

CASE REPORT

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Periodic Severe Angioedema without Exogenous Hormone Exposure

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ABSTRACT

Hereditary angioedema (HAE) is characterized by recurrent attacks of skin and mucosal swelling in any part of the body including the digestive and respiratory tract which generally improve spontaneously within 12-72 hours. The underlying mechanism in HAE is related to bradykinin dysregulation which causes these attacks not to respond to common treatment strategies including epinephrine or corticosteroid. There are several types of HAE with different etiology but with the same clinical picture. Type 1 is due to the deficiency of C1 Inhibitor (C1-INH) protein and type 2 is related to dysfunctional C1-INH protein. The third type of HAE which comprises the minority of cases is associated with the normal amount and function of C1-INH protein. The presented case in this report was a 15-years old girl with a history of spontaneous angioedema attacks from the age of 14. The frequency of attacks was initially every two months but consequently increased to every two weeks after using some hormonal medications for ovarian cyst. Each episode has lasted around 10 days without any symptoms in between. Complement studies including C4, C1q, and C1-INH protein, both quantitative and qualitative, were reported as normal. A genetic assessment revealed a mutation in the exon 9 on the gene related to factor XII, hence the diagnosis of HAE type 3 was confirmed. This was a rare type of angioedema with normal amount and function of C1-INH protein which is predominantly seen in women during periods of imbalanced estrogen increments like pregnancy, lactation, and menopause, and hence it is responsive to hormonal manipulation strategies such as the use of progesterone containing medications.

Keywords: Bradykinin; Complement C1 inhibitor protein; Factor XII; Hereditary angioedema

INTRODUCTION

Angioedema is defined by swelling of the skin, mucous membranes, or both, including the respiratory

and gastrointestinal tracts, which typically lasts for 2 or 3 days and heals spontaneously.¹ Angioedema can be dangerous, notably in the cases of airway involvement and it can rarely lead to asphyxia. Most patients may also suffer from repeated episodes of severe abdominal pain due to intestinal edema.²

Angioedema attacks may have multiple diverse underlying mechanisms, either histamine or non-

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histamine mediated. Exposure to allergens such as food, medications, and insect bites may be the cause of activation of immune cells such as mast cells and basophils and consequent secretion of histamine leads to angioedema associated with urticaria in histaminergic forms.

Furthermore, there are other mediators such as bradykinin, rather than histamine, which triggers attacks in the absence of allergen exposure. Bradykinin promotes vasodilation and increases vascular permeability much more potent than histamine and its production is regulated by a protein called C1 Inhibitor (C1-INH) protein. Any defect or dysfunction of C1-INH protein may lead to a distinct form of angioedema which can be either hereditary or acquired.

Hereditary angioedema (HAE) is a genetic syndrome that is due to mutations of the C1 inhibitor protein-coding sequence gene which causes protein deficiency or dysfunction. C1-INH protein is a regulatory protein in the complement pathway as well as the coagulation system. The absence or dysfunction of it may lead to increment amounts of kallikrein which causes bradykinin production from proteolysis of high-molecular-weight kininogen (HMWK).³

In HAE type I which comprises 85% of all patients, deficiency of C1-INH protein is the underlying etiology but in HAE type II, it is functionally defective despite normal or even elevated levels of C1-INH protein.⁴

Bork et al, described the third type of HAE at the beginning of this century, which is clinically indistinguishable from the other types with a characteristic normal level of C4 and C1-INH protein during and between attacks and predominantly can be seen in women.⁵ Reports showed that the attacks may exacerbate in estrogen-enhancing situations such as taking oral contraceptives (OCP) or pregnancy.⁶ The pathogenetic basis of the third type of HAE is the mutation in coagulation factor XII that results in increased coagulation factor XII activity and subsequent conversion of higher amounts of prekallikrein to kallikrein which lead to increased production of bradykinin.⁷ Initial genetic tests revealed the presence of two missense mutations (*Thr328Lys* and *Thr328Arg* or *Thr309Lys/Arg*) in the same region of the factor XII gene which encoding for coagulation factor XII in some of the affected patients.⁸ Other mutations including the deletion of 72 bp (c.971_1018+24del72)⁹ and duplication of 18 bp (c.892_909dup)¹⁰ were reported in the course of

