

A Case of Angioedema Associated with Decreased C1 Inhibitor Activity

Chizuko Yano¹, Arihito Ota¹ and Hidemi Nakagawa¹

ABSTRACT

Background: We report a case of a 31-year-old woman who began to notice swelling of her arms at age 20. She was once given a diagnosis of cellulitis, but her symptoms spontaneously resolved. The patient had swelling of the left forearm and palm and was referred to our department for evaluation. She had slight pain but no obvious weight gain.

Case Summary: Antinuclear antibody and other autoantibodies, including anti-ds-DNA antibody, anti-RNP antibody, anti-Sm antibody, and anti-SS-A antibody were not detected. C1 inhibitor activity was low, C3 was normal, C4 was low, CH₅₀ was low, and C1q was normal.

Discussion: Based on the presence of the typical clinical features and the positive results on the complement tests, we diagnosed hereditary angioedema. A decrease in C1 inhibitor activity and an increase in specific protein concentrations indicated type 1.

KEY WORDS

Angioedema, C1 inhibitor, complement, HAE, triggering factor

INTRODUCTION

Hereditary angioedema (HAE) is an autosomal dominant disorder characterized by recurrent episodes of subcutaneous and submucosal edema.¹ Triggering factors in angioedema include surgical procedures (e.g., tooth extraction), severe heat or cold, strenuous exercise, infections, and in women, menstrual periods. Increased understanding of the pathophysiology of HAE has led to development of specific treatment with intravenous self-administration of human C1-INH concentrate. However, because of concerns about viral infection, this is not often used. Patients are usually given preventive treatment and are carefully observed. This report describes a woman with HAE involving the upper extremities.

CLINICAL SUMMARY

A 31-year-old lactating woman had swelling of the left forearm and palm and was evaluated by our department in October 2005. She began to notice occasional swelling of her arms at age 20. There was no itching. This occurred a maximum of 4 or 5 times per year. She was once given a diagnosis of cellulitis by her

family physician, but during that episode, symptoms spontaneously resolved in 2–3 days without treatment.

Her left forearm showed some erythema but no edema. The palm was swollen, with involvement of all the fingers (Fig. 1).

The patient denied generalized symptoms of dyspnea, laryngeal edema, abdominal pain, or diarrhea. She had no weight gain.

Hereditary angioedema was suspected although her family had no previous experience of angioedema, and a variety of laboratory tests were performed.

PATHOLOGICAL FINDINGS

Laboratory findings were as follows: WBC $4.9 \times 10^3 / \mu\text{L}$ (Neut 54.3%, Eosino 3.6%, Baso 0.6%, Mono 8.4%, Lymph 33.1%), RBC $4.58 \times 10^6 / \mu\text{L}$, Hb 14.1 g/dL, Ht 40.6%, Plt $267 \times 10^3 / \mu\text{L}$, IgE 146 U/mL, IgG 1561 mg/dL, IgA 92 mg/dL, and IgM 89 mg/dL. Biochemical analysis was generally normal. There was no eosinophilia, and the IgM was within normal limits. Antinuclear antibody tests were normal and complement tests showed a normal C3, decreased C4,

¹Department of Dermatology, The Jikei University School of Medicine, Tokyo, Japan.

Correspondence: Chizuko Yano, Department of Dermatology, The Jikei University School of Medicine, 3–25–8 Nishishinbashi, Minato-ku, Tokyo 105–8461, Japan.

Email: yanoc@jikei.ac.jp

Received 19 September 2006. Accepted for publication 28 December 2006.

©2007 Japanese Society of Allergology

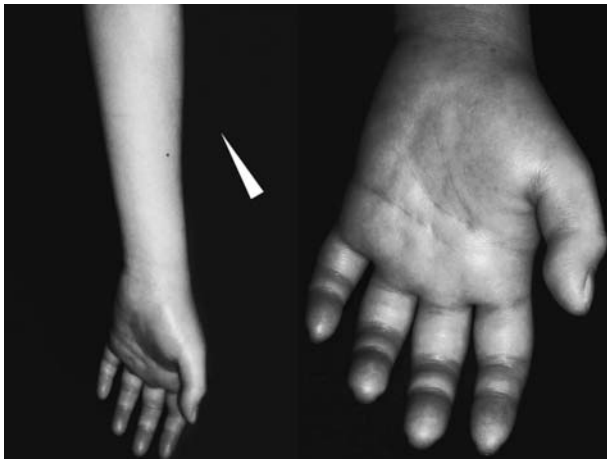


Fig. 1 The left forearm showing some erythema but no edema. The palm was swollen, with involvement of all fingers

