

Hereditary angioedema in a Chinese family

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Hereditary angioedema is characterised by recurrent episodes of peri-orbital and peri-oral swelling which can cause an upper airway obstruction, abdominal pain, vomiting, diarrhoea, and even hypotensive collapse. This potentially fatal condition is frequently misdiagnosed; its early recognition and appropriate treatment are thus important. We report a familial cluster of hereditary angioedema in a Chinese family and describe the clinical course of two patients.

HKMJ 1997;3:436-8

Key words: Angioneurotic edema; Complement 1 inactivators; Immunologic deficiency syndromes

Introduction

Hereditary angioedema (HA) is a rare autosomal dominant condition that is characterised by the deficiency or functional anomaly of the complement 1-(C1)-esterase inhibitor. If not diagnosed and treated appropriately during an acute attack, this condition is potentially fatal, as up to 50% of cases may develop laryngeal oedema which can result in an acute upper respiratory tract obstruction.¹ Although HA is well described in the West, its report among Orientals is lacking in the literature.^{2,3} In this case report, we describe the occurrence of HA in two members of a Hong Kong Chinese family in which two members had previously succumbed during an acute attack.

Case 1

A 30-year-old man who had lived in the Netherlands presented to the Prince of Wales Hospital with an acute attack of HA in March 1996. He had been disease-free for some years in the Netherlands and was non-compliant with danazol therapy; he carried self injectable adrenaline and C1-esterase inhibitor concentrate for emergency use. On presentation, he had orofaciolingual angioedema with an incomplete upper airway obstruction. He was treated successfully with prompt tracheal intubation and an infusion of the C1-esterase

inhibitor concentrate that he possessed. The C1-esterase inhibitor level was not checked during the acute phase.

The patient had a strong family history of HA (Fig) and had had recurrent angioedema attacks since the age of 3 years. Furthermore, his aunt (described in Case 2) had previously been treated at our hospital with similar attacks. The patient gave a history of proteinuria 1 year earlier, with an elevated creatinine level of 170 $\mu\text{mol/L}$ (normal range, 50-110 $\mu\text{mol/L}$). A renal biopsy performed in the Netherlands had confirmed the diagnosis of mesangiocapillary glomerulonephritis.

After the acute attack, danazol was given at a dose of 200 mg/d. His C1-esterase inhibitor level at 4 weeks was 0.10 g/L (normal range, 0.10-0.27 g/L). He remained asymptomatic until 8 months later, when he developed abdominal colic. This was associated with swelling of his limbs 2 days after commencing treatment with enalapril for deteriorating renal function. There was no upper airway involvement and the attack was again rapidly treated with an infusion of the patient's C1-esterase inhibitor concentrate. Administration of enalapril was stopped and there have been no attacks of angioedema since.

Case 2

A 65-year-old woman, the cousin of the previous patient's father, first presented to our Accident and Emergency department in 1994. She had complained of a puffy face and swollen lips after having taken an unknown medication for epigastric pain. There was no evidence of respiratory disturbance. Since she gave a vague history of similar 'allergic attacks' in the past after taking various medications, her symptoms were

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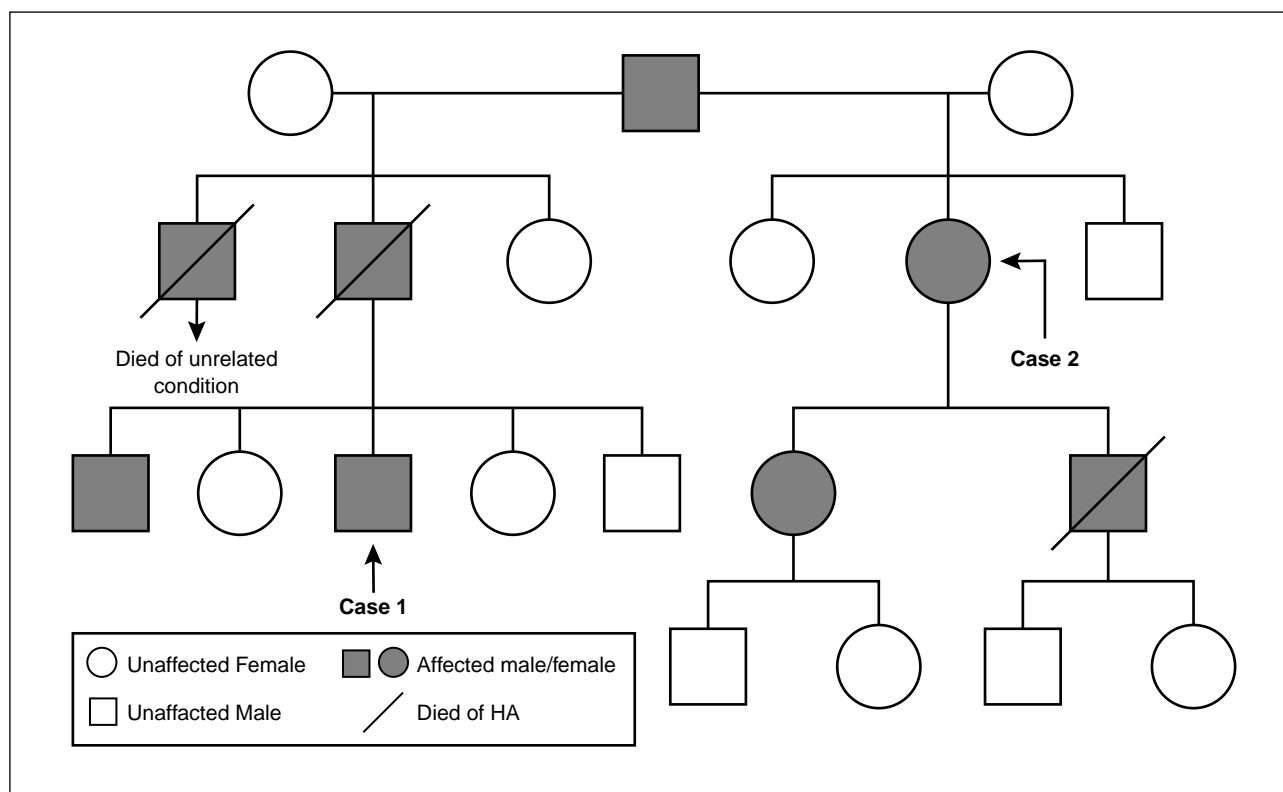


