
Case report

Hereditary angioedema presenting in late middle age after angiotensin-converting enzyme inhibitor treatment

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Background: Angioedema due to C1 esterase inhibitor (C1-INH) deficiency may be hereditary (HAE), commonly first occurring in childhood, or acquired (AAE), with onset usually in middle age. Type I HAE exhibits low levels of functionally normal C1-INH. Dysfunctional C1-INH typifies type II HAE. Patients with type I AAE have low levels of C1-INH, C1q complement, and C4 complement. In type II AAE, there is immune blockade of C1-INH.

Objective: To describe a man who first presented at the age of 52 years with type I HAE triggered by the administration of an angiotensin-converting enzyme (ACE) inhibitor.

Methods: The patient had C1-INH levels, a complement profile, and a lack of underlying co-pathology that led to the diagnosis of type I HAE triggered by the administration of an ACE inhibitor.

Results: The patient presented with life-threatening angioedema. His C4 complement and C1-INH serum levels were below the reference ranges, and his C3 complement, total hemolytic complement assay, and C1q complement levels remained within the reference ranges. During the 10 years between his initial episode of angioedema and the second, he had not developed any secondary medical conditions, and he had been taking the ACE inhibitor lisinopril for 7 years.

Conclusion: Physicians must remain aware of the possibility of unmasking HAE in the adult and geriatric population with the common use of ACE inhibitors for the treatment of hypertension, cardiovascular diseases, and metabolic diseases.

Ann Allergy Asthma Immunol. 2007;98:397–401.

INTRODUCTION

Hereditary angioedema (HAE) is a rare, autosomal-dominant inherited disorder with a prevalence of 1:50,000.¹ Two types of HAE have been described. Type I HAE, the most common phenotypic variant, is characterized by low levels of functionally active C1 esterase inhibitor (C1-INH). Type II HAE is characterized by a normal antigenic level of a dysfunctional C1-INH. The C1-INH modifies several metabolic pathways, and its deficiency or dysfunction leads to uncontrolled activation of the classical pathway of complement, contact, and fibrinogen systems.^{2,3}

Angioedema caused by acquired deficiency of C1-INH, usually referred to as AAE, is a rare, life-threatening disease first described by Caldwell et al.⁴ Type 1 AAE is characterized by low functional C1-INH levels, low amounts of C4 complement, and normal amounts of C3 complement. The concentration of C1q complement is low in this condition, whereas in HAE, the C1q complement level is usually within the reference range. There is excessive consumption of C1-INH by immune complexes formed by the anti-idiotypic antibody IgG and autoantibody to C1-INH.

When angioedema is associated with a lymphoproliferative malignancy or a rheumatologic disorder, there is usually an underlying production of anti-idiotypic antibodies directed against B-cell surface immunoglobulins, resulting in the formation of immune complexes.⁵ It is thought that these immune complexes activate C1 complement, which leads to the consumption of C1-INH.³ Type II AAE is characterized by immune blockade of the C1-INH molecule's active site by autoantibodies producing a nonfunctional cleaved C1-INH.^{2,3}

Both HAE and AAE are characterized by subcutaneous nonpruritic swelling without accompanying urticaria. Patients commonly develop involvement of the upper respiratory tract manifested as dysphagia, voice change, respiratory stridor, or asphyxia. Patients may develop involvement of the gastroin-

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Received for publication October 3, 2006.

Received in revised form November 17, 2006.

Accepted for publication November 26, 2006.

testinal tract, with a clinical presentation resembling that of an acute abdomen.^{2,3}

In HAE, the first episode of angioedema usually occurs in childhood.⁶ However, Berkun and Shalit⁷ reported this condition in a 90-year-old woman whose condition was unmasked by administration of an angiotensin-converting enzyme (ACE) inhibitor. In contrast, AAE has the onset of angioedema usually in the fourth decade of life or later and usually has an absence of a family history of angioedema. Because of the significant benefits of ACE inhibitors in the treatment of patients with hypertension, cardiovascular diseases, and metabolic diseases, the adult and elderly population is at increased risk for HAE and AAE.

We describe a patient who had experienced angioedema for the first time at the age of 52 years and was asymptomatic until the age of 62 years, when he presented with severe angioedema while being treated with an ACE inhibitor for 7 years. Further evaluation established the underlying diagnosis of type I HAE.

CASE REPORT

The patient was a 62-year-old white man who was referred to the internal medicine service at St Francis Medical Center after being seen in the emergency department for throat swelling and dyspnea. In the emergency department, he was treated with prednisone and diphenhydramine, and he was discharged after several hours of observation. This was the first episode of severe angioedema experienced by the patient, and there was no associated urticaria. Ten years before this event, he developed angioedema of the lips and extremities after eating shrimp cocktail and crab cakes. At that time, the patient was not taking an ACE inhibitor. However, he had been consuming these foods for the past 2 years without incident. He could not, however, recall all the foods consumed before the current reaction but denied any shellfish consumption. His medications were simvastatin, ezetimibe, amlodipine, lansoprazole, valdecocix, and lisinopril. He had been taking lisinopril for the past 7 years. Except for lisinopril, none of his medications significantly interacted with ACE inhibitors or C1-INH pathways.

