

Therapy in hereditary angioneurotic oedema

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Gwynn, C. M. (1974). *Archives of Disease in Childhood*, 49, 636. **Therapy in hereditary angioneurotic oedema.** Two branches of a family suffering from hereditary angioneurotic oedema underwent trials of therapy of ϵ -amino caproic-acid (EACA) to ascertain the optimum dosage required to alleviate symptoms without giving rise to unpleasant side effects.

It was found that children under 11 years tolerated 3 g/day and patients over 11 years 6 g/day without side effects, but with incomplete control of symptoms in some of the patients. However, if the dose was doubled for a period of less than 4 days during times of expected and experienced trauma, better control was achieved and unpleasant muscle cramps were not experienced. These doses, though effective, were much smaller than those used in previous studies.

This rare disease has been recognized for many years; among the first to describe it was Sir William Osler (1888) who called it 'the neurotic oedema'. It is characterized by internal and external episodic swellings, which consist of noninflammatory, circumscribed oedema, and may be accompanied or preceded by an erythematous, serpiginous rash. When the oedema affects the alimentary tract the symptoms are severe abdominal pain and profuse vomiting, which may simulate an acute surgical emergency. Oedema of the larynx and pharynx can cause death in this condition, the mortality rate being as high as 30% in some series (Landerman, 1962).

The disease is inherited as an autosomal dominant, and the episodic swellings are secondary to deficiency of the serum inhibitor of the activated first component of complement (C1-inhibitor). The first component of complement is normally found in the serum in an inactive state, but under certain conditions becomes activated and so triggers off the complement cascade (Fig. 1). C1-inhibitor closely regulates the initial reaction of the cascade, so that a deficiency of this enzyme may lead to uncontrolled activation of the complement cascade and an excessive production of fragments, many of which have vasoactive properties, the fragments of C2, C3, and C5. It is thought that the excess of C2 fragment gives rise to the symptoms of this disease (Klemperer, Rosen, and Donaldson, 1969).

Functionally, C1-inhibitor inhibits a number of other plasma enzymes besides C1. These include plasma kininogenase and plasmin (Hadjiyannaki and Lachmann, 1971).

An attack appears to be precipitated by exhaustion of the local inhibitor which may be consumed by any one of a number of factors. The following illustrate some of the factors. Osler (1888) described episodes of oedema after 'very hard work', and later investigation showed that blood taken from people after strenuous exercise (Biggs, Macfarlane, and Pilling, 1947), or anxiety (Macfarlane and Biggs, 1946) formed clots which dissolved more readily than those of unchallenged patients, indicating increased fibrinolytic properties. In addition, it is well known that substances may be released from tissues after minor trauma which can activate fibrinolysis (*New England Journal of Medicine*, 1972). Strenuous exercise, anxiety, and minor trauma are all common precipitating factors in this disease. Thus, clinical and laboratory observations imply that increased fibrinolytic activity may initiate bouts of hereditary angioneurotic oedema.

Laboratory observations have shown that plasmin (a fibrinolytic enzyme of plasma) can activate C1 (Pillemer *et al.*, 1953). Similar conclusions are reached by using urokinase (a known activator of plasminogen). When this substance is incubated with the plasma of a known sufferer of hereditary angioneurotic oedema in remission, the rate of generation C1 is increased (Donaldson, 1968a). It can thus be seen that there are several mechanisms