Table 1 Classification of Recurrent Angioedema⁷

1. Hereditary angioedema due to deficiency of C1 inhibitor protein and activity (hereditary angioedema type 1)
2. Hereditary angioedema due to deficiency of C1 inhibitor activity (hereditary angioedema type 2)
3. Hereditary angioedema with normal C1 inhibitor activity in women (hereditary angioedema type 3)
4. Acquired angioedema due to increased consumption of C1 inhibitor or autoantibody formation (acquired angioedema type 1 and 2)
5. Recurrent angioedema due to angiotensin-converting enzyme inhibitors or angiotensin II-receptor antagonists
6. Urticaria-related angioedema
7. Idiopathic angioedema

and normal C1q. These findings confirmed a diagnosis of hereditary angioedema. A decrease in C1 inhibitor activity and an increase in these protein concentrations indicated type 1.

A skin biopsy was not performed because the patient refused to give consent for this procedure. The patient also declined a skin biopsy or blood testing of her parents and sister. The patient was observed without specific treatment. The angioedema resolved almost completely by the next day. She subsequently has had only one mild episode of edema and has not returned for follow-up.

DISCUSSION

Recurrent angioedema can be inherited or acquired (Table 1).² HAE is an autosomal dominant disorder characterized by recurrent episodes of subcutaneous and submucosal edema.^{1,2} HAE is due to a deficiency or dysfunction of complement 1 inhibitor (C1-INH) protein. In type 1, there is decreased C1-INH protein and activity. In type 2, there is normal production of

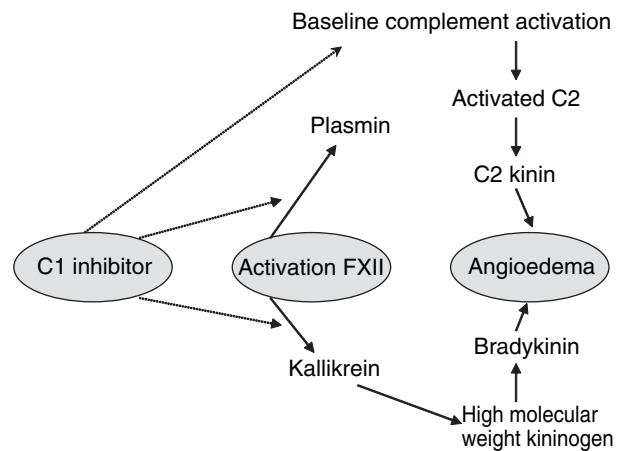


Fig. 2 Hypothesized mechanism for the initiation of an attack of angioedema⁵

C1-INH but without biochemical activity.² A new type 3 HAE, a sex-linked disorder occurring only in women, has also recently been reported.³

About 10% of new cases are due to a gene mutation, and a negative family history does not rule out HAE. Pappalardo *et al.* report a 20% mutation rate of the C1-INH gene even in the absence of a family history, and the rate may be as high as 50%.⁴ The causative gene is located on the long arm of chromosome 11.

In type 3 HAE, occurring only in women, both C1 inhibitor function and C4 are normal.^{2,3} The higher prevalence in women who are pregnant or using oral contraceptives suggests an estrogen-related effect, but the causative gene has not been identified.

C1 inhibitor not only inhibits C1, but it also inhibits many enzymes in the kallikrein-kinin, coagulation, and fibrinolytic systems (Fig. 2).⁵ C1 inhibitor deficiency or dysfunction plays a role in the mechanism of HAE by activation of the complement system. Low C1 inhibitor leads to uncontrolled activation of factor XII, which generates kallikrein and plasmin. Kallikrein liberates bradykinin from high molecular weight kininogen, whereas plasmin cleaves off C2 kinin from activated C2. Activated C2 is continuously produced during baseline complement activation, which is increased as a result of insufficient control of autoactivation of C1 caused by C1 INH deficiency. Kinin system activation, in association with bradykinin production, is an important triggering factor in HAE.

However, if this was the sole mechanism, one might expect chronic angioedema. But in fact, other activating factors such as trauma and surgery often play an important role. Thus, much remains unknown about the pathophysiology of HAE.

