Case Report
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# A Case of Hereditary Angioedema in a 7-Year-Old Korean Girl

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Hereditary angioedema (HAE) is a rare autosomal dominant disease that usually occurs in adolescence and early adulthood. It is characterized by recurrent non-pitting edema involving the skin and intestinal tract, especially the extremities and face. It is not associated with urticaria and pruritus. The cause is known to be the deficiency of C1 inhibitor. We herein report a 7-year-old girl with HAE who had recurrent episodes of swelling of the extremities and face without urticaria and pruritus. Her great grandmother had suffered from the same symptoms. The level of serum C4 was 8.01 mg/dL (normal: 10-40 mg/dL). The level of C1 inhibitor was 5.0 mg/dL (normal: 18-40 mg/dL). To our knowledge, this is the first pediatric case with typical clinical symptoms of HAE and C1 esterase inhibitor deficiency in Korea.

**Key Words:** Hereditary angioedema; angioedema; young children; Korea

## INTRODUCTION

Angioedema is a localized, transient, episodic edema of the deeper layer of the skin or of the gastrointestinal tract mucosa. It usually affects the face and extremities.[1,2] Angioedema of the skin is non-pitting, with ill-defined margins. Attacks of angioedema may last a few days and usually resolve spontaneously.

Angioedema can be divided into two types, allergic angioedema accompanying urticaria and non-allergic angioedema without urticaria.[3,4] Hereditary angioedema (HAE) is a rare autosomal dominant disorder that results from a deficiency or dysfunction of C1 inhibitor. It is not associated with urticaria or pruritus,[2] and usually occurs in adolescence and early childhood.

Several cases of HAE manifesting in adults have been reported in Korea.[5-9] However, a case of HAE manifesting in young children has not yet been reported. Herein, we report a 7-year-old girl with HAE which was confirmed by a low level of serum C4 and C1 inhibitor.

## CASE REPORT

A 7-year-old girl visited Samsung Medical Center because of episodic angioedema lasting 3 years. She had experienced attacks of painless swelling on her face or extremities, which were not associated with urticaria or pruritus. There were no symptoms involving gastrointestinal tract. These attacks occurred sporadically without any precipitating factors such as exercise, trauma, food or drugs. Her symptoms did not respond to antihistamine treatment, and lasted 24-48 hours with spontaneous resolution.

Her past medical history was unremarkable except for angioedema. Vaccinations were given as scheduled with no side effects. The patient's great-grandmother had suffered from the same events, but her grandparents, parents and even her younger brother have not experienced swellings like the patient.

Her physical examination on the first visit revealed nothing significant. Laboratory findings included a leukocyte count of 11,820/mm$^3$, hemoglobin 13.2 g/dL, platelet count 404,000/mm$^3$, and eosinophil count 50/μL. Serum specific IgE antibodies (UniCAP®) for cow's milk, egg white, buckwheat, soy, wheat, *Dermatophagoides pteronyssinus*, and *Dermatophagoides farinae* were all negative. Skin prick tests were all negative for 25 common food allergens and 6 inhalant allergens. Serum total IgE was 92.3 kUA/L. Cryoglobulin, antinuclear antibody and rheumatoid factor in serum were not detected. The level of C4 was low (8.01 mg/dL, normal range 10-40 mg/dL). The levels of CH50 and C3 were 4.7 CH50/mL (normal range 13-35 CH50/mL)

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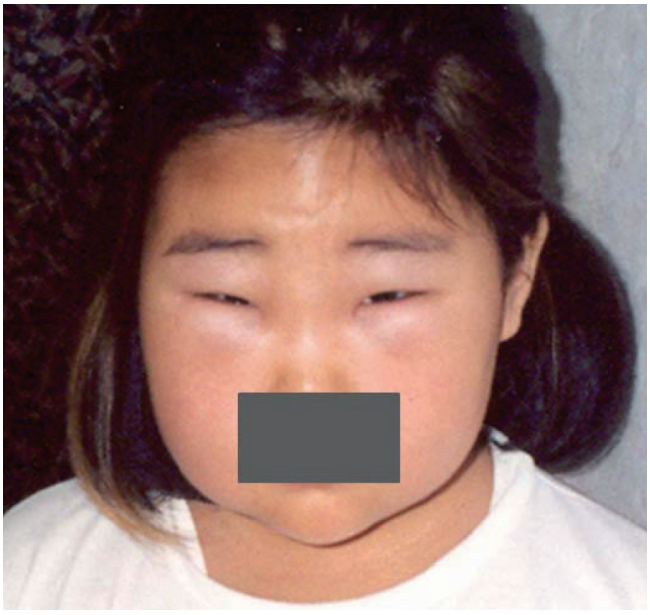

**Figure.** The swollen face of the patient during an attack of angioedema.

and 139 mg/dL (normal range 77-195 mg/dL), respectively. The level of C1 inhibitor was 5.0 mg/dL (normal range 18-40 mg/dL), as measured by a nephlometer in Mayo Clinic (Rochester, NY, USA).