research which can be affecting the same proline-rich region of the FXII protein, Similar to previous mutations. The result of all these mutations is an increase in the activity of factor XII and subsequently increased the production of bradykinin. However, mutations of the plasminogen gene and angiotensin II have been recently reported as the possible causes of this type of HAE.¹¹

The following case is an example of HAE type 3 or HAE with normal C1-INH protein.

CASE REPORT

The patient was a 15-years-old unmarried girl with episodic angioedema of lips, tongue, and cheeks since she was 14. Her parents stated that the first episode started soon following eating a piece of cake at a birthday party that was treated by taking antihistamines but multiple episodes recurred without exposure to any possible allergens. Initially, each episode lasted for at least 14 days and repeated every 2 or 3 months. Attacks were invariably the same in each episode without any urticaria, gastrointestinal, upper, and lower airway manifestations. Hemodynamic parameters were reported to be stable in all episodes and the patient remained completely asymptomatic between attacks. There was no history of such attacks in her family. Each episode was treated with a cocktail of antihistamines, corticosteroids, and anti-leukotrienes with no or minimal effect. The patient was referred to an allergy and clinical immunology clinic for further workup (Figure 1). All tests, including C4, C1q, and C1-INH protein, both quantitative and qualitative, were reported as normal. The frequency and severity of attacks gradually increased and dramatically affected her quality of life, hence danazol and tranexamic acid were given orally as a prophylactic measure but it was unfortunately unsuccessful. Two months after the danazol administration, the patient experienced severe abdominal pain. Ultrasound studies showed some ovarian cysts which were regarded as the probable cause of devastating pain; hence danazol was discontinued, and OCP was prescribed by the gynecologist.

After a course of OCP consumption, the cysts were improved, but the angioedema attacks became more severe and more frequent (every other week).



Figure 1. Angioedema attack in lips, which is accompanied by severe swelling of the lips

Epinephrine, corticosteroid, antihistamines, anti-leukotrienes, and fresh frozen plasma (FFP) were used several times during attacks without any effect. She became exhausted because of the severity and frequency of the attacks which significantly disrupted her daily social activities.

All laboratory tests, including quantitative and qualitative C1-INH protein, were repeated in another well-equipped center which revealed normal values again.

Because of no identified allergic basis and no response to antihistamines, no history of use of medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors, and normal values and function of C1-INH protein, differential diagnosis of “HAE with normal C1-INH protein” were suspected and the genetic test was performed which revealed a missense mutation on exon 9 of coagulation factor XII and, therefore, the patient regarded as “HAE type 3”. Gain-of-function mutations in coagulation factor XII are the basis of this rare genetic syndrome with a similar clinical presentation of HAE type 1 or 2. In this type of hereditary angioedema, attacks tend to be exacerbated by estrogen either endogenous or exogenous.

Following the diagnosis of type 3 HAE, further consumption of OCP is prohibited and other therapeutic modalities are recommended to reduce estrogen levels such as lowering BMI and the use of estrogen-lowering drugs and progesterone boosting drugs.

DISCUSSION

HAE is a rare hereditary condition characterized by uncontrolled activation of the contact system and increased production of bradykinin resulting in episodes of recurrent angioedema.¹²

In most cases of HAE, the *SERPING1* gene mutation encoding C1-INH protein has been identified as the leading cause of symptoms. C1-INH protein is an important regulatory protein in different pathways including the complement cascade. Following the activation of the complement cascade, the C1-INH protein binds to the first part of this cascade, including C1r and C1s, and prevents inappropriate or excessive activation of the classical pathway by antigen-antibody complexes. In cases of C1-INH protein deficiency, activation of the classical pathway persists which can be led to reducing C4 so that C4 levels are below normal in 95% of patients with HAE.¹³