A diagnostic flow sheet is helpful in evaluating angioedema (Fig. 3).⁶ Family history, age at onset, severity of symptoms, and other underlying disorders may provide useful information. Screening includes measurement of C3 and C4 complement levels. If C3

Angioedema Decreasing C1INH Activity

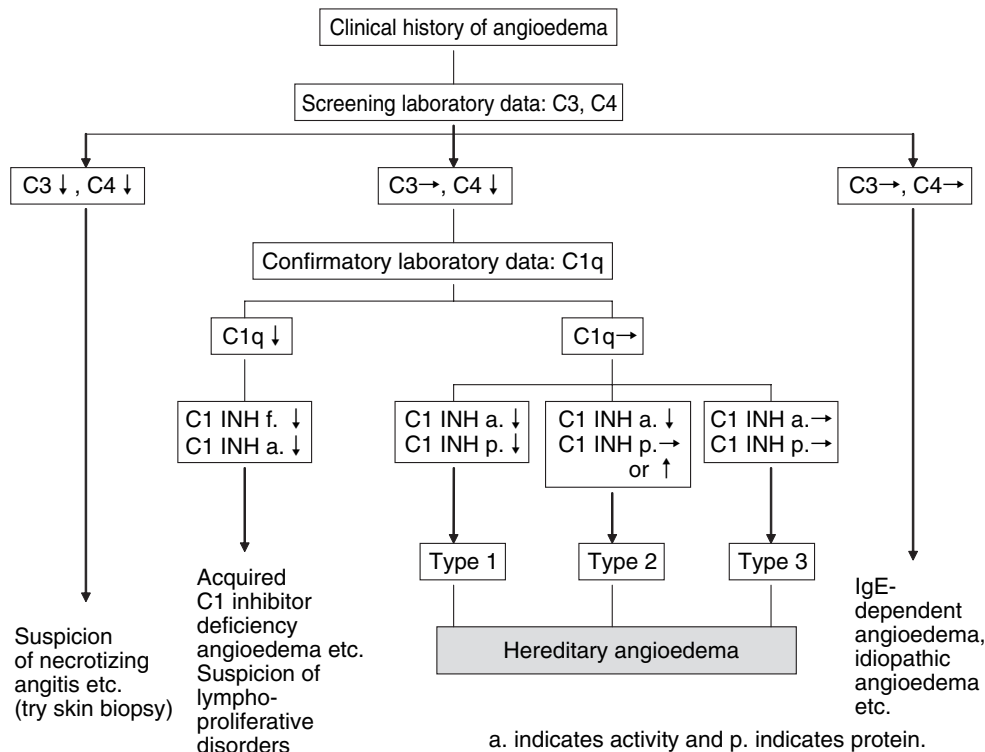


Fig. 3 Flow sheet for patients with a clinical history of angioedema, revised from⁶

is normal and C4 is decreased, C1q should also be determined. If the latter is normal, HAE should be suspected.

Triggering factors include surgical procedures (e.g., tooth extraction, tonsillectomy), infections, menses, pregnancy, delivery, cold stress, exercise, and emotional stress. Fatigue after birth and delivery may have been a precipitating factor in the present case.

Our patient had no severe episodes of angioedema, but caution and preventive measures have been recommended. The management of HAE requires attention to three areas: treatment of acute episodes of angioedema, long-term prophylaxis, and short-term prophylaxis,⁷ including tranexamic acid, C1 inhibitors, and androgen derivatives.

HAE is not common in daily clinical practice, but in patients with angioedema, measurement of CH50, C3, and C4 are important screening tests. If C3 is normal but CH50 and C4 are decreased, HAE should be strongly suspected.

This was a typical case showing angioedema to the extremities. It turned out to be type 1 HAE, not the new type 3, showing low levels of C4 on blood tests. We believe that exhaustion during nursing may have

caused angioedema. We plan to measure bradykinin in future cases and observe its correlation with the clinical course.

REFERENCES

1. Devis AE III. The pathophysiology of hereditary angioedema. *Clin. Immunol.* 2005;**114**:3-9.
2. Bork K, Fischer B, Dewald G. Recurrent episodes of skin angioedema and severe attacks of abdominal pain induced by oral contraceptives or hormone replacement therapy. *Am. J. Med.* 2003;**114**:294-298.
3. Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 2000;**356**:213-217.
4. Pappalardo E, Cicardi M, Duponchel C *et al.* Frequent de novo mutation and exon deletions in the C1inhibitor gene of patients with angioedema. *J. Allergy Clin. Immunol.* 2000;**106**:1147-1154.
5. Angelo A, Emel AP, Karen EB *et al.* Hereditary and acquired angioedema: Problems and progress: Proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J. Allergy Clin. Immunol.* 2004;**114**:S51-S131.
6. Markovic SN, Inwards DJ, Frigas EA, Phyllyk RP. Acquired C1 esterase inhibitor deficiency. *Ann. Intern. Med.* 2000;**132**:144-150.
7. Zuraw BL. Current and future therapy for hereditary angioedema. *Clin. Immunol.* 2005;**114**:10-16.