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Hereditary Angio-Edema (HAE)

by

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Hereditary Angio-Edema has fascinated scientists for almost a century. As early as 1888 Sir William Osler, in a lecture to the Philadelphia Neurological Society, described the affection in a family with the following characteristics: 1. The occurrence of local swellings in various parts of the body—face, hands, arms, legs, genitals, buttocks and throat. Death sometimes resulted from sudden edema of the glottis; 2. Associated with the edema, there is almost invariably gastro-intestinal disturbance, colic, nausea, vomiting and sometimes diarrhoea; 3. A strongly marked hereditary disposition. He concluded that we have to contend with clinical facts and observations which urgently call for a scientific solution, and that at that time we possessed extremely scanty data for any adequate explanation of angioneurotic edema. In spite of his vigorous encouragement, it was not until 1963 that Donaldson and Evans discovered an underlying biochemical defect, *viz.* a serum deficiency of C_1-esterase inhibitor protein (C_1-INH abbreviated).

C_1-INH is functionally one of a series of naturally occurring inhibitors in the serum of complement activation, kinin formation and fibrinolysis (Donaldson and Evans, 1963; Frank, 1976). It derives its name from its ability to inhibit the esterase activity of the first component of complement, which is normally present in an inactive form in the serum. The complement system is composed of nine known serum components, which are activated by each other in a strict sequence, resulting in a cascade or waterfall effect (Blohmé *et al.*, 1972). The first component of the complement system acquires esterase activity with regard to the complement components C_4' and C_2' after activation by Ag/Ab reactions, vascular traumata and infections, and it contributes in this way to the advancement of complement fixation. During the progress of this complement fixation, polypeptides, which enhance vascular permeability (kinin-like C_2 fragment; kinin and PIF dil) are released (Fig. 1). They are probably responsible for the edema in HAE (Birkenhäger *et al.*, 1971; Ohela, 1977).

If the inhibiting action of C_1-INH is deficient, these reactions can progress disproportionately, even after minor inciting events. Accordingly, the attacks of gross muco-cutaneous edema in HAE patients may occur after minor physical or emotional trauma. They last 24 to 48 hours until the components of the complement system are consumed. That is the reason why the attacks are self-limiting.

HAE is a rare (1 : 150,000) familial disease transmitted as an autosomal dominant trait with incomplete penetrance (Dennehy, 1970; Beck *et al.*, 1973). Without treatment the mortality is inordinate. The diagnosis is confirmed by a decreased serum-concentration of C_1-INH and by alterations of C_2 and C_4 (Frank, 1976). Differential diagnosis includes hereditary allergic angio-edema, non-hereditary allergic angio-edema and non-hereditary non-allergic angio-edema.

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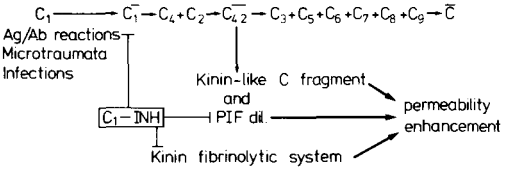


FIG. 1
Pathophysiology of HAE.

Corticosteroids, antihistamines and epinephrine are therapeutically effective in these different types of angio-edema, but are of no value in HAE.

Material and Methods

A 42-year-old woman was admitted to the hospital with an attack of laryngeal edema causing inspiratory stridor and dyspnoea. Because therapy with antihistamines and corticosteroids had a negligible effect, nasotracheal intubation was necessary for two days. The preceding history included recurrent attacks of localized skin edema involving different parts of the body, and of epigastric pain once or twice a month. The familial history revealed that there were several other members with comparable attacks of muco-cutaneous edema. Bearing the possibility of HAE in mind, the diagnosis was confirmed by a C_1-INH level of 0 per cent. In view of this case report, the family pedigree was investigated (Fig. 2).

The family, consisting of 35 members, was traced back for five generations. The living members totalled 28. From this group 24 were seen personally and information about the remainder was obtained from other members of this family and from old case histories. The patient data were collected by using a questionnaire on the following items: attacks of peripheral edema, abdominal pain, oro-pharyngeal and laryngeal edema, urinary retention, headache and accompanying symptoms; age at onset, frequency, duration and possible inciting events (trauma, mental stress, menstruation, pregnancy, drugs), prodromal symptoms, therapy given, and response to treatment.

