they may spontaneously remit and recur. African Americans experience ACE inhibitor–induced angioedema at a rate 4 to 5 times greater than do white Americans.

Angioedema induced by ACE inhibitors may occur anytime during the course of treatment, typically without urticaria. Elevated bradykinin levels in patients with ACE inhibitor–induced angioedema typically result from reduced degradation of bradykinin. Discontinuation of ACE inhibitor use is currently the best treatment for such patients, who can often tolerate alternative antihypertensive agents. Most patients with ACE inhibitor–induced swelling tolerate angiotensin receptor blockers. However, swelling has been reported in some individuals switched from ACE inhibitors to angiotensin receptor blockers.

Gleich syndrome is characterized by episodic angioedema associated with eosinophilia and elevated levels of IgM antibodies. A quantitative immunoglobulin level test and a complete blood cell count with differential cell enumeration can help in the diagnosis of this syndrome when complement studies yield normal results.

Figure 4. Differential diagnostic algorithm for hereditary angioedema (HAE) and other forms of angioedema (AE). A low level of C1 inhibitor (C1-INH) supports a diagnosis of HAE in the absence of a family history, because 25% of HAE cases are spontaneous. C1 and C4 are complement proteins. Reprinted with permission from Zingale et al, 2006. © Canadian Medical Association. This work is protected by copyright and the making of this copy was with the permission of Access Copyright. Any alteration of its content or further copying in any form whatsoever is strictly prohibited unless otherwise permitted by law.
Treatment

All patients with HAE will require an individualized management plan to reduce their disease burden. Prophylaxis may help reduce the frequency and severity of HAE attacks in many patients.

Routine Prophylaxis

Only 2 agents are currently approved by the US Food and Drug Administration (FDA) for long-term prophylaxis of HAE attacks—human C1-INH concentrate and the attenuated androgen danazol.

Cinryze (C1 esterase inhibitor [human]; ViroPharma Inc, Exton, Pennsylvania) is approved for routine prophylaxis of HAE attacks in adults and adolescents. Cinryze is administered intravenously at a dose of 1000 U every 3 or 4 days. C1 esterase inhibitor concentrate works by increasing plasma levels of C1 esterase inhibitor, thus correcting the underlying deficiency.

In a double-blind, placebo-controlled, crossover study, 24 adults and adolescents who had HAE and a history of 2 or more episodes per month were randomized to 1 of 2 treatment arms: (1) 12 weeks of C1 esterase inhibitor concentrate followed by 12 weeks of placebo, or (2) 12 weeks of placebo followed by 12 weeks of C1 esterase inhibitor concentrate. Among the 22 patients who completed the study, patients receiving C1 esterase inhibitor concentrate prophylaxis reported half the number of HAE attacks of patients receiving placebo (P <.001). Patients receiving active therapy who had attacks reported that the attacks were significantly less severe (P <.001) and of significantly shorter duration (P <.001) than those in patients receiving placebo who had attacks.

The results of this crossover study demonstrated clinically meaningful symptom reductions in patients with HAE who were given C1 esterase inhibitor concentrate. Upper respiratory infection, sinusitis, rash, and headache were the most common adverse reactions from using this prophylactic agent.

Danazol is FDA approved for prophylaxis of HAE attacks in adults. Danazol is available in 200-mg, 100-mg, and 50-mg capsules. The recommended initial dosage is 200 mg up to 3 times daily. The initial dosage may be reduced to the lowest effective dose once symptom control is achieved. Attenuated androgens, such as danazol, are believed to work by increasing C1-INH levels via hepatic stimulation.

In a retrospective analysis of clinical records of 118 patients who received long-term danazol prophylaxis, treatment was found to be associated with an 83.8% reduction in the mean number of annual HAE attacks. Nearly one-quarter of patients reported being symptom-free during danazol treatment. The other 75% of patients continued to have attacks, although at a reduced frequency. Of all patients, 14.4% continued to have 11 or more attacks per year.

