of the optic nerve and the patchy nature of the arteritis, allowing sufficient flow into the plexus to prevent infarction of the nerve.

This case emphasizes the need to consider the possibility of a systemic vasculitis when an unusual clinical picture is present.

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Hereditary angio-oedema: treatment with Cl esterase inhibitor concentrate[1]

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The case of a woman with hereditary angio-oedema and her successful treatment using Cl esterase inhibitor concentrate is reported. The rationale for the use of this treatment is discussed.

Case report

The patient, Mrs S P, a 40-year-old nurse, comes from a family in which at least five generations have been affected by hereditary angio-oedema (Figure 1). Her grandfather died at the age of 39 from an attack of laryngeal oedema. Her two oldest children (aged 13 and 11) have been shown to have inherited the biochemical abnormality, but are asymptomatic at the time of writing. Her third child died from a 'cot death', and may have been affected.

The patient suffered with attacks of giant urticaria in childhood which were controlled by antihistamines. She still has attacks of cholinergic urticaria which require no treatment.

At the age of 23 she was started on a combined oestrogen-progestogen contraceptive pill, and whilst taking this developed recurrent attacks of angio-oedema. These became more severe and frequent during her 4 pregnancies, and stopped after delivery in each case. Typical attacks began with swelling around a large joint such as the knee; progressively severe and incapacitating abdominal colicky pain, vomiting and diarrhoea would follow. Symptoms would increase over a period of 12–24 hours. If untreated, attacks lasted up to 48 hours before gradually subsiding. Towards the end of her last pregnancy such attacks were occurring every 7–10 days. Fortunately there were no attacks of laryngeal oedema.

Investigations revealed the 'classical' abnormality of hereditary angio-oedema, i.e. an absolute deficiency of C1 esterase inhibitor: 0.11 g/l (normal range 0.18–0.26) and reduced C4: 0.11 g/l (normal range 0.14–0.54). C3 activity was normal. These abnormalities persisted in the non-pregnant state even though there were no attacks of angio-oedema.

During her first three pregnancies and the early part of her last pregnancy attacks of angio-oedema were usually treated with the anti-fibrinolytic drug ε-aminocaproic acid (4–6 g six-hourly by mouth) together with the antiemetic Gravol (dimenhydrinate 100 mg suppositories). This combination reduced both the severity of the symptoms and the length of the attacks to approximately 36 hours.

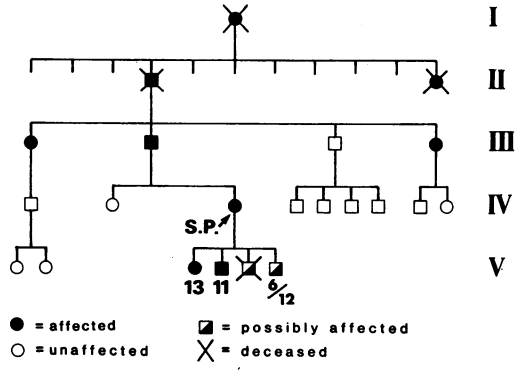

Figure 1. Hereditary angio-oedema: pedigree of family of Mrs S P

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In the final weeks of her last pregnancy, attacks were sufficiently frequent and severe to justify the use of C1 esterase inhibitor concentrate. This was given on three occasions by her general practitioner. An initial dose of 10 000 iu was given intravenously within three hours of the onset of an attack. A second dose of 10 000 iu within 30 minutes of the first was found to be necessary to control symptoms. On each occasion after adequate dosage (at least 20 000 iu) the patient experienced rapid improvement in her symptoms. The advance of her peripheral oedema was halted immediately. The vomiting, diarrhoea and abdominal pain subsided within 30 minutes, whilst the oedema gradually disappeared over the next 12–24 hours. This represented a more rapid improvement of symptoms than she had experienced with previous treatments.

Discussion

C1 esterase inhibitor is a plasma α_2-globulin. It inhibits not only the activated first component of complement (first stage in the classical pathway), but also plasmin, kallikrein, Factor XI and Factor XII (Guenther 1983). Patients with hereditary angio-oedema may have either a quantitative or functional deficiency of this inhibitor. This may lead to reduced control of complement activation, kinin generation, fibrinolysis or either arm of the coagulation cascade. It is not known which of these effector systems is most important in causing the symptoms of angio-oedema. However, it is likely that the kinin-like activity of C2 fragment is an important final common pathway (Klemperer *et al.* 1968).

Therapy of hereditary angio-oedema with antihistamines, corticosteroids or adrenaline is usually ineffective. Patients with frequent attacks, especially if there is a history of laryngeal obstruction, are best managed prophylactically with attenuated androgens such as danazol or stanozolol. These drugs stimulate hepatic synthesis of C1 esterase inhibitor and they may completely prevent attacks. However, dose-related side effects are fairly common, especially menstrual irregularities, weight gain, myalgia and headaches. Androgens are also unsuitable for use during pregnancy or in childhood. Anti-fibrinolytics such as ε-aminocaproic acid are an alternative to the androgens, but are inconvenient to take as long-term treatment. Side effects are dose-related, and include myalgia and deep-vein thrombosis.

Acute attacks of hereditary angio-oedema may be managed by large doses of antifibrinolytics by mouth. However, in life-threatening situations it may be necessary to administer fresh frozen plasma. This requires hospitalization and establishing an intravenous infusion. Usually up to one litre of plasma will be required to control an attack, thereby exposing the patient to the risks associated with the administration of blood products. There is also a theoretical hazard of exacerbating angio-oedema because fresh plasma contains additional substrates for C1.

