

Hereditary Angioedema: A Rare But Potentially Lethal Disease

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Hereditary angioedema, although uncommon, should be considered in the differential diagnosis of all patients with facial edema. In this article, we present a case of hereditary angioedema and discuss the presentation, diagnosis, and management of the disease.

CASE PRESENTATION

An 18-year-old woman presented with the chief complaint of facial swelling for 4 days. The patient also noted hand and labial swelling for the same duration. She stated that she had had similar symptoms in the past, starting at the age of 7 years. Over the past 11 years, the episodes had increased in frequency to the point that at the time of presentation the patient experienced symptoms three times a month lasting 7 to 10 days per episode. She denied any fever, chills, or shortness of breath; however, she experienced a sore

throat and palpitations with some episodes. The patient was 6 weeks pregnant at the time of presentation.

Past medical history was pertinent for a recent history of urethritis and a remote history of hereditary angioedema diagnosed at age seven. The diagnosis was confirmed by low C1-esterase inhibitor levels. The patient's father, sister, paternal grandfather, paternal uncle, and two paternal cousins had a history of angioedema. Social history was noncontributory. The patient was receiving no medications and had no drug allergies.

Physical examination at the time of admission re-

CME INFORMATION

TARGET AUDIENCE

The May/June Clinical Case of the Month is intended for family physicians, general internists, general practitioners, emergency medicine physicians, pediatricians, allergy-immunologists, dermatologists, and obstetricians-gynecologists.

EDUCATIONAL OBJECTIVES

After reading this article, physicians should be able to better identify and understand the epidemiology, clinical presentation, pathogenesis, diagnosis, and treatment of hereditary angioedema.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) hour of category 1 credit toward the AMA Physician's Recognition Award. Each physician

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DISCLOSURE

Dr. Kamboj has nothing to disclose.
Dr. Lillis has nothing to disclose.
Dr. Wegmann has nothing to disclose.
Dr. Wild has nothing to disclose.
Dr. Lopez discloses that he is a member of the *LSMS Journal* Board and the *LSMS Journal* Editorial Board.
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vealed normal vital signs, diffuse facial swelling, periorbital edema, and perioral edema. The genitourinary exam was pertinent only for swelling of the left labia minora. Laboratory studies included C3 level of 113 mg/dl (83 - 180 mg/dl), C4 level of 3 mg/dl (18 - 45 mg/dl), and a urine pregnancy test that was positive. The patient was admitted to the hospital with a diagnosis of an exacerbation of hereditary angioedema. She was treated with methylprednisolone, diphenhydramine, and famotidine. Her facial swelling resolved over the following 2 days without evidence of respiratory compromise. She was discharged on the third hospital day with instructions to be followed closely by her allergist. Recommendations for evaluation of her family members were also discussed.

DISCUSSION

First described clinically by Osler in 1888,¹ hereditary angioedema (HAE) is an autosomal dominant disease caused by C1- esterase inhibitor (C1-INH) deficiency.² The approximate incidence is between 1 in 10,000 and 1 in 150,000 persons.^{3,4} It is characterized by recurrent attacks of edema involving the skin, mucous membranes, gastrointestinal tract, and airways.^{5,6,7}

CLINICAL PRESENTATION

Patients with HAE develop recurrent episodes of localized subcutaneous or submucosal edema.^{7,8} The angioedema may involve any part of the body, but most frequently affects the skin, upper respiratory tract, oropharynx, and gastrointestinal tract.⁸ As in the case of our patient, the skin lesions are most commonly seen over the face, extremities, and genitalia. These lesions are non-erythematous and usually not pruritic or painful.⁸ Patients do, however, describe a sensation of skin tightness associated with the lesions. The non-pitting

edema typically lasts 2 to 5 days and then regresses over a similar period.⁷ An important characteristic of C1-INH deficiency related angioedema is that it is *not* associated with urticaria. In HAE, an erythematous rash may develop, but unlike urticaria, it is not warm or pruritic.