Among all patients in the retrospective analysis of danazol prophylaxis, 78.8% reported adverse events. Weight gain, menstrual irregularities, virilization in women, headache, myalgia, depression, and acne were the most common adverse events. Adverse cardiovascular events (eg, myocardial infarction, stroke, deep vein thrombosis) were reported in 3 patients. In addition, 1 case of acute pancreatitis and 1 case of liver cell adenoma were reported. In my own clinical experience, I have found that patients using danazol may experience cholesterol abnormalities—specifically, increased levels of low-density lipoprotein cholesterol and decreased levels of high-density lipoprotein cholesterol.

The antifibrinolytics, e-aminocaproic acid and tranexamic acid, have been used for HAE attack prophylaxis in Europe. These agents have also been used in the United States for children and pregnant women who require long-term prophylaxis—but they are not FDA-approved for these purposes. Common adverse events associated with antifibrinolytics include nausea, vertigo, diarrhea, postural hypotension, fatigue, and muscle cramps.

Procedural Prophylaxis

Danazol is the only medication to my knowledge indicated for procedural prophylaxis of HAE attacks. The short-term dosage of 600 mg daily is typically administered for 1 week before and after a surgical, medical, or dental procedure.

Fresh frozen plasma is used in clinical practice to increase C1-INH levels and is typically administered 1 to 12 hours before a procedure. Likewise, C1-INH concentrate has been used safely and effectively to prevent postprocedure HAE attacks.

Management of Acute Attacks

Two medications are currently FDA-approved for the treatment of patients with acute HAE attacks. Berinert (plasma-derived C1 esterase inhibitor [human]; CSL Behring, King of Prussia, Pennsylvania) is approved for the treatment of adults and adolescents who have acute abdominal or facial HAE episodes. Berinert is supplied in vials of 500 U. The approved dose is 20 U/kg of body weight.

Berinert was studied in 125 adults and adolescents with HAE in a randomized, double-blind, placebo-controlled clinical trial. Patients received either Berinert (10 U/kg or 20 U/kg) or placebo. Patients randomly assigned to receive 20 U/kg of active drug reported statistically significantly reduced time to symptom relief compared with patients who received placebo (P = .0025). No treatment difference was observed between Berinert 10 U/kg and placebo. Common adverse reactions associated with plasma-derived C1 esterase inhibitor included subsequent HAE attack, abdominal pain, diarrhea, headache, muscle spasms, nausea, pain, and vomiting.