Many of these problems may be overcome by the use of purified C1 esterase inhibitor concentrate. This is produced by ion exchange chromatography and ammonium sulphate fractionation of human venous plasma (obtained from unpaid volunteer donors). Such extraction techniques allow more rational use of specific plasma constituents. The concentrate is rigorously tested by radioimmunoassay to exclude the presence of hepatitis B surface antigen. During manufacture antihepatitis B immunoglobulin is added, such that the risk of transfer of hepatitis B should be eliminated. However, it is not possible to exclude the hazard of transmitting the agent of hepatitis non-A non-B.

The final product is presented as a freeze-dried powder with a refrigerated shelf-life of one year. One vial, when reconstituted with 10 ml of water, has an activity of C1 esterase inhibitor equivalent to one litre of fresh plasma (10 000–15 000 units). The concentrate must be administered intravenously within three hours of reconstitution. Studies in Italy have shown that adult patients will require 24 000–36 000 units for control of symptoms (Agostoni *et al.* 1980). Oedema of the mucous membranes and gastrointestinal tract begins to reduce 15–60 minutes after adequate dosage; peripheral oedema begins to subside more slowly (1–3 hours). None of Agostoni's patients required tracheostomy. Control of symptoms occurs when plasma activity of C1 esterase inhibitor reaches approximately 50% of normal, and activities reach pretreatment levels within 48 hours of injection of a therapeutic dose.

The drawbacks of this treatment are its expense, limited availability at present, risk of hepatitis, intravenous-only route and potential for stimulating antibodies against the inhibitor. However, it has several advantages. It may be kept at home in the refrigerator and administered by the general practitioner at the earliest sign of an attack or, if necessary, by a suitably instructed and responsible relative. Hospital admission may thus be avoided. It is suitable for use in pregnancy and childhood. It may be useful for those patients intolerant of other therapy or in whom such therapy is ineffective. Since the C1 esterase inhibitor concentrate can be stored, it may also be the preferred treatment in patients who suffer very infrequent attacks in whom continuous prophylaxis with danazol, etc., is undesirable. Further, as surgical procedures may precipitate attacks, infusion of the concentrate

one or two hours preoperatively (as an alternative to plasma infusion) may prevent angio-oedema. This is especially so for dental procedures and surgery of the head and neck which may precipitate laryngeal oedema.

Thus C1 esterase inhibitor concentrate is a useful addition to the therapeutic armamentarium for hereditary angio-oedema. It is likely that it will eventually become more widely available. At present the major manufacturer is Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Plesmalaan 125, 1066 CX Amsterdam, PO Box 9190, Holland (Tel: (0) 20-512.3355). A small supply is also available through: Immuno Ltd, Arctic House, Rye Lane, Dunton Green, Near Sevenoaks, Kent TN14 5HB (Tel: (0732) 458101).

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Endocarditis with rare parvobacillus: host response and difficulty in diagnosis[1]

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A case is reported of a patient who presented with pyrexia, arthralgia anaemia, lymphadenopathy, splenomegaly and microscopic haematuria. No organism or site of infection was found on repeated investigation until after removal of the spleen, when the gram-negative parvobacillus *Actinobacillus actinomycetem comitans* was identified from blood cultures. The patient was successfully treated with intravenous and oral penicillin and erythromycin. He was able to work during the illness, which is unusual for patients with this systemic infection.

[1]Case presented to Clinical Section, 14 October 1983. Accepted 20 June 1984

Case report

A 44-year-old journalist complained of swelling and stiffness in the fingers, malaise and night sweats. A dry cough had been present for three weeks. A haematoma over his right elbow, sustained after a fall, had been aspirated one month previously. There was no history of recent dental work, foreign travel or contact with animals and his only previous illnesses had been benign essential hypertension and rubella-associated polyarthralgia in 1975. The only abnormalities on examination were two subungual splinter haemorrhages. The sedimentation rate was 72 mm in the first hour and haemoglobin 12.3 g/dl. His symptoms improved without treatment, but three months later he was found to have pyrexia, a palpable spleen tip and microscopic haematuria. No cardiac murmurs could be heard.

He had developed a normochromic normocytic anaemia (Hb 9.8 g/dl), and the ESR had risen to 132. The white cell count, differential count and chest X-ray were normal. Subacute bacterial endocarditis (SBE) was suspected but six sets of blood cultures remained sterile after ten days' incubation. Coxiella titres were negative and cultures of liver and marrow biopsies were sterile. Echo- and electrocardiography were normal.

There was no evidence of tuberculosis on radiology or on culture of early morning urine, liver or marrow, and Mantoux tests were negative at 1 and 10 units tuberculin purified protein derivative. Serologic tests for a wide range of pathogens were negative. Intravenous urography and urine cytology did not indicate renal neoplasia and there was no blood in the stool. In a search for connective tissue disease, radiology of hands, feet and pelvis, muscle biopsy, antinuclear and rheumatoid factors were found to be normal. A Kveim test was also negative. Antimitochondrial antibodies were strongly positive in the absence of primary biliary cirrhosis on liver biopsy histology; liver biopsy showed marked fatty change and nonspecific hepatitis but no granulomas. Computerized tomographic (CT and ultrasound) scans of the abdomen demonstrated splenomegaly and minimal enlargement of the para-aortic nodes, which was confirmed by lymphangiography.

The patient left hospital after two weeks and returned to work for four months. He complained of intermittent night sweats and fatigue but no new diagnostic or clinical features

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