

CLINICAL VIGNETTE

Hereditary Angioedema

Bruce Landres, M.D.

Case Report

A 26-year-old male presented with no acute problems. However, his mother had died at the age of 28 due to a bout of hereditary angioedema involving her larynx. The patient was diagnosed with hereditary angioedema as a young child when he was observed to develop large "urticarial" swellings on various parts of his body. He was free of major complications until the age of 23, when he developed episodic abdominal pain reportedly due to "swelling of his intestines", as well as painful swelling of his hands and feet. He had never had airway involvement. He had seen several other physicians but they had failed to correlate the hereditary angioedema with his bouts of pain. He also noted empirically that meperidine parenterally helped to break the attacks, which could last up to half a day. He had never been treated with epsilon aminocaproic acid or attenuated androgen therapy.

His physical examination was normal. Because of his medical and family history, blood was drawn for C1 inhibitor, C2, and C4 by both assay and function during an asymptomatic period. The results are listed in Table 1.

Table 1: Laboratory Test Results

C2 levels: 11 mgm/L (N: 7-23 mgm/L)
C2 functional levels: 1829 u/mL (N: 2800-7600 u/mL)
C4 levels: 6 mgm/dL (N: 14-53 mgm/dL)
C4 functional levels: 287 u/mL (N: 11000-48000 u/mL)
C1 INH quantitative: 5 mgm/dL (N: >11 mgm/dL)
C1 INH functional: 1 ngm/mL (N: >20 ngm/mL)

Due to the abnormal levels in his C1 inhibitor, C2, and C4, the patient was referred for androgen therapy and was treated with stanozolol. He has no further attacks since that time.

Discussion

Hereditary angioedema is a disease characterized by episodic bouts of subcutaneous or submucosal swelling involving the face, limbs, and soft tissues. It can also occur intra-abdominally, causing severe pain, nausea, and vomiting. In some patients, hereditary angioedema can involve the larynx, potentially leading to asphyxiation and death.

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Hereditary angioedema is a genetic disease involving different point mutations within an abnormal C1 inhibitor gene on chromosome 11. This condition is described as an autosomal dominant trait with variable penetrance.¹ However, more than 20% of patients with hereditary angioedema do not have a family history of the disease and a spontaneous mutation may be responsible.² A new form of hereditary angioedema with an X-linked dominant mode of inheritance has recently been reported.³

There are three basic phenotypes of hereditary angioedema. Type I hereditary angioedema is characterized by an absolute deficiency of C1 inhibitor, and type II is characterized by normal or high levels of a functionally defective C1 inhibitor. The third variety occurs only in women who have normal C1 inhibitor levels but a clinical presentation of hereditary angioedema.³ The biochemistry and incidence of this new type of hereditary angioedema have yet to be fully explicated. The incidence of type I hereditary angioedema is more than five times as high as type II.⁴ The overall incidence varies from 1 in 150,000 to 1 in 10,000.^{2,5,6,7}

The mechanism of action is believed to involve the function of the C1 inhibitor, which regulates multiple immune system reactions, including the complement, coagulation, and kinin systems. Individuals with this malady show low plasma C4 levels indicating activation of the complement system and activation of Hageman factor, leading to high levels of kininogen, a substrate for bradykinin activation via the kallikrein system. The lack of inhibition of these mechanisms leads to the formation of vasoactive peptides and the subsequent clinical presentations.^{1,4}

Clinically, hereditary angioedema presents as recurrent bouts of submucosal and subepithelial swelling. While any part of the body may be involved, the limbs are most commonly affected with non-pitting subepithelial edema. "Typically, there is no pruritus or pain beyond that caused by distention of the skin. Cutaneous involvement tends to be well circumscribed."⁴ On occasion, a perioral attack may involve both submucosal as well as mucosal tissues.

With intra-abdominal cavity involvement, severe abdominal pain with some nausea and vomiting is generally present without diarrhea until the attack begins to dissipate. Fever and leukocytosis are absent, and there is no rigidity to the abdomen, although there might be tenderness on palpitation. Fluid loss through the third spacing is notable and can result in dehydra-

tion. Due to the severity of the pain, these attacks are difficult to distinguish from acute abdominal diseases thus increasing the risk for these patients to undergo unwarranted abdominal surgeries.^{4,8}

When the bowel itself is involved, radiologic studies can show thumb-printing of affected areas and separation of adjacent loops of bowel suggestive of mesenteric edema. These features disappear as the attack dissipates.⁴

Interestingly, Cicardi postulates that the pulmonary tree is spared from these attacks because of the presence of enzymes within the surface cells of the lungs which deactivate kinins.² It is this very reason, he theorizes, that prevents angioedematous attacks from involving the lungs or becoming more generalized; any vasoactive kinins are deactivated as they pass through the pulmonary vasculature. However, the upper airways are not spared, and laryngeal edema with danger of asphyxiation in patients with hereditary angioedema remains a medical emergency. The literature cites an incidence of death from asphyxiation in hereditary angioedema ranging from 14% to 56%. In a 1999 study, Bork and colleagues reviewed the clinical experiences with laryngeal edema in Germany over the previous fifty years.^{1,7} They found the death rate to be 40% with the average age of asphyxiation at 39 years. Upper airway obstruction was reported at all ages ranging from 4 weeks to 78 years. They also found that the risk of asphyxia with hereditary angioedema had no relationship to the number or frequency of previous episodes of laryngeal edema. The study also showed the time course from onset of an attack to airway obstruction to be highly variable, ranging from 20 minutes to a maximum of 14 hours with an average of 7 hours.