In the respiratory tract, laryngeal edema is a common and ominous symptom as it is a major cause of death in these patients due to asphyxiation.^{7,9} Laryngeal edema can occur at any age. Episodes have been reported in patients from 4 weeks to 78 years of age.¹⁰

The presentation may mimic that of an acute abdomen if the gastrointestinal tract is involved.⁴ Swelling of the intestine may cause severe crampy abdominal pain and even vomiting secondary to obstruction.^{6,8} In the case of colonic involvement, patients may present with profuse watery diarrhea. Patients with gastrointestinal involvement may develop hypotension and shock secondary to loss of fluid into the swollen intestine.¹¹ Unlike patients with an acute abdomen, patients with gastrointestinal angioedema usually do not have fever, leukocytosis, or rebound tenderness.⁸

Less common presentations of HAE include migraine and transient ischemic attacks.^{11,12}

The frequency of angioedema attacks is variable among patients and also changes in each individual patient over time.¹³ At puberty, there is an increase in disease activity and more than 50% of patients will develop symptoms by adolescence.⁸ Some patients may not develop symptoms until later in adult life. Patients experience a decreased frequency of symptoms after the fifth and sixth decades of life.

PATHOGENESIS

HAE is inherited as an autosomal dominant disorder. According to different reports in the literature, 10% to 25% of new cases are spontaneous mutants who do not have a family history of HAE.^{4,10} Our patient had several family members with the disease. Defects in the genomic sequence of the C1 esterase inhibitor gene, located on chromosome 11, are responsible for HAE.³ In hereditary angioedema, there is deficiency of C1-INH protein.² This deficiency may be quantitative (Type 1 HAE), as in the case of our patient, or qualitative (Type 2 HAE). Type 1 HAE is found in approximately 85% of patients.⁴ Patients with Type 2 HAE have normal levels of a nonfunctional C1 esterase inhibitor.

The liver is the main source of C1-INH synthesis.¹⁴ Production may also occur in skin fibroblasts, blood monocytes, and umbilical cord endothelial cells. Although named *C1 esterase inhibitor*, C1-INH is important in the inhibition of more than just the first component of the complement cascade. C1-INH regulates the

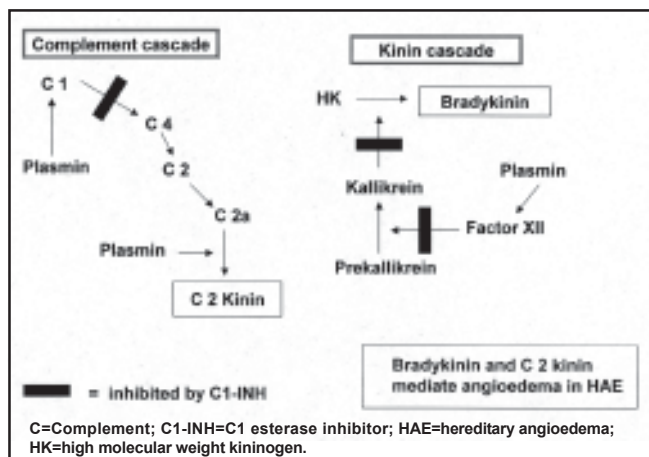


Figure. Functions of C1 inhibitor.

Table 1. Evaluation of the patient with suspected C1- inhibitor deficiency.

1. Check complement 4 level (C4).
 - If normal, diagnosis of HAE excluded; STOP work-up.
 - If low, proceed to # 2.
2. Check C1 esterase inhibitor level.
 - If normal, proceed to # 3.
 - If low, proceed to # 4.
3. Check C1 esterase inhibitor function.
 - If normal, diagnosis of HAE excluded; STOP work-up.
 - If low, proceed to # 4.
4. Check C1q.
 - If normal, diagnosis of HAE confirmed.
 - If low, C1 inhibitor deficiency due to other causes must be considered (eg, C1-INH deficiency associated with lymphoproliferative and autoimmune disorders), but the diagnosis of HAE must be excluded.