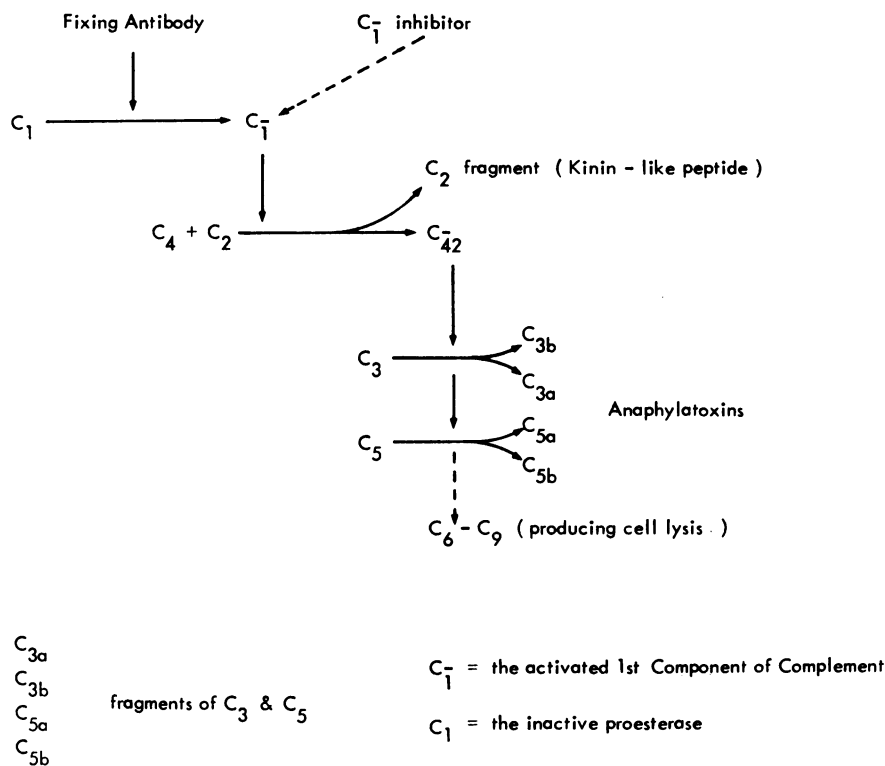


FIG. 1.—A simplified diagram of the early steps of the complement cascade.

which can initiate the conversion of plasminogen to plasmin, which in turn can trigger the complement cascade and produce the clinical picture seen in this condition.

Diagnosis

The diagnosis of this disease is made from the typical family history and clinical picture, together with the demonstration of low levels of C1 esterase inhibitor (which may be estimated either immunologically or by the esterolytic technique). The latter technique has the advantage of detecting the rare form of this disease, characterized by an abnormal C1 esterase inhibitor molecule which is present in the serum in normal immunochemical quantity, but is not functional. The former method was used in this study as the first patient investigated was found to be deficient in C1 esterase inhibitor. Low levels of C2 and C4 are also found between attacks and may disappear during an attack. It must be remembered, however, that sporadic cases are not uncommon in keeping with most potentially lethal inherited diseases, these arising as new mutations.

Treatment

Therapy in this condition is aimed at prophylaxis and the management of the occasional acute life-threatening laryngeal oedema. During an attack of oedema, administration of the deficient inhibitor in the form of fresh frozen plasma has been shown to cause the oedema to subside (Pickering *et al.*, 1969). This method of treatment has the theoretical danger that the plasma also supplies substrates for the plasma enzymes, and so may aggravate the situation. This, however, was not experienced by Pickering.

It seems feasible that prophylaxis could be successful if the activation of the plasma proteases, such as plasmin and plasmin-like substances, were inhibited. This can be achieved by the use of ϵ -amino caproic-acid (EACA) and its derivatives which produce an 'inhibitor-sparing' effect in addition to inhibiting C1 activation themselves. EACA has been used successfully on several patients with this disease, and two small double-blind trials with adult patients have been carried out which show the benefit of this drug in prophylaxis (Champion and Lachmann, 1969; Frank *et al.*, 1972). There has been little published about the

