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Hereditary angioneurotic oedema

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ANGIONEUROTIC oedema was first described by Quincke in 1882. It is either hereditary, allergic or idiopathic in type. Hereditary angioneurotic oedema is better called hereditary angioedema (HAE) because the pathogenesis is due to an enzymatic defect.

Sir William Osler in 1888 recognized that HAE could be hereditary. It is a rare disease and Landerman (1962) found only 414 cases of HAE in fifty-five families in the world literature. The mortality rate of HAE varies from 15 per cent (Frank *et al.*, 1976) to 30 per cent (Donaldson and Rosen, 1976), due to airway obstruction requiring either intubation or tracheostomy. HAE is characterized by episodic swelling of the extremities, face, abdominal viscera or airway (Osler, 1888; Landerman, 1962; Donaldson and Rosen, 1976). Unnecessary laporotomies have been reported (Beck *et al.*, 1972). The episodes are often induced by trauma (Landerman, 1962), particularly dental manipulation (Jaff *et al.*, 1975), but a minor blow or anxiety can precipitate the attack (Landerman, 1962), and Osler found that episodes of oedema could occur after very hard work.

HAE is inherited as an autosomal dominant trait, so that both male and female are equally affected. Its pathogenesis is due to an abnormality in the complement system.

Discussion

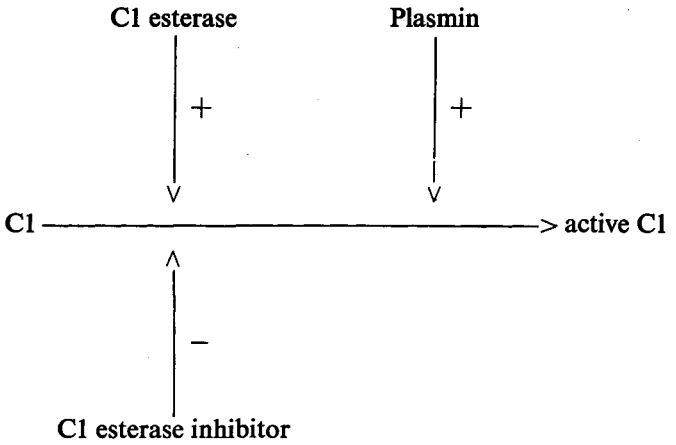
HAE is inherited as an autosomal dominant disease owing to abnormalities of the serum inhibitor of the activated first component of the complement (C1 esterase inhibitor C1—1NH) (Donaldson and Rosen, 1964). The complement is defined as a plasma component which has aided or complemented the union of antigen to antibody. At least nine components can be sequentially activated in a Cascade manner, like that described in the clotting of blood (Walter and Israel, 1974).

Normally C1 is activated mainly by C1 esterase (Lew *et al.*, 1958) and to a lesser extent by plasmin (Lew *et al.*, 1958; Ratnoff and Naff, 1967). Such activation is balanced by C1 esterase inhibitor (C1—1NH) which is synthesed by hepatic paranchyma (Johnson *et al.*, 1971) and in a very high level with hepatoma (Strunk *et al.*, 1975).

The majority of patients (85 per cent) with HAE have both immunochemical and functional concentration of C1—1NH, less than 50 per cent of normal (Frank *et al.*, 1976; Beck *et al.*, 1972); the rest of the patients (25 per cent) have a normal or even increased level of an antigenically identical but functionally deficient protein (Frank *et al.*, 1976).

Therapy is intended to provide prophylaxis, both long and short term, and treatment for the acute attacks of airway obstruction (Hopkinson and Sutcliff, 1979).

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Long term prophylaxis

The aim is to inhibit the activation of C1. It is unpractical to give the patient purified C1—1NH because it is expensive and its half life is only 4 days (Jaff *et al.*, 1975). It is possible to keep the active C1 at a low level either by:

(1) enhancing the synthesis of a high level of functional C1—1NH by liver paranchyma. Androgen therapy is effective.

or (2) counteracting the action of plasmin (fibrinolytic enzymes of plasma). Antifibrinolytic therapy may be used.

In 1960 Spandling used androgen therapy in HAE and he reported successfully treating five patients with HAE by the daily administration of methyltestosterone, but this drug may cause cholestatic jaundice. Danazol, a derivative of ethinyltestosterone, has been effective in preventing the attacks (Gelfard *et al.*, 1976). Androgen therapy is hazardous in children and pregnant women (Rosen and Austen, 1976).

Antifibrinolytic therapy can inhibit the activation of C1 indirectly by counteracting the action of plasmin. Two drugs are known to have this action: the first is Epsilon amino-caproic acid (EACA) (Frank *et al.*, 1972), the second Tranexamic acid (Scheffer *et al.*, 1972). The use of EACA is risky because there are possibilities of irreversible thrombosis. Teratogenic effects (Rosen *et al.*, 1971) have been demonstrated in rats, and for this reason EACA is contraindicated in pregnancy (Frank *et al.*, 1976). Tranexamic acid has fewer side-effects, is safer and has been used in both HAE and the idiopathic type. Tranexamic acid seems to be safe in pregnancy (Strunk *et al.*, 1975).