Fig. Family tree of a Chinese family with hereditary angioedema

treated as a case of drug allergy, although no formal drug testing was performed. She returned to our hospital in 1995 with a similar attack; on this occasion, there was no prior drug intake. A detailed history obtained at the time revealed a familial recurrence of angioedema. The diagnosis of HA was subsequently confirmed when the level of C1-esterase inhibitor was found to be low (0.07 g/L). In addition, the level of serum complement 3 was normal while that of complement 4 was suppressed to less than 0.1 g/L (normal range, 0.2-0.4 g/L). She was given danazol and later tranexamic acid, but her compliance was poor. She has not had a recurrence since.

Family history

A strong family history of HA was present in the two cases, as illustrated in the Figure. Two of the seven affected members in the family had died at the ages of 36 and 40 years, following an upper airway obstruction during an acute attack of angioedema. The diagnosis of HA was not known prior to either fatal attack.

Discussion

This case report demonstrates the importance of the early recognition and appropriate treatment of a rare but potentially fatal condition. Hereditary angioedema is frequently misdiagnosed as an allergic reaction to

food or drugs, and is sometimes mislabelled as an anaphylactic reaction. Apart from the typical orofacial angioedema and upper airway obstruction, symptoms of HA may include recurrent abdominal pain and vomiting due to intestinal mucosal oedema. Hereditary angioedema may also sometimes be associated with adult respiratory distress syndrome,⁴ disseminated intravascular coagulation,⁵ or various glomerulopathies.⁶ The diagnosis of HA is thus sometimes difficult.

Most cases of HA occur in family clusters; sporadic cases have rarely been reported. To the best of our knowledge, this is the first case report of a family cluster of HA and its association with mes-angiocapillary glomerulonephritis among the Hong Kong Chinese. A few categories of mutations within the C1-esterase inhibitor gene which are associated with HA have been described in Caucasians.^{7,8} The genetic basis for HA in the Chinese, however, remains unknown.

The acute laryngeal oedema associated with HA does not usually respond to adrenaline, antihistamines or corticosteroids. A C1-esterase inhibitor concentrate, prepared from pooled human plasma, is now the treatment of choice.⁹ This is not available in Hong Kong, however, and acute treatment requires the infusion of fresh frozen plasma which contains C1-esterase inhibitor. As fresh frozen plasma contains

complements 1 and 2, it may in turn exacerbate an acute attack of HA. Preventive therapy is thus indicated in all patients. Androgens such as danazol or stanozolol can be given to raise the level of C1-esterase inhibitor, probably by stimulating its hepatic synthesis. If patients are unable to tolerate the virilising side effects of androgens, plasmin inhibitors such as epsilon aminocaproic acid may be used.

Angioedema associated with the use of angiotensin converting enzyme inhibitors (ACEIs) is also an important but poorly recognised phenomenon. In a recent epidemiological study, up to 40% of patients presenting with angioedema to the Accident and Emergency department in a teaching hospital were taking an ACEI.¹⁰ These patients were more likely to have multiple episodes of angioedema but in many instances, the association with ACEIs remained unrecognised and administration of the drug was continued for 50% of the patients. The mechanism for this association is uncertain and it has been proposed that ACEIs predispose to angioedema by inhibiting the metabolism of bradykinin.^{11,12} In Case 1 of this report, the angioedema resolved promptly after the infusion of a C1-esterase inhibitor concentrate that was supplied by the patient. This suggests that the complement cascade may be involved in the pathogenesis of this reaction. The incidence of angioedema associated with ACEIs is likely to increase because of the increasing popularity in using ACEIs to treat cardiac conditions.

In summary, medical practitioners should be aware that HA is a rare and potentially fatal but treatable condition. They also need to be alert to the possibility of ACEI-induced angioedema when treating patients with recurrent angioedema attacks.

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