Kalbitor (ecallantide; Dyax Corp, Cambridge, Massachusetts) is a kallikrein inhibitor that is FDA-approved for the treatment of patients aged 16 years or older who have acute HAE attacks. Kalbitor is supplied in vials of 10 mg. The
<table>
<thead>
<tr>
<th>Angioedema Type</th>
<th>Clinical Description</th>
<th>Laboratory Results</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HAE</strong></td>
<td></td>
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<tr>
<td>□ Type 1</td>
<td>Recurrent episodes of swelling in any part of body, without urticaria</td>
<td>Low</td>
<td>C1-INH Low Normal Normal Low</td>
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<td></td>
<td>Family history of HAE</td>
<td></td>
<td>C1q Low Normal Normal</td>
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<td></td>
<td>First symptoms in childhood; worsening symptoms at puberty</td>
<td></td>
<td>C3 Normal Low</td>
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<tr>
<td></td>
<td>Erythema marginatum precedes attack in one-third of cases</td>
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<td>C4 Low</td>
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<td></td>
<td>Attacks can last 3-5 days</td>
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<td></td>
<td>Swelling resolves in 48 hours in less severe cases</td>
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<td></td>
<td>C1-INH concentrate (may require doses &gt;1000 U)</td>
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<td></td>
<td></td>
<td>Antihistamines required for procedural prophylaxis</td>
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<tr>
<td>□ Type 2</td>
<td>Same as type 1</td>
<td>Normal</td>
<td>C1-INH Low Normal Normal Low</td>
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<td></td>
<td></td>
<td>C1q Low Normal Normal</td>
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<td></td>
<td>C3 Normal Low</td>
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<td></td>
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<td></td>
<td>C4 Low</td>
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<tr>
<td>□ Type 3</td>
<td>Same as type 1, with possible estrogen sensitivity</td>
<td>Normal</td>
<td>C1-INH Normal Normal Normal Normal Low</td>
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<td></td>
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<td></td>
<td>C1q Normal Normal</td>
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<td>C3 Normal Normal</td>
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<td>C4 Normal Normal</td>
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<td><strong>AE</strong></td>
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<tr>
<td>□ Acquired</td>
<td>Appears in middle age</td>
<td>Low or normal</td>
<td>C1-INH Low Normal Low Low</td>
</tr>
<tr>
<td></td>
<td>No family history of episodic swelling</td>
<td></td>
<td>C1q Low or normal</td>
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<td></td>
<td>C3 Normal Low</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>C4 Low</td>
</tr>
<tr>
<td>□ Idiopathic</td>
<td>3 episodes of swelling in 1 year with no apparent cause</td>
<td>Normal</td>
<td>C1-INH Normal Normal Normal Normal Low</td>
</tr>
<tr>
<td></td>
<td>May be more prevalent in women</td>
<td></td>
<td>C1q Normal Normal</td>
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<tr>
<td></td>
<td>Urticaria is present in half of cases</td>
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<td>C3 Normal Normal</td>
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<td></td>
<td>C4 Normal Normal</td>
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<tr>
<td>□ ACE inhibitor-induced</td>
<td>Closely resembles HAE</td>
<td>Normal</td>
<td>C1-INH Normal Normal Normal Normal Low</td>
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<tr>
<td></td>
<td>Common sites include lips, tongue, face; rarely bowels</td>
<td></td>
<td>C1q Normal Normal</td>
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<tr>
<td></td>
<td>Typically presents in first 3 months of ACE inhibitor use</td>
<td></td>
<td>C3 Normal Normal</td>
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<tr>
<td></td>
<td>Adverse event caused by any ACE inhibitor</td>
<td></td>
<td>C4 Normal Normal</td>
</tr>
<tr>
<td>□ Allergic</td>
<td>Swelling, typically with urticaria; possibly pruritic</td>
<td>Normal</td>
<td>C1-INH Normal Normal Normal Normal Low</td>
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<tr>
<td></td>
<td>Possible anaphylaxis</td>
<td></td>
<td>C1q Normal Normal</td>
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<td></td>
<td>Caused by exposure to environmental allergen or drug</td>
<td></td>
<td>C3 Normal Normal</td>
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<tr>
<td></td>
<td>Reactions have 24-72 hour duration</td>
<td></td>
<td>C4 Normal Normal</td>
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<tr>
<td>□ Gleich Syndrome</td>
<td>Episodic swelling associated with eosinophilia and elevated IgM antibodies</td>
<td>Normal</td>
<td>C1-INH Normal Normal Normal Normal Low</td>
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<tr>
<td></td>
<td>Also useful in diagnosis is quantitative immunoglobulin level test</td>
<td></td>
<td>C1q Normal Normal</td>
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<td></td>
<td>and complete blood count with differential cell count</td>
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<td>C3 Normal Normal</td>
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<td></td>
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<td>C4 Normal Normal</td>
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approved dose of 30 mg is achieved in 3 10-mg subcutaneous injections.

The use of Kalbitor was studied in 143 individuals with HAE in 2 randomized, double-blind, placebo-controlled clinical trials. Patients who had 1 or more moderate to severe HAE symptoms during an attack at any anatomic site were randomized to receive either 30 mg of Kalbitor subcutaneously or placebo. Patients who received active drug reported statistically significant improvement on measures of symptom severity and symptom response to treatment, compared to patients who were given placebo (P < .05). A larger percentage of patients who received placebo required additional treatment for unresolved symptoms, compared to patients receiving active drug. Common adverse events associated with Kalbitor included headache, nausea, diarrhea, pyrexia, injection site reactions, and nasopharyngitis. Kalbitor carries an FDA “black box” warning for the risk of anaphylaxis.