The patient denied any history of urticaria, asthma, rhinitis, nasal polyposis, aspirin sensitivity, latex sensitivity, or other allergic manifestations. His medical history revealed gastroesophageal reflux disease, hypertension, hyperlipidemia, and benign prostatic hypertrophy. His surgical history revealed an umbilical hernia repair. Except for a nephew with angioedema, he denied any other family history of allergic disorders. The patient is estranged from his nephew, and no further information detailing the nephew's medical condition is available. Physical examination revealed an obese man in no significant distress. There was no edema, cyanosis, clubbing, jaundice, or lymphadenopathy. His height was 5 ft 9 in; weight, 297 lb; pulse, 78/min; and blood pressure, 122/80 mm Hg. The remainder of his physical examination was unremarkable.

Selective allergy skin testing revealed negative prick test results to the major allergy food groups, including milk, egg, peanut, lobster, clam, shrimp, and crab. The C4 complement level was 0.6 $\mu\text{g/mL}$ (reference range, 0.9–3.6 $\mu\text{g/mL}$); C3 complement level, 12.5 $\mu\text{g/mL}$ (reference range, 9.0–18.0 $\mu\text{g/mL}$); C1-INH level, 1.2 $\mu\text{g/mL}$ (reference range, 2.1–3.9 $\mu\text{g/mL}$); total hemolytic complement assay (CH_{50}) level, 4.3 $\mu\text{g/mL}$ (reference range, 2.2–6.0 $\mu\text{g/mL}$); and quantitative C1q complement level, 1.22 $\mu\text{g/mL}$ (reference range, 0.90–2.23 $\mu\text{g/mL}$). His antinuclear antibody level, rheumatoid factor level, serum protein electrophoresis findings, cryoglobulin levels, sedimentation rate, and thyroid function test results (thyrotropin and free thyroxine) were all unremarkable or normal. The blood cell count revealed a white blood cell count of 8,600 cells/dL without eosinophilia.

In view of the patient's age, a search was made for a malignancy. Findings from computed tomography of the neck, lungs, abdomen, and pelvis were negative except for an enlarged prostate. The patient refused treatment for HAE in view of his medical history and the potential adverse effects of danazol and antifibrinolytic therapy. Since discontinuation of use of the ACE inhibitor, the patient has been symptom free for 24 months, although the complement abnormalities have continued to the present (C4 complement level, 0.4 $\mu\text{g/mL}$; C3 complement level, 10.7 $\mu\text{g/mL}$; C1-INH level, 1.5 $\mu\text{g/mL}$; CH_{50} level, 3.7 $\mu\text{g/mL}$; and C1q complement level, 0.92 $\mu\text{g/mL}$).

DISCUSSION

The patient fulfilled the criteria for type I HAE. He had life-threatening angioedema of the upper airway associated with low C4 complement and C1-INH levels and normal C3 complement, CH_{50} , and C1q complement serum levels. His condition may have been unmasked by the use of an ACE inhibitor for hypertension. Both HAE⁷ and AAE^{8–10} have been described only after the administration of ACE inhibitors. We recently saw a patient with combined type I and II AAE that became evident only after administration of an ACE inhibitor.

The ACE inhibitors have been recognized as an important treatment modality in patients with congestive heart failure,¹¹ diabetic renal disease,¹² postmyocardial infarction,^{13,14} essential hypertension,¹⁵ and the renovascular hypertension of scleroderma.¹⁶ Cough and angioedema are the most common adverse effects of these medications.

Independent risk factors for angioedema include a history of drug rash, age older than 65 years, seasonal allergies, being black, and a history of angioedema.¹⁷ In 1 study, 39 (17%) of 231 consecutive patients with angioedema without urticaria were receiving ACE inhibitors.¹⁸ In certain patients, the angioedema encountered may be life-threatening.¹⁹ Angioedema may occur in up to 0.7% of patients taking ACE inhibitors,¹⁷ and it may occur after several years of treatment with an ACE inhibitor.^{18,20}

The potential for severe life-threatening angioedema in patients with HAE prescribed ACE inhibitors was first rec-

ognized by Shepherd.²¹ In addition to its inhibition of the first component of complement, C1-INH also inhibits plasma kallikrein, the serum protease that cleaves kininogen and releases bradykinin.²² Several recent studies^{23–27} have indicated that bradykinin is responsible for the symptoms of acute HAE. Supporting data include the following: (1) large amounts of activated kallikrein are present in the individual blister fluids of patients with HAE²⁷; (2) levels of prekallikrein and high-molecular-weight kininogen are decreased during acute HAE exacerbations²⁸; (3) plasma bradykinin levels increase significantly in persons with acute HAE and in those experiencing ACE inhibitor therapy–related angioedema²³; and (4) venous blood bradykinin levels are significantly higher in samples taken from the affected vs the unaffected arms of patients with localized HAE exacerbations.²⁴

Angiotensin receptor blockers (ARBs) (ie, losartan, also known as angiotensin II receptor blockers) have been associated with angioedema. Treatment of patients with ARBs results in increased angiotensin II receptor blockers and a 3-fold increase in the expression of bradykinin receptors, which would result in a more severe episode of angioedema in patients with HAE.²⁹ It is interesting that the study by Cicardi et al³⁰ found no statistically significant difference in the outcome when patients with ACE inhibitor–related angioedema were switched to ARBs, calcium antagonists, or other treatments (β -blockers, α -lytic agents, diuretics, or no treatment).