Other less common areas of involvement are the central nervous system resulting in focal neurologic deficits, the urinary bladder leading to urinary obstruction, and the pleura leading to cough and pleural effusions.⁴

In affected individuals both the age of onset and the frequency of attacks were highly variable. The first clinical manifestations of hereditary angioedema have been reported in patients as young as a few weeks of age to individuals as old as 70 years.^{4,7} However, two-thirds of all cases are seen in adolescents.⁵ The frequency of attacks is also variable with a reported range of less than one attack per year to weekly attacks. Some individuals may have only one attack over several decades but then show a flurry of bouts of hereditary angioedema at an increased

frequency.⁴ The duration of the attacks typically lasts between 24 and 72 hours before remitting but can range from four hours to one week.^{6,9}

Events are precipitated by a variety of agents. Classically, dental procedures are well described as leading to bouts of hereditary angioedema. Physical traumas and even insignificant repetitive injuries such as typing, mowing the lawn or hammering have been associated with attacks. Standing still for prolonged periods of time and emotional duress have been reported to lead to bouts of hereditary angioedema. Women seem to have an increase in attacks during menses, and birth control pills may exacerbate the symptoms. The last few months of pregnancy seems to confer some level of protection from these attacks. There also seems to be an association of hereditary angioedema with systemic lupus erythematosus and other autoimmune diseases.⁴

The diagnosis of hereditary angioedema should be considered in patients who present with a history of clinical manifestations and a family history of the disease. The diagnosis should be confirmed by laboratory testing with measurements of both the absolute and functional levels of C1 inhibitor, C2, and C4. In patients with hereditary angioedema, C1 inhibitor levels will be less than 30% of normal and usually between 15% and 20% of normal. C2 and C4 are the next components of the activated complement cascade, and their levels are measured to gauge the levels of complement consumption present. If the levels of C1 inhibitor, C2, and C4 are normal during an attack, hereditary angioedema is excluded.^{4,8}

Treatment can be characterized in two separate ways - acute and chronic. During an acute attack, treatment is directed toward supportive measures. Minor bouts of swelling of the soft tissues of the body do not require intervention. However, episodes characterized by abdominal pain may require intravenous hydration and narcotics for pain relief. In patients with angioedema of the face and neck, close observation is mandated for signs of laryngeal obstruction and the need for emergent tracheostomy and respiratory assistance.^{6,8}

Patients suffering from hereditary angioedema do not respond to steroids, antihistamines or epinephrine, although these are often prescribed in emergency departments.^{4,5,10} For acute intervention the drug of choice is C1 inhibitor concentrate.^{4,5,8} In a study by Visentin and colleagues, C1 inhibitor concentrate given intravenously in a non-blinded small cohort of patients was shown to arrest attacks of hereditary

angioedema within 30 to 71 minutes.⁵ C1 inhibitor concentrate is used extensively in Europe where adverse reactions or incidents of transmission of hepatitis C or HIV have not been reported.

Other means of acute intervention include the use of fresh frozen plasma, which has been shown to alleviate attack. However, there are reports of exacerbation possibly due to a retransfusion of substrate for the complement cascade reaction of hereditary angioedema.^{4,8} Infusions of tranexamic acid and epsilon aminocaproic acid are also used which have been shown to reduce attacks by as much as 90%. These infusions have a known low risk of thrombosis, myonecrosis, and hypotension.^{4,5,8}

Long term management with attenuated androgens has been successful in over 90% of cases. Both danazol (50-400 mg daily) or stanazol (2-4 mg daily) have been shown to substantially reduce the incidence of acute attacks by raising the level of C1 inhibitor through increased hepatic synthesis of that molecule.^{4,11} These androgens are not effective in acute attacks. The original recommendation for the use of attenuated androgens was for individuals with one or more angioedema attacks per month. However, in view of Bork's studies on asphyxiation in patients with hereditary angioedema, treatment must be considered in all patients with hereditary angioedema, regardless of the frequency of their attacks.⁷

The safety of danazol and stanazol has been extensively studied.^{12,13} Menstrual irregularities in female patients were noted, as well as weight gain, polycythemia, thrombocytosis, alopecia, and hirsutism. Muscle cramps, transaminase elevations, headaches, and elevated total cholesterol were also noted. Two patients were able to undergo successful pregnancies with a temporary interruption of androgen therapy. There have been recent reports of hepatocellular adenoma and hepatocellular carcinoma in patients with hereditary angioedema taking danazol for more than thirteen years. Arterial hypertension is also reported.^{7,13} Notwithstanding these findings, androgens remain the mainstay of treatment for all patients with hereditary angioedema.

Conclusion

Hereditary angioedema is an uncommon genetically mediated disease occurring in as few as 1 in 150,000 persons. However, it carries an approximate risk of 30%-40% of death from laryngeal edema and asphyxiation over an affected individual's lifetime. Present medications allow for effective treatment and preven-

tion of acute attacks, making recognition of this disease imperative for the well being of the patient.

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