Although C1-INH concentrate, epinephrine, and fresh frozen plasma are common off-label treatments in the United States for patients with HAE, some of these agents have questionable efficacy. For example, epinephrine has no proven efficacy against HAE, and fresh frozen plasma may introduce adverse effects and exacerbate an attack.

Attenuated androgens and antifibrinolytics are often used for HAE attack prophylaxis, but these agents require several days to produce beneficial effects and, therefore, have no efficacy against acute attacks. Similarly, corticosteroids and antihistamines provide no benefits for patients with HAE, because HAE is not a hypersensitivity disorder. Newly approved medications, such as Cinryze, Berinert, and Kalbitor, are directed at the underlying pathologic mechanisms of HAE and, thus, are more efficacious for patients with this condition.

Investigational Agents

Firazyr (Jerini AG, Berlin, Germany), a bradykinin antagonist, is currently approved in Europe for management of acute HAE attacks. It remains under investigation in the United States. In addition, Rhucin (Pharming Group NV, Leiden, The Netherlands), a recombinant C1-INH, is being studied for management of acute HAE attacks.

Treatment and Follow-Up in Hypothetical Cases

Case 1 describes a 19-year-old man with severe abdominal pain who required hospitalization. His history of attacks, as well as his family history, were key points that helped to broaden the differential diagnosis, especially since other diagnostic modalities were inconclusive. A test for C4 complement protein was performed first, revealing low levels of the protein. A finding of decreased C1-INH protein level and functional assay confirmed the diagnosis of HAE.

The potential prophylactic treatments were discussed with the patient, and he was started on danazol 600 mg daily, which was tapered to 250 mg daily over 2 months. The patient had less frequent abdominal attacks with this treatment, but he developed hyperlipidemia. Subsequently, the patient’s danazol dosage was further reduced to 150 mg daily to help minimize metabolic adverse effects. The patient’s abdominal attacks now occur less than twice per year and are managed effectively with Berinert in the emergency department.

Case 2 describes a woman who presented to the emergency department with her first episode of facial and laryngeal swelling. Hypersensitivity to dental anesthetic was suspected. The use of epinephrine, antihistamines, and intravenous corticosteroids had no impact on her swelling. She required nasotracheal intubation, which was challenging because of her swollen airway. The patient’s history of recurrent extremity swelling and irritable bowel disease was suggestive for attacks of HAE. Although she had no family history of facial or laryngeal swelling, it was important to pursue the HAE diagnosis because 25% of patients with HAE do not have a family history of the condition.

The patient’s swelling resolved after 24 hours of close observation. After the diagnosis of HAE was confirmed by laboratory tests, the potential therapeutic options were discussed with the patient, and she was started on prophylactic treatment with Cinryze. She has not had a facial swelling episode or abdominal symptoms since beginning this prophylactic treatment.

Conclusion

Hereditary angioedema is an inherited condition associated with a substantial disease burden and an increased risk of medical emergency. Symptoms are mediated by the overproduction of bradykinin and subsequent edema, resulting from a deficiency of or a dysfunction in C1-INH. Symptoms can be unpredictable and may vary considerably even among related individuals.

Insufficient awareness of HAE among physicians can contribute to a substantial lag in diagnosis, with some patients waiting more than 20 years for an accurate diagnosis of their condition. Therefore, all patients who present with recurrent bouts of swelling without a known cause and all patients with a family history of episodic swelling should be evaluated for HAE.
For patients suspected of having HAE, medical emergencies are typically not associated with extremity and urogenital attacks. However, abdominal attacks with hypotension and all laryngeal attacks constitute medical emergencies that must be addressed to prevent hypovolemic shock and airway obstruction.

The FDA has approved medications for management of acute HAE attacks and routine prophylaxis of HAE attacks. These new medications are directed at the underlying pathologic mechanisms of HAE. The results of ongoing studies will determine if these medications receive approval for the additional indication of procedural prophylaxis.

Acknowledgments
The author thanks Clay Isbell, MA, and Innovative Strategic Communications Inc for assisting in the preparation of this article and for providing other editorial support that was paid for by ViroPharma Inc of Exton, Pennsylvania.

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