A Girl with Severe Hand Swelling and Abdominal Cramps

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CASE DESCRIPTION

A 16-year-old girl presented to the emergency room with severe swelling of her left hand and forearm. Her symptoms began 12 h earlier with left forearm swelling that progressed to the tips of her fingers. She reported her forearm felt normal, but her hand had a tingling sensation and she was barely able to move her fingers. She also reported having had moderately painful abdominal cramps earlier that day. She denied urticarial or pruritic rashes, respiratory distress, and throat tightness. During the previous week she had felt stressed because of schoolwork and also had developed a mild headache, clear rhinorrhea, and cough. She had never had episodes of swelling in the past.

Family history revealed similar episodes in multiple family members. The patient’s father and 15-year-old sister had histories of numerous episodes of painful localized edema since childhood. Her paternal grandmother, great-grandfather, and great-great-grandfather died of asphyxiation due to attacks of angioedema and swelling of the throat. Her mother and 13-year-old brother were healthy.

On examination, the patient appeared well and in no respiratory distress. Vital signs were stable. Her skin had no rashes. Her left upper extremity was severely swollen from the midforearm to the fingertips. Her left hand was cold and capillary refill was mildly delayed. The patient reported a tingling sensation when her fingers were superficially palpated. Flexion and extension of her fingers were greatly reduced. The patient’s abdomen was soft but diffusely tender, without hepatosplenomegaly. There was no swelling of other body parts. Physical examination results were otherwise unremarkable.

Complete blood count showed mild leukocytosis with neutrophilic predominance. C-reactive protein was 15 mg/L (reference interval <5 mg/L), C3 was 1170 mg/L (reference interval 830–1770 mg/L), and C4 was <60 mg/L (reference interval 140–420 mg/L).

DISCUSSION

Angioedema in a patient with positive family history and low C4 is characteristic of hereditary angioedema (HAE).2

HAE, a rare genetic disorder with autosomal dominant inheritance, is caused by a deficiency of C1 inhibitor (C1-INH). The incidence of HAE is estimated to be 1 in 10 000 to 1 in 150 000, with no differences between sexes or ethnicities. The disease is characterized by recurrent episodes of localized subcutaneous or mucosal swelling that most commonly affect extremities but can also involve the face, genitals, trunk, tongue, lips, and larynx. Cutaneous attacks can be temporally disfiguring but are not dangerous. In addition, patients with HAE frequently have episodic abdominal pain due to swelling of the bowel. Abdominal-pain attacks occasionally lead to unnecessary surgery owing to suspicion of acute abdomen. HAE attacks do not usually involve urticaria or pruritus, a characteristic that helps in differentiating HAE from allergic angioedema. However, approximately one-third of HAE patients may have a nonraised serpiginous rash preceding angioedema attacks. Episodes are usually self-limited and last 1 to 5 days, having a gradual onset and gradual resolution. When the larynx is compromised, however, attacks can lead to asphyxiation and, if not treated in time, to death. Most attacks are sporadic and do not have a recognizable inciting factor. Nevertheless, patients report that episodes are triggered by local trauma or pressure, and in about one-third of cases, by emotional stress. Other reported triggers are infections, dental work, surgery, menstruation, pregnancy, oral contraceptives, and angiotensin-converting–enzyme inhibitors. The age at which attacks begin is variable, with most patients having their first attack in childhood or adolescence. The frequency of attacks ranges from weekly to once every few years.

Despite the fact that HAE is frequently classified as an allergic disease, it is not, and HAE attacks are not...
mediated by histamine (3). In 1963, Donaldson and Evans recognized that the concentration of a serum protein now known as C1-INH was decreased in most HAE patients (4). Subsequently, more than 190 different mutations of the gene that encodes C1-INH, serpin peptidase inhibitor, clade G (C1 inhibitor), member 1 (SERPING1), have been described (5). Approximately 25% of patients have no family history, indicating their disease is attributable to de novo mutations.

There are 2 main variants of HAE. Type I, which affects 85% of patients, is characterized by low C1-INH concentrations attributable to mutations that lead to no synthesis or failure to secrete the protein. Type II affects the remaining 15% of patients, who secrete a mutant nonfunctioning C1-INH protein, and thus have normal or increased concentrations of C1-INH in plasma. A rare third type has been described in patients, predominantly women, who have C1-INH concentrations within the reference interval and normal C1-INH function. This type of HAE may be due to increased activity of coagulation factor XII (6).