The prevalence of hereditary angioedema due to C1-inhibitor protein deficiency is estimated to be 1:50,000 in the general population. It comprises of two main groups: type I (HAE-1), with no or reduced C1-INH protein which is seen in 85% of cases, and type II (HAE-2) with no or reduced C1-INH protein functional levels which include nearly 15% of patients.¹⁴

Since 2000, a new subtype of HAE was described, which was clinically indistinguishable from the other variants but it had unique characteristics. Some clinically indistinguishable from the others but it has unique features that distinguish it from other variants. Some important features include 1) less frequent

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abdominal pain during attacks, 2) attacks occur more on the face and tongue, 3) most patients are female, the majority of them remained symptomatic, 4) attacks tend to be exacerbated by estrogen, either endogenous or exogenous, 5) diagnosis is difficult and often delayed.^{15,16}

Approximately 25% of HAE patients with normal C1-INH protein show exon 9 mutation on coagulation factor XII genes as the pathophysiological basis of the disease. This region is the proline-rich domain and the most common reported mutations are missense mutation of *T328K* and *T328R* which result in defective glycosylation of coagulation factor XII that leads to hyperactivation of the contact system. As a result, the conversion of pre-kallikrein to kallikrein enhances which will increase the production of bradykinin. On the other hand, deficiency of C1-INH protein is associated with less dissociation of bradykinin which is a major pro-inflammatory cytokine.^{17,18}

Our patient was a young girl who had developed symptoms of the disease around adolescence. Her attacks were initially reported as mild and the intervals were several months apart, but an important hint was the increasing severity and frequency of attacks following consumption of OCP. Worsening of symptoms following the use of estrogen-containing medication, lack of family history, normal results of laboratory tests, and ineffective use of other therapeutic modalities shed light on another possible form of angioedema: HAE type 3.

Genetic sequencing is useful in early diagnosis of HAE with normal C1-INH protein but detection of mutation is affordable in only one-third of patients including our patient.¹⁹

Non-histaminergic idiopathic angioedema is another type of angioedema with normal C1-INH protein values and is a major differential diagnosis of HAE type 3 in which no detectable genetic mutation can be found.

The management of the disease consists of both therapeutic and prophylactic modalities. Medications that are already used in the treatment of attacks include C1-INH protein concentration, FFP, inhibitors of kallikrein such as ecallantide, and the selective and specific antagonist of bradykinin B2 receptors such as icatibant.²⁰⁻²²

Because of the unavailability of definitive therapeutic options, effective prophylaxis is a major task in these potentially life-threatening diseases.

Prophylactic measures are consisting of two categories. First of all, is avoiding known triggers such as physical stressors and traumas and the use of medications especially estrogen-containing pills. The second prophylactic measure is the regular consumption of some medications as listed below:

- 1) Weak androgens, such as danazol which can reduce the frequency of attacks by increasing C1-INH protein.²³ But in our patient the drug must be unfortunately discontinued because of ovarian cysts, however, the appearance of ovarian cysts is not related to the use of this drug.
- 2) Anti-fibrinolytic agents such as tranexamic acid that prevents activation of coagulation factor XII.¹⁹ It did not affect controlling the attacks of our patients.
- 3) Progesterone-containing medications to counteract endogenous estrogen.² Different types of progesterone can be used in this regard; hence progesterone tablets have been started for the patient. Its effects on the severity and frequency of attacks seemed to be helpful according to initial pieces of evidence.
- 4) Suppression of ovulation to dramatically reduce the level of endogenous estrogen is the last remedy and will be considered if the other options are failed.

In conclusion, HAE type 3 is a rare type of hereditary angioedema that genetic assessment is useful in confirmation of the disease in only 25% of patients. Due to the role of estrogen in the pathogenesis of the disease, hormonal therapy is an interesting subject for further research on this topic.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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