control of components of the complement, kinin, and clotting cascades. C1-INH inhibits activation of C1r and C1s. It also inhibits the conversion of high molecular weight kininogen (HK) to bradykinin by inhibition of activated kallikrein. Additionally, C1-INH is the sole plasma inhibitor of factor XII (Hageman factor). Injury to blood vessels activates factor XII, which initiates the kinin cascade, leading to activation of kallikrein and generation of bradykinin (a vasoactive peptide). Plasmin activates C1, activates factor XII, and promotes kallikrein production (Figure). This activation of C1 by plasmin leads to cleavage of C2 generating C2a. Further cleavage of C2a by plasmin produces C2 kinin. The permeability of postcapillary venules is increased by bradykinin and C2 kinin leading to endothelial cell contraction and gaps in the blood vessel wall.¹⁵ Through these mechanisms, deficiency of C1 esterase inhibitor causes leakage of fluid from vascular space to other body compartments producing edema. In HAE, the alternative pathway of complement activation is not affected.

Patients may have attacks without any precipitating event, but episodes usually are triggered by minor trauma, excessive exercise, exposure to extremes of temperature, menstrual periods, mental stress, and anxiety.^{6, 13} Minor trauma (eg, dental procedures) and instrumentation of the airways (eg, endotracheal intubation) may precipitate swelling in the upper airways and cause laryngeal edema.⁸ In pregnancy, attacks usually lessen in the second and third trimesters.¹³ Angioedema attacks are rare at the time of delivery despite the associated injury to the birth canal.

Symptoms may worsen, however, in the postpartum period.⁶ Use of oral contraceptives is associated with decreased C1-INH levels.

DIAGNOSIS

A detailed history and physical examination are the first steps in evaluation of a patient presenting with angioedema. Other causes of urticaria and angioedema are physical agents (eg, cold), allergy to food, drugs (eg, ACE inhibitors, NSAIDs), and insect stings; angioedema secondary to serum sickness, blood product reaction, and contrast dyes should also be excluded.

Although the angioedema associated with C1-INH deficiency is mediated by bradykinin and C2 kinin, decline of serum complement C4, a marker of complement activation, is a hallmark finding.^{16, 17} Therefore, the first screening laboratory test is a complement C4 level, which is low during attacks as well as during remission.^{8, 13} Our patient's low C4 level was consistent with the diagnosis of HAE. If the C4 level is low, C1-INH quantitative and qualitative (functional assay) tests should be done to confirm the diagnosis. In Type 1 HAE, C1-INH levels are low (< 30%). In Type 2 HAE, the C1-INH levels may be normal but have decreased functional activity (< 30%). Complement C2 levels may be low during attacks, but C1 and C3 levels are normal. Table 1 includes a stepwise approach to the diagnostic evaluation of patients with suspected HAE.

MANAGEMENT

The treatment of HAE can be divided into two categories: management of acute attacks and long term management.

Management of Acute Attacks

Vapor-heated C1-INH concentrate administration is the treatment of choice for acute attacks, but is not commercially available in the USA.^{7, 8} Fresh frozen plasma (FFP) may be useful in acute attacks as it contains C1-INH.¹⁰ Paradoxically, it may exacerbate the symptoms of HAE in some patients. The attenuated androgens (eg, stanozolol) are also started, initially every 4 hours for 4 doses and then continued once a day. These agents increase the C1-INH synthesis from the liver by increasing transcription, translation, and secretion of C1-INH. Our patient was unable to use attenuated androgens because of her pregnancy. Initially, she was treated with corticosteroids and histamine H1 and H2 blockers.

The history of allergy or HAE may be useful in directing therapy. Anaphylaxis should be ruled out and treated appropriately if suspected. Patients with laryn-

Table 2. Key Points of Hereditary Angioedema.