Two weeks later after the first visit, she developed an attack of angioedema. Her face, especially in periorbital areas, was swollen without overlying erythema and urticaria (Figure). Involved skin was non-pitting with ill-defined margin, and did not show warmness and tenderness. The swelling lasted more than 24 hours and subsided without specific treatment.

Currently, the patient is 16 years old, and she has experienced episodic swelling of the face or extremities several times a year for 9 years. However, at present the attacks of angioedema have occurred less frequently and are less severe than several years ago.

## DISCUSSION

Angioedema is defined as a recurrent, non-pitting, self-limiting swelling due to a transient increase of endothelial permeability in the capillaries of the deep cutaneous and mucosal layers. Two forms of angioedema are well defined, and can be distinguished by the response to treatment, those that respond to antihistamine treatment and those that do not.[3] By far, the most common form of angioedema is allergic in origin, and is due to the release of histamine from mast cells activated when membrane-bound IgE antibodies are cross-linked to a specific allergen. The other prototype of angioedema, although rare, is due to a deficiency or dysfunction of C1 inhibitor. This form of angioedema is due to bradykinin release. The activation of C1 is an essential step in the complement cascade, and is regulated by C1 inhibitor. The reduced levels of functional C1 inhibitor lead to uncontrolled activation of the classical complement pathway. This gives rise to the release of bradykinin, which causes increased capillary permeability.

Deficiency or dysfunction of C1 inhibitor is hereditary or acquired. HAE has an autosomal dominant pattern of inheritance, and it is estimated that 20%-25% of cases are the result of sporadic mutations in persons with no family history of disease.[10] It is characterized by recurrent non-pitting edema, mainly involving the skin and gastrointestinal tract. Involved skin is swollen, tender, and warm, but is not associated with urticaria. Frequently a burning sensation is present, but pruritus is typically uncommon. It usually lasts 48-72 hours but can persist up to 1 week.[2] Often, the onset of the episodic attack is associated with stress or trauma, infection, or changes in temperature.

The diagnosis of HAE is suspected by family history and characteristic patterns of angioedema.[11] The clinical characteristics that help distinguish angioedema due to C1 inhibitor deficiency from allergic angioedma are absence of coexisting urticaria or pruritus and equal frequency of facial and peripheral involvement for cutaneous attacks. A functional assay for C1 inhibitor level (type I, 85%), and C1 inhibitor activity (type II, 15%) can be used as a confirmative method for HAE diagnosis.

In the present patient, the swelling was not associated with urticaria and pruritus, and involved the face and extremities. Thus, the diagnosis of HAE was suspected at first, so we checked C4 level; diminished C4 concentration was highly suggestive for the diagnosis.

In patients with HAE, long-term prophylaxis with danazol, stanozolol or antifibrinolytic agents is usually effective.[12] It is necessary in acute severe attacks to perform replacement therapy with a concentrate of purified C1 inhibitor or with fresh frozen plasma. In our case, the attacks of angioedema were not severe and were not associated with respiratory and gastrointestinal symptoms. Her symptoms subsided spontaneously, and no aggressive treatment was required.

It has been reported that in 50% of HAE patients, the symptoms first occur during childhood, usually between 5 and 11 years of age.[13-15] In Korea, adult cases with HAE have been reported.[5-9,16] However, the patients diagnosed during early childhood have not been reported up to now in Korea. Lee et al.[8] reported 32 year-old male patient with HAE, who experienced repeated attacks of angioedema without urticaria since 17 years old. His great grandfather had suffered from the same events. In another report of adult patients with HAE, their age ranged from 26 to 43 years.[5-7] In Korean children, several patients aged 7-14 years have been reported to have reduced level of C1 inhibitor.[17,18] However, they manifested chronic urticaria, pruritus or dermographism, not typical symptoms of HAE such as non-pruritic angioedema. In contrast, our case showed intermittent painless swelling of face or extremities, which were not associated with urticaria or pruritus. Therefore, HAE was diagnosed

on the basis of these typical symptoms plus abnormal laboratory findings. In particular, our patient began to suffer from the attacks of angioedema at age 4, when the symptoms of HAE occasionally appear. Although our case does not have a classical family history of HAE, this is the youngest patient with typical clinical manifestations of HAE and C1 inhibitor deficiency in Korea.

Here we report a 7-year-old girl who presented typical symptoms of HAE with C1 inhibitor deficiency at age 4. To our knowledge, this is the first pediatric case of HAE in Korea.

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