Serum from venous blood was collected and frozen and later examined for levels of C_1-INH. The biological activity of C_1-INH was determined by means of an enzymatic inhibition technique according to Levy and Lepow (1959) in The Netherlands Red Cross Blood Transfusion Service, Amsterdam. The normal range is 60 to 140 per cent of a standard serum pool.

Results

The family was found to have 12 affected members. Two children appeared to have been asymptomatic until the time of the enquiry, but had a low C_1-INH serum level. This brings the total amount of biochemically affected members to 14; this is about 40 per cent of the kindred. The ratio of male-to-female was 6 : 8. No generation was exempt in the family pedigree. Thus, the inheritance appears to be autosomal dominant with a high penetrance.

Onset of symptoms

In two women the first symptoms of HAE appeared during the first pregnancy (19 and 20 years) and in two during the menarche (nine and 10 years). In two patients the disease started in early childhood (three and four years), and in six during adolescence.

Localization of attacks

The typical triad (of attacks of abdominal

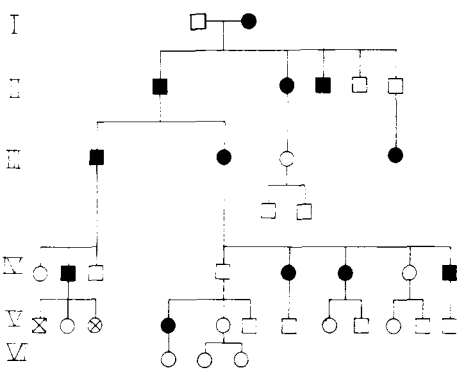


FIG. 2
Pedigree of family with HAE.

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pain, peripheral edema and laryngeal edema) was present in four patients within the group of 12. There was a remarkable difference between patients in the main symptoms and also in the same patient from one attack to another. Peripheral edema as well as abdominal attacks were the dominating symptoms in the majority of cases. Laryngeal edema always occurred with a much lower frequency. Peripheral edema as the main symptom occurred in three patients, especially in the hands and feet, less often in the face. This edema is a typical non-pitting, non-pruritic and non-painful edema. Abdominal attacks were present in three patients as the main symptom; they consisted of abdominal pain and swelling, usually associated with nausea and vomiting, and sometimes with diarrhoea. Laparotomy was performed in one patient during an abdominal attack without any abnormal signs being found. It is well known that there is a risk of HAE-patients being subjected to surgical interference during an abdominal attack. In four patients abdominal and peripheral attacks succeeded each other with about the same frequency. Laryngeal edema has occurred in six patients, but always with a much lower frequency than the abdominal and peripheral attacks; in two patients it was the only symptom. Twice a nasotracheal intubation, and once a tracheotomy was necessary for severe dyspnoea. Four patients died during laryngeal attacks, one after a tonsillectomy. The mortality among the patients in this family was 33 per cent.

Particular attacks

During laryngeal attacks, two patients developed temporary loss of vision lasting for twelve hours, with no other ophthalmological signs. One patient had urinary retention, probably due to swelling of the urinary tract during an abdominal attack.

Prodromal symptoms

Most patients (nine in 12) had symptoms preceding the attacks such as tiredness, apathy, thirst, loss of appetite and tightness in the skin.

Inciting events

Two of eight women reported an increase in attacks during their menstrual periods, and three during pregnancy. A minor bump or repeated traumata appeared to precipitate attacks in all patients, as well as surgery. Oral and pharyngeal surgery in particular can provoke life-threatening oro-pharyngo-laryngeal edema. Three patients mentioned emotional upset as a precipitating factor. In all patients attacks also occurred without any clues as to the cause.

Frequency of symptoms

The frequency of attacks varied from once a week to four times a year. The average duration of an attack was two days. Six patients mentioned a higher incidence of symptoms in the spring and autumn.

Laboratory investigation

In all the patients investigated (eight), the C_1-INH serum level was 0 per cent. The C_1-INH serum level of the other family members was within the normal range.

Discussion

Patients in this family have the more common form (85 per cent) of HAE, with a low C_1-INH serum level on biochemical analysis. A less common form (15 per cent), with a normal or even an increased level of an antigenically identical but functionally deficient protein, has been described (Frank *et al.,* 1972). In the more common form, C_1-INH serum levels vary between 0 and 30 per cent (Rosen *et al.,* 1971). This accounts for the fact that the genetic defect does not concern the structural gene responsible for C_1-INH synthesis (otherwise 50 per cent value would be expected). Its production in the hepatic parenchymal cells is quantitatively diminished, probably due to a disturbed messenger RNA synthesis (Shokeir, 1973).