- Urticaria is not associated
- Triggers: mild trauma, excessive exercise, menstrual periods
- Family history of angioedema usually present, but not always
- Autosomal dominant inheritance
- New mutations (10% to 25%)
- Complement 4 level is best screening test
- C4 always low
- C2 low during acute attack
- C1q always normal
- Bradykinin and C2 kinin mediate the angioedema, not histamine
- Epinephrine, antihistamines, corticosteroids not helpful in treatment
- Asphyxiation is the most common cause of death
- ACE inhibitor use absolutely contraindicated

geal edema should be given epinephrine. If the laryngeal edema is secondary to mast cell activation (ie, anaphylaxis), it usually responds to epinephrine, whereas laryngeal edema of HAE is refractory to this therapy. Though administered to our patient, antihistamines and corticosteroids are also ineffective. The patient's airway should be maintained and emergency tracheostomy should be done if laryngeal edema fails to respond to medical management. Endotracheal intubation should not be performed in these patients, as trauma to the larynx may further increase laryngeal edema. Patients with hypotension and shock should be given intravenous fluids and vasopressors as needed.

Long Term Management

In addition to treating the affected patient, first-degree family members (siblings, parents, and children) should also be screened for the disease and sent for genetic counseling. Attenuated androgens (danazol and stanozolol) are used to increase plasma C4 and C1-INH levels.⁸ The dose may vary for different individuals, but usually stanozolol or danazol is effective. The patient's serum C4 levels should be monitored to determine response to therapy, and liver function tests should be monitored for toxicity. Attenuated androgens are contraindicated in pregnancy, during lactation, and in patients with prostate cancer. In children, androgens should be used only for a short course if dental work or surgery is planned; otherwise, these agents are contraindicated in children. Angiotensin converting enzyme is the major enzyme responsible for the degradation of

bradykinin, the mediator of angioedema in HAE. Because these agents may precipitate or potentiate an attack of angioedema, ACE inhibitors should be avoided in patients with a history of HAE.

CONCLUSION

Although relatively rare, hereditary angioedema is a potentially lethal disease. Prompt diagnosis and treatment, ideally under the care of an allergist, are essential for improved outcomes (Table 2). In addition, family members of the patient should be screened for the disease. The patient should be counseled on the events likely to trigger an attack and instructed to seek prompt medical attention in the event of an attack.

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CME QUESTIONS

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For each question, choose the one answer that is most correct.

1. Angioedema associated with C1 esterase inhibitor deficiency:
 - a) is pruritic
 - b) is erythematous
 - c) commonly affects extremities, face, and genitalia
 - d) is pitting
2. True or False: Patients with Hereditary Angioedema or C1 esterase inhibitor deficiency, commonly present with both angioedema and urticaria.
- 3) The best screening test for Hereditary Angioedema is:
 - a) Complement 4 (C4) level
 - b) C1 esterase inhibitor quantitation
 - c) C1 esterase inhibitor function
 - d) CH 50
4. True or False: Ten percent to 25% of patients with Hereditary Angioedema have no family history of angioedema.
5. The majority (85%) of patients with Hereditary Angioedema (Type I HAE) have symptoms resulting from
 - a) an increased breakdown of bradykinin and its metabolites
 - b) a functional deficiency of c1 esterase inhibitor
 - c) a quantitative deficiency of c1 esterase inhibitor
 - d) inactivation of plasma kallikrein
6. In which patient population is screening for Hereditary Angioedema indicated?
 - a) patients presenting with urticaria and angioedema
 - b) patients presenting with angioedema alone
 - c) patients presenting with urticaria alone
7. Which of the following events *is not* a common trigger of angioedema in patients with C1 esterase inhibitor deficiency?
 - a) dental procedures
 - b) airway instrumentation
 - c) spontaneous vaginal delivery
 - d) menstrual period
8. Which of the following is an important, therapeutic option in the long-term management of patients with Hereditary Angioedema?
 - a) fresh frozen plasma infusions
 - b) plasmapheresis
 - c) attenuated androgen therapy
 - d) oral contraceptive therapy
9. True or False: Angiotensin converting enzyme (ACE) inhibitor therapy is absolutely contraindicated in patients with a history of Hereditary Angioedema.
10. True or False: Epinephrine, antihistamines, and corticosteroids are usually ineffective in the treatment of acute angioedema due to C1 esterase inhibitor deficiency.