Since the discovery that the gene responsible for HAE is located on chromosome 11, more than 100 mutations have been identified. Although HAE has a known metabolic defect, the clinical manifestations, as noted by the present patient, may show a wide range of severity.¹ Patients have been observed for several years with minimal amounts of angioedema, which are not life-threatening. However, severe attacks of upper airway obstruction or asphyxia may occur in patients with no history of major swelling episodes.³¹

The attenuated androgen danazol was first recognized to considerably reduce the attacks of HAE in 1976.³² Since that time, danazol or stanozolol has been used for long-term prophylaxis in HAE. However, long-term administration of anabolic steroids at times may result in several adverse effects, including weight gain, virilization of women, decreased libido, acne, muscle cramps, myalgia, fatigue, headaches, hemorrhagic cystitis, arterial hypertension, hepatic necrosis or cholestasis, and hypercholesterolemia.^{33–36} Recently, hepatocellular adenoma and liver cell carcinoma have been reported after several years of danazol treatment in patients with HAE.^{37–39} In the present patient danazol use could have resulted in an exacerbation of his hypertension, hyperlipidemia, obesity, and benign prostatic hypertrophy, all common geriatric conditions. In most cases, though, these adverse effects are mild, and patients usually opt to continue therapy.

Alternative treatments for long-term prophylaxis include the antifibrinolytic agents ϵ -aminocaproic acid and tranexamic acid.⁴⁰ However, their efficacy is lower than that of androgens. In approximately 70% of patients, attacks occur

less frequently and are usually milder. However, a considerable reduction in the number and severity of attacks is reached in only 30% of patients. Antifibrinolytics are associated with an increased risk of thromboembolic events. ϵ -aminocaproic acid therapy may also result in postural hypotension, muscular pain, weakness, myositis, increased creatine kinase and aldolase levels, and anal pruritus. The dose is usually 8 to 12 g in 4 equally divided daily doses. Because of the many adverse effects associated with ϵ -aminocaproic acid, tranexamic acid is often substituted. The dose is usually 1 to 3 g/d. Adverse effects of tranexamic acid use are uncommon but include abdominal discomfort, mild transient diarrhea, nausea, headache, and anal pruritus. However, the oral form is no longer marketed in the United States.^{40,41}

Several new treatments are currently being evaluated for acute attacks of HAE. Multiple studies^{42–48} have demonstrated the successful use of C1-INH concentrate for prophylaxis. Infusion of C1-INH concentrate every 4 to 5 days has been shown to be effective for long-term prophylaxis against acute HAE attacks.^{49,50} Use of C1-INH concentrate (Berinert; Aventis Behring, Liederbach, Germany), a 1,500-U dose intravenously, successfully treated severe ACE inhibitor–associated angioedema of the face and neck within 20 minutes of the infusion.⁵¹ Recombinant transgenic C1-INH, which is harvested from rabbit breast milk, has been shown to be fully functional and effective in the treatment of acute HAE attacks. Treatment with recombinant C1-INH has not been associated with allergic or clinically relevant allergic responses.⁴⁸

DX-88, a plasma kallikrein inhibitor, has received orphan drug designation and is being evaluated for the treatment of acute HAE attacks. An alternative strategy to the inhibition of plasma kallikrein is to antagonize the binding of bradykinin to its receptor, the bradykinin B₂ receptor.⁴⁸ Icatibant is a synthetic decapeptide second-generation bradykinin B₂ receptor antagonist that displays high affinity, no residual agonist activity, and an impressive resistance to peptidases. DX-88 and icatibant have shown efficacy in the treatment of acute HAE, and both may be given by subcutaneous injection because of their small molecular size.⁴⁸

In conclusion, this patient fulfilled the clinical features and complement abnormalities found in HAE despite his advanced age at presentation. We believe that his HAE may have been unmasked by use of the ACE inhibitor lisinopril. A repeatedly normal C1q complement level and the absence of a secondary medical condition for several years is sufficient evidence to exclude AAE in this patient. Although this patient refused medical intervention, treatment of HAE and AAE with attenuated androgens and antifibrinolytic agents may result in serious adverse effects in the geriatric population.⁵⁰ These elderly patients, however, may benefit from the several new drugs that are currently under development. Replacement purified plasma–derived or recombinant C1-INH therapy or treatment with a recombinant plasma kallikrein inhibitor or bradykinin B₂ receptor antagonist all have

the potential to treat acute HAE. They may be a more favorable treatment option for this patient population.

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