Short term prophylaxis

The patient with HAE who is being prepared for surgery should be treated pre-operatively either with transfusions of Fresh Frozen Plasma (FFP) (Jaff *et al.*, 1975), or tranexamic acid, two to three days before the operation. Two units of FFP will restore the deficient C1—1NH if given 24 hours before surgery.

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Acute attacks

In the acute attack antifibrinolytic, hormonal agents and steroids have no place in treatment as the problem is airway obstruction, and this should be relieved immediately, either by tracheostomy or intubation. Although adrenalin may be of benefit (Roth *et al.*, 1975), in a dosage of 1 mg subcutaneously each hour to a total of 11 mg, it may be dangerous, especially in a hypoxic patient.

FFP has been shown to be effective and to produce improvement within 40 minutes of its administration (Pickering *et al.*, 1969) and it could be used only in mild airway obstruction to prevent further oedema formation.

Case 1

A 23-year-old man presented at the Casualty department with a history of difficulty in breathing and swallowing over a 4-hour period. Seven days previously he had had abdominal pain which settled down under metoclopromide and antacids. On the previous day he had had a sore throat and penicillin had been administered. In the past he had had attacks of swelling during infancy which had become worse during the last year. He usually developed a local, tense swelling which became larger and then subsided after two days. The swelling involved the hands, forearm or elbow, feet and ankles, but never the face or neck. His G.P. treated him with antihistamines but without any improvement. He had had an appendicectomy 5 years previously. There was no history of atopy. His father had similar attacks, which frequently involved the neck and had necessitated treatment with adrenalin to relieve respiratory obstruction. One of his brothers had a history of swelling on the hands following trauma.

Examination

He had a normal temperature but pulse and respiratory rates were rapid, with moderate stridor. No oedema was visible in the extremities, neck or face. Indirect laryngoscopy showed gross oedema of the pharynx and vocal cords, but part of the subglottic region was still visible.

Treatment

A provisional diagnosis of angeioneurotic oedema of allergic type was made and he was given 300 mg of hydrocortisone and oxygen inhalation in Casualty. This produced some improvement, but after 15 minutes further deterioration occurred. An anaesthetist intubated him blindly, using oxygen and helium inhalation, and a tracheostomy was carried out. Direct laryngoscopy showed gross oedema of the laryngeal inlet and it was difficult to identify any anatomical structures apart from the epiglottis, which was slightly swollen.

Further investigation and follow-up

Investigations for hereditary angioedema were carried out and showed that the C1 esterase inhibitor level was 20 per cent of normal. The patient was therefore started on Danazol 200 mg b.d. After 12 days treatment with Danazol the C1 esterase inhibitor level rose to 33 per cent of normal. The larynx returned to normal in three days and the tracheostomy was allowed to close after three weeks.

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When he was discharged, he was taking 400 mg of Danazol b.d. and was given a supply of tranexamic acid tablets to be taken in the event of any further outbreak of swelling (in which case he should also seek medical help). The histology report on his appendix following his appendicectomy was normal. The following investigations were normal: Hb, F.B.C., urea and electrolyte, liver function test, blood glucose and chest X-ray. The C1 esterase inhibitor level returned to normal eight weeks after Danazol treatment started.

Arrangements were made with the family doctor for the whole family to be screened for HAE.

Case 2

A 52-year-old patient was admitted via Casualty as an emergency. She had a 2-hour history of sudden swelling in her face and dysphagia. She noticed that her lower lip began to swell and the swelling extended around her mouth, involving her tongue and pharynx. In addition there was a fine erythematous rash over the shoulders. There had been no previous episodes. The family history showed that her son has nettle rash, her daughter developed hayfever three years previously and her brother had died in his forties of acute laryngeal obstruction. The post-mortem findings suggested acute epiglottitis, and haemophilus bacilli were isolated from a swab from the epiglottis.

On examination the patient's lips and the right side of her face were swollen. Further general examination showed nothing abnormal. Indirect laryngoscopy revealed a normal epiglottis and vocal cords but there was oedema of both arytenoids extending to the right pyriform fossa. The diagnosis of HAE was doubtful; she was given 200 mg of hydrocortisone intravenously and was put under observation. The initial investigations, including F.B.C., chest X-ray and X-ray of the soft tissues of the neck, were normal.

On the following day she developed an erythematous rash over her shoulders and spiked a temperature, but the swelling on her face and arytenoid was very much improved.

Although the late age of onset and the erythematous rash were against a diagnosis of HAE, the C1 esterase inhibitor level was estimated because of the mode of presentation and the strongly positive family history. The level was found to be 33 per cent of normal, confirming the diagnosis of HAE.

The patient rapidly recovered and became free of symptoms. No treatment was given, but the diagnosis was given to her in writing and we informed her G.P. C1 esterase inhibitor levels were estimated in all the near blood relatives.

If during follow-up troublesome symptoms develop, long term treatment may be necessary.

Summary

HAE is transmitted by an autosomal dominant gene. It is due to a defect in the complement system and should be distinguished from the other two types of angio-oedema, i.e. allergic and idiopathic types. Pathogenesis and treatment are discussed and two new cases of HAE have been reported here. I would stress here two points: first, that the family should be investigated for the possibility of HAE; secondly, that the patient should carry a medical card similar to those

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carried by haemophilic patients, containing the diagnosis, name of the G.P. and emergency treatment.

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