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The diagnosis may be difficult, especially in patients in whom the attacks are localized mainly in one site. Nearly all patients in the family presented were unacquainted with the character of their disease and the possibilities of treatment in spite of frequent medical consultations. Because HAE has a significant morbidity rate, which rises markedly when the disease is unsuspected, it is important to recognize the clinical picture. The mortality can be reduced almost to zero with adequate treatment and guidance. The therapy of HAE can be divided in three forms: 1. Long-term prophylaxis; 2. Short-term prophylaxis; and 3. Treatment of acute attacks.

Long-term prophylaxis is not required for all HAE patients. Patients who have mild and infrequent attacks do not need life-long treatment, but patients who suffer from life-threatening and/or frequent attacks (>one or two/month) do need long-term prophylaxis. Two groups of drugs can be used (Schindera *et al.*, 1978): 1. The fibrinolytic inhibitor Epsilon Aminocaproic Acid (EACA) and its derivative tranexamic acid (Frank *et al.*, 1972), and 2. The hormonal agents methyl-testosterone and danazol (Gelfand *et al.*, 1976: Rosen and Austen, 1976). The favourable effect of androgens was first reported by Spaulding in 1960. Subsequently, the effectiveness of other androgens was demonstrated. Danazol, a derivative of ethyltestosterone, appears to be the drug of choice in a dose of three times a day 200 mg. (Pitts *et al.*, 1978). It is an attenuated androgen, producing a dose-dependent reduction of serum gonadotropins. The basic defect in HAE is abolished by stimulating the synthesis of C_1-INH due to induction of m-RNA synthesis in the hepatic parenchymal cells. The increased serum levels can thereby prevent the manifestations of the disease. In the family reported, one patient with a high frequency of attacks was treated initially with EACA without any improvement. After treatment with danazol, the attacks disappeared completely and the C_1-INH serum level increased from 0 to 21 per cent.

For short-term prophylaxis (before surgical intervention), anti-fibrinolytic components, fresh frozen plasma, kallikrein inhibitor and C_1-INH concentrate have been used (Marasini *et al.*, 1978; Rosen *et al.*, 1971). The therapeutic effect of C_1-INH concentrate (for short-term prophylaxis and also for attacks) is excellent and is to be preferred to other agents. Serum-level of C_1-INH increases to 50 per cent of normal value within 15 minutes, after the intravenous infusion of 36,000 U of C_1-INH concentrate. The effect lasts for 1½ to two days, but that is long enough. In the family reported, this therapy was successfully used in three patients, as short-term prophylaxis before dental treatment and endoscopy.

When the diagnosis of HAE has been made, it is necessary to perform a family study. The chance of finding affected members is relatively high, because of the autosomal dominant inheritance, and the high mortality can be reduced with adequate therapy and guidance. The patient should carry a medical alert card containing the diagnosis, name of the GP and emergency treatment. For acute attacks the patient or his GP should keep an ampoule of C_1-INH concentrate in the refrigerator at home. The shelf life of C_1-INH concentrate exceeds 12 months at 4 °C. Patients suffering from frequent attacks can be successfully treated with Danazol.

Summary

Hereditary Angio-Edema (HAE) is manifested by recurrent attacks of acute circumscribed edema of the extremities, face, trunk, and respiratory or abdominal tract, occurring after minor physical or emotional trauma, or spontaneously. The clinical diagnosis can be confirmed by low serum-levels of the inhibitor of the activated first component of complement (C_1-INH).

A family of 35 members over six generations was investigated. About 40 per cent of the members were HAE-patients. An autosomal dominant inheritance with high penetrance was present. Four patients died by suffocation from laryngeal edema. In all

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HAE-patients the C_1-INH serum-level was diminished, and also in two children who have yet had no complaints.

Adequate medical advice, including the provision of a medical alert card and the prescription of C_1-INH concentrate (for short-term prophylaxis and the treatment of attacks of laryngeal edema), is necessary. In patients with frequent serious attacks, long-term prophylaxis with Danazol is indicated.

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