C1-INH is a serpin-type protease inhibitor, active against multiple plasma proteases. It mimics the substrate of the protease and traps it by binding covalently to its active site. C1-INH regulates many of the mediator cascades in serum, most importantly the complement and contact systems. The complement system consists of proteins that participate in the humoral immune defenses of the body. It has 3 different pathways (classical, alternative, and lectin) that differ in their mechanisms of activation. All 3 pathways converge into a final common pathway at the level of activation of the complement component C3 and therefore have the same biologic effects, which include opsonization, lysis of pathogens or altered host cells, inflammation, and chemotaxis. C1-INH acts as the primary regulator of the classical complement pathway by inhibiting C1r and C1s, 2 early components of this pathway. In addition, C1-INH exerts inhibitory effects on mannose-binding lectin–associated serine proteases 1 and 2, 2 early enzymes of the lectin pathway (7). C1-INH has also been reported to be a regulator of the alternative pathway convertase by binding to C3b, although not through a covalent bond (8) (Fig. 1).

The contact or kallikrein-kinin system is a network of proteins that modulate inflammation, blood pressure, coagulation, and pain. Activated factor XII converts prekallikrein into kallikrein, and the latter cleaves high–molecular-weight kininogen into bradykinin, which mediates many of the biologic effects of this system. C1-INH is a major inhibitor of kallikrein and coagulation factor XII (Fig. 1).

Pathophysiologically, angioedema is caused by postcapillary venule leakage and edema formation in subcutaneous or mucosal soft tissues. After years of debate about whether angioedema is caused by activation of the complement or the contact systems, it is now generally agreed that bradykinin is probably the only mediator of angioedema attacks in HAE (9).

**DIAGNOSIS OF HAE**

HAE is diagnosed by evaluation of C1-INH in serum. Both quantitative and functional tests are available, which help determine if a patient has HAE type I or...
type II. C2 and C4, both early components of the classical complement pathway, are almost always low in HAE patients, with C4 being a common screening test for this condition owing to its widespread availability. Because HAE often involves constant low-grade spontaneous activation of complement, C4 can also be low when patients are asymptomatic. C1q, another early complement protein, is within reference intervals in HAE, but C1q measurement is useful to differentiate HAE from acquired angioedema, a condition in which C1q is usually low. Acquired angioedema can be associated with lymphoproliferative disorders or antibodies against C1-INH and should be suspected in patients without family history and with symptom onset at an older age. Genetic testing for the SERPING1 gene can also be done but is usually unnecessary.

TREATMENT OF HAE
Treatment of HAE can be prophylactic or directed to acute attacks. Attenuated androgens have been successfully used for prophylaxis. Adverse side effects restrict their use in children, however, and often lead to treatment discontinuation, especially in women. For angioedema attacks no approved treatments are available in the US. New emerging therapies that should radically change the treatment of HAE include purified C1-INH, which has been effectively used in Europe for years, and recombinant C1-INH. FDA clearance for the use of both treatments in the US is currently being sought. Other promising new therapies that directly address the pathophysiology of HAE are being tested, including a kallikrein inhibitor and a bradykinin-receptor antagonist (10).

CASE RESOLUTION
The case patient was observed in the emergency room for a few hours, during which she experienced gradual decreases in extremity swelling and abdominal pain. Additional studies showed a C1-INH concentration of 7 mg/L (reference interval 210–390 mg/L), and a C1-INH functional assay revealed 38% of normal enzymatic activity (reference interval >68%). The diagnosis of HAE type I was established. Subsequent gene sequencing of SERPING1 revealed a nonsense mutation (Arg472stop). The patient was discharged in good condition and after 48 h the swelling resolved completely. She was instructed to consult the nearest emergency room for any symptoms of oropharyngeal swelling and to inform her dentist about her condition. She was also advised against traveling to remote areas with difficult medical access. In the following year, she developed 2 new episodes of extremity swelling, likely triggered by stress and/or viral infections. Because of the rarity of this patient’s attacks and her young age, no prophylactic treatment was started.

