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## Hereditary Angioedema: Not An Allergy

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### Abstract

Hereditary angioedema is a genetic disorder due to a deficiency or malfunction of C1 esterase inhibitor. We herein describe a case of 25-year-old male who presented with swelling over face since one day. There was history of similar episodes since two years with gradual subsidence of swelling without any treatment. Investigations revealed grossly reduced complement C4 and C1 esterase inhibitor level. Patient was diagnosed to have hereditary angioedema type 1 and started on stanazolol 2 mg three times a day with no recurrence in one year of follow-up. Hereditary angioedema resembles angioedema of an allergic reaction. However, the cause is different.

**Keywords:** *C1 esterase inhibitor, hereditary angioedema, stanazolol*

### Introduction

#### What was known?

Hereditary angioedema is a genetic disorder due to a deficiency or malfunction of C1 esterase inhibitor.

Hereditary angioedema (HAE) is an autosomal dominant disorder of C1 inhibitor (C1-INH) deficiency manifested by painless, nonpruritic, and nonpitting swelling of the skin. Type I HAE is defined by low plasma levels of a normal C1-INH protein. Type II HAE is characterized by the presence of normal or elevated levels of a dysfunctional C1-INH. Type III HAE has been recently identified as an estrogen-dependent inherited form of angioedema occurring mainly in women with normal functional and quantitative levels of C1-INH. We report the case of HAE (type 1) who responded well to stanazolol.

### Case Report

A 25-year-old male presented with swelling over face since one day. There were similar episodes since two years with gradual subsidence of swelling without any treatment. Patient also gave the history of minor trauma prior to each episode. However; there was no history of wheals, associated systemic complaints, drug intake, food allergy, and similar complaints in family.

On cutaneous examination, there was edema of eyelids, left cheek, and lips. Based on the cutaneous finding, angioneurotic edema was suspected and patient was treated in emergency department with inj. hydrocortisone, inj. epinephrine, and inj. chlorpheniramine without any significant outcome. Swelling gradually subsided over a period of three days [Figures 1 and 2].

Laboratory investigations including complete blood count, liver and renal function tests, urine examination, antinuclear antibody test, chest X-ray, and X-ray of paranasal sinuses were all within normal limit. Considering the history of repeated episodes of angioedema without wheals without any precipitating factor with no response to usual line of management special investigations like complement C4 and C1 esterase inhibitor levels were done. Complement C4 and C1 esterase inhibitor levels were 1.44 mg /dl (N 10 -40 mg/dl) and 38 mg /L (N 275 – 400 mg/L), respectively, suggested the diagnosis of HAE (type 1). C1q level was not done because of unavailability of the test in India.

Patient was started on stanozolol 2 mg thrice a day with no recurrence in one year of follow-up.

## Discussion

HAE (inherited C1 inhibitor deficiency), also known as Quinke's edema, was originally described and named by Osler in 1888. This is a rare disorder, accounting for only 5% of all cases of angioedema without wheals and only about 1% of all cases of angioedema. It is transmitted as an autosomal dominant trait on chromosome 11. A family history is usually, but not invariably apparent. Over 50% of cases present before puberty,[1] but the onset may be delayed even into late adult life.

There are recurrent episodes of swellings of the skin and mucous membranes throughout life often associated with nausea, vomiting, colic, and urinary symptoms. These attacks may occur regularly every few weeks or may be less frequent. Between the attacks, the patient is completely well. During an episode, the swelling increases slowly over 12 to 18 hours, then slowly subsides over the next 48 to 72 hours. Swelling involves the extremities (96%), face (85%), oropharynx (64%), and intestinal mucosa (88%). Obstruction of the upper respiratory tract is responsible for the 30% mortality rate. The skin and mucosal lesions are often solitary and may be painful. They seldom itch. They may appear spontaneously or after trauma, dental trauma, being especially hazardous. Ordinary urticaria does not occur, but there may be rather distinctive reticulate erythema, perhaps with minimal edema which occurs prodromally.[2]

The blood of these patients is deficient in a natural inhibitor of C1 esterase which is made in the liver under genetic control.[3] C1 esterase inhibitor deficiency is responsible for inappropriate activation of C1 and generation of C2 kinin which leads to increase vascular permeability and angioedema develops. The inhibitor is present either in reduced amount (type 1) or in 15% of affected families in an inactive form, although it can be detected in normal amounts immunologically (type 2). A third type of HAE has been proposed recently (type 3), limited to women with family history of recurrent angioedema, including swelling of the upper airway, but with normal levels of plasma C1 esterase inhibitor and C4,[4] although this remains controversial. This C1 esterase inhibitor deficiency may be detected antigenically, but functional assays are necessary to detect type 2 HAE. The components of complement (C2, C4, and CH 50) are low during, after and to some extent even between attacks, or in symptomless carriers. Complement C4 is nearly always low and its measurement may be used as an initial screening test. There is a weak association with autoimmune disease including Sjogren's syndrome.[5]

Acquired C1 inhibitor deficiency (acquired angioedema AAE) is a rare disease that occurs in two forms, AAE 1 and AAE 2. AAE 1 is associated with malignancy (B – cell lineage, breast cancer, etc); AAE 2 is an autoimmune disorder and has C1-INH auto antibodies. There is a lack of evidence of inheritance and the onset of symptoms is in middle age. C1q levels are normal in HAE and depressed in AAE.

The response of HAE to conventional treatment for allergy associated angioedema is generally poor. Antihistamines, steroids, and even epinephrine are said to be of little or no use. Treatment may be considered as long prophylaxis, short term prophylaxis, and the emergency management of an established attack. Estrogen therapies, such as oral contraceptive pills, may induce or exacerbate HAE and should be avoided if possible.

Androgens have been used prophylactically for many years with some success, but more recently the lives of many of these patients have been revolutionized by use of attenuated androgen/anabolic drugs such as danazol and stanozolol. They stimulate the production of the deficient inhibitor. The usual starting doses are danazol 200-600mg daily or stanozolol 1-5 mg daily. The dose is assessed on clinical

response, rather than on any changes in laboratory tests, as improvement may occur even when the C1 esterase inhibitor levels remain low. Such therapy may also be used for short term prophylaxis, for example 6 days before and 3 days after a dental surgery at higher dose ranges.[1] Some but not all cases of acquired variant of the disease also respond to this therapy. Epsilon amino caproic acid 12-18 g daily or related tranexamic acid 2.0-4.5 g daily has been found to help some patients. They are less effective than danazol or stanozolol, but are useful where androgens are contraindicated, especially for short term prophylaxis. Replacement therapy with fresh frozen plasma has been used for short term prophylaxis. However, a partly purified preparation of the inhibitor is treatment of choice for severe attacks, especially laryngeal edema and abdominal colic, or it can be used for short term prophylaxis[6] prior to procedures placing the patient at risk of laryngeal swelling, including dental extraction, endoscopy or intubation. Symptoms subside in 30-90 min.[1]

In clinical practice, generally, angioedema is considered allergic in origin, but HAE is familial condition characterized by deficiency of C1 esterase inhibitor. As this is a fatal condition, proper diagnosis is a must as treatment differ from usual treatment of angioedema. One must do C4 level as a screening test and C1 esterase level as a definitive test once the angioedema without associated urticaria is encountered.

#### What is new?

In spite of resemblance this condition is not an allergic disorder.

#### Footnotes

**Source of Support:** Nil

**Conflict of Interest:** Nil.

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#### Figures and Tables

**Figure 1**



Edema of left lower eyelid, cheek, and lips

**Figure 2**



Photograph after three days

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