### POINTS TO REMEMBER

- **HAE**, an episodic swelling disorder of autosomal dominant inheritance, is caused by deficiency of C1-INH.
- Deficiency of C1-INH causes activation of the complement and contact system. Bradykinin has been identified as the substance most likely responsible for the angioedema.
- Clinical manifestations include episodic swelling of extremities, recurrent abdominal pain, and laryngeal angioedema attacks. The latter can be life-threatening.
- Diagnosis is confirmed by quantifying and measuring functional activity of C1-INH. C4 is a good screening test because it is usually low in HAE patients.
- Acquired causes of angioedema must be considered in older patients who do not have a family history of HAE.

During the last decades, combined clinical and laboratory research have elucidated the genetic cause and clarified the pathophysiology of what used to be a mysterious clinical syndrome. This improved understanding of HAE is now leading to new therapies that target the mechanisms of disease and likely improve the lives of patients who suffer from this disease. HAE provides a clear example of how basic science contributes to the understanding of disease mechanisms and leads to effective specific therapies.

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References


Commentary

Michael M. Frank

In the past 50 years, our understanding of hereditary angioedema (HAE) has markedly expanded. Although HAE was first defined in general terms in the 19th century, we now have extensive insight into the clinical expression, cause, pathophysiology, and treatment of this disease, so that HAE represents a success story of modern medicine. We know that emotional stress, trauma, and endocrine factors all can contribute to disease expression. The disease has unique clinical symptomatology, and often a diagnosis can be made with clinical history alone. The observations that the disease can become very severe during puberty and that estrogens markedly exacerbate symptoms led to the empirical use of impeded androgens in treatment. In turn, this treatment led to a major decrease in mortality because patients had fewer life-threatening airway attacks.

Because HAE is such a rare disease, the diagnosis is often missed regardless of the characteristic clinical history. Patients often go for decades without proper diagnosis. When we published our detailed studies of clinical expression of the disease in 1976, we found that after the onset of attacks an average of 21 years passed before patients received a proper diagnosis (1). These patients were at high risk of airway attacks and asphyxiation. We also noted that approximately 30% of afflicted relatives of our patients had died of upper-airway edema. More recently, a pharmaceutical company reported that in European patients 9 years had passed between the onset of attacks and diagnosis. This time lapse is obviously unacceptable, given the fact that successful treatment is available, and shows that both physician and patient education is still desperately needed. As noted in the clinical case study, new and better therapies for HAE are on the horizon. Even in the absence of gene therapy, this inherited disease may come to be considered a minor condition and not a life-threatening illness.

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Reference

Commentary
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Hereditary angioedema (HAE) is an uncommon disease caused by mutations in the *SERPING1* gene, which codes for the C1-inhibitor (C1-INH) protein and is transmitted in an autosomal dominant fashion with high penetrance. Clinical suspicion should be triggered by a history of recurrent angioedema, as in the patient described in the case report by Borzutzky et al. Diagnosis requires laboratory confirmation. Screening patients by measuring the C4 concentration is useful to exclude the diagnosis of HAE. Even while asymptomatic, HAE patients almost always have a low C4, and the C4 concentration is invariably low during attacks. To establish the diagnosis, a decrease in C1-INH concentration or function must be demonstrated. In the 85% of patients with type I HAE, the diagnosis can be established by measuring C1-INH antigenic concentrations. Type II HAE requires demonstration of low functional activity of C1-INH. The diagnostic sensitivity of this assay is not ideal, however. Therefore, in rare cases sequencing the *SERPING1* gene is required to establish the diagnosis of Type II HAE. Although mutations leading to type I C1-INH occur throughout the gene, almost all type II C1-INH mutations occur near the Arg444-Thr445 reactive center of *SERPING1*, thereby simplifying the sequencing strategy.

HAE with normal C1-INH function primarily, but not exclusively, affects women, and appears to be transmitted in an autosomal dominant fashion with low penetrance. In some families, individuals with HAE with normal C1-INH function have a gain-of-function mutation in coagulation factor XII that may result in enhanced generation of bradykinin. With current methods it is difficult to confirm a diagnosis of HAE in patients with normal C1-INH function. In addition to normal C1-INH function, these patients have C1-INH concentrations within reference intervals. Sequencing of coagulation XII may confirm the diagnosis, but in only a subset of patients. Better understanding of the underlying molecular etiology and diagnostic strategy for this disease is urgently needed.

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