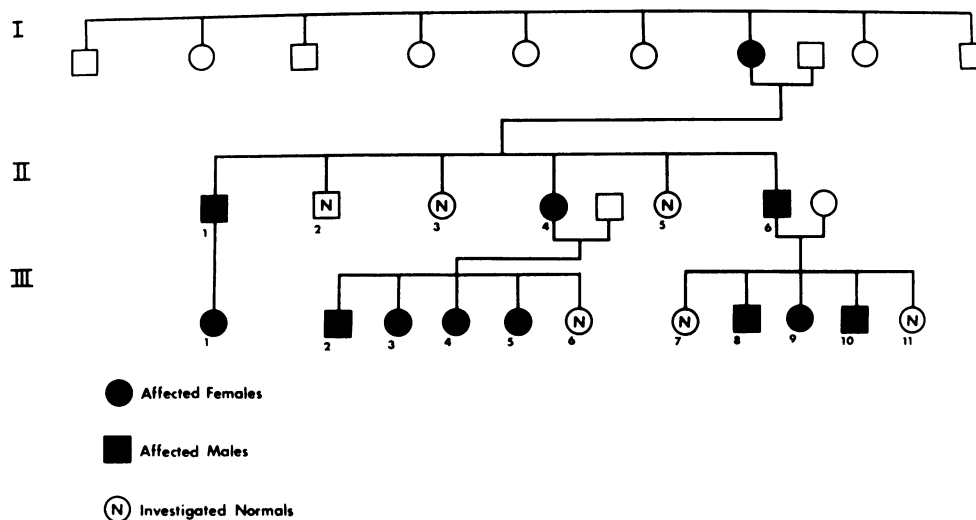


FIG. 2.—Pedigree of family suffering from hereditary angioneurotic oedema.

condition in children (Donaldson and Rosen, 1966), though symptoms start during childhood.

Patients and methods

Two families consisting of 9 affected patients who fulfilled the diagnostic criteria, i.e. a typical history together with low C4 and C1 esterase inhibitor levels, were studied. Their pedigree is shown in Fig. 2.

The patients were II.4, II.6, and their respective children. The children had all developed symptoms between the ages of 4 and 6 years, intermittent abdominal pain and limb oedema being the commonest complaints.

The C3 and C4 levels were measured immunochemically by the single radial diffusion technique (Mancini, Carbonara, and Heremans, 1965). C1 esterase inhibitor was estimated semi-quantitatively by double diffusion using a specific antiserum. C2 was not measured because of technical difficulties, but functional assessment was carried out by measuring the total

haemolytic complement. Table I shows the complement levels of the patients between attacks. Three trials were undertaken.

Trial I. A double-blind cross-over trial of therapy, consisting of two 6-week periods, was carried out between the two kindreds. The patients under 11 years were given 3 g EACA as an elixir 6-hourly (during the day) and those over 11 years 6 g 6-hourly. This dose approximated 0.1 g/kg used in this hospital in the treatment of haemophilia, but was rounded into two age groups for ease of administration over a long period. The patients were also supplied at the appropriate time with a placebo of similar taste and colour. They were asked to keep a daily record of any symptoms that occurred, whether or not they felt that these were related to their disease.

Trial II. A trial of intermittent therapy was undertaken over the following 12-week period. The patients

TABLE I
C1 inhibitor activity and serum concentrations of C3 and C4

Patient	Age (yr)	C3 (mg/100 ml)	C4 (mg/100 ml)	C1 inhibitor
II.6	36	160	7.5	Moderately reduced
III.8	12	160	11.0	Moderately reduced
III.9	10	181	4.5	Moderately reduced
III.10	9	143	12.0	Moderately reduced
II.4	40	140	4.5	Grossly reduced
III.2	17	185	5.0	Grossly reduced
III.3	13	185	7.0	Grossly reduced
III.4	9	164	4.5	Grossly reduced
III.5	7	143	3.5	Grossly reduced

Normal values were C3, 60–160 mg/100 ml and C4, 13–50 mg/100 ml.

were asked to take half the original dose of EACA at the first sign of the rash or oedema, or as a prophylaxis when minor trauma was to be expected, e.g. dental treatment.

Trial III. EACA was then taken continuously for a third 12-week period but the dosage was halved at 3-weekly intervals to ascertain the lowest effective dose required. During the first 3 weeks those patients aged over 11 years took 1.5 g 6-hourly and those under 11 years 0.75 g 6-hourly.

Results*

Trial I. Table II illustrates the results of giving EACA and placebo. The attacks of abdominal pain and vomiting experienced by patient III.8 and patient III.9 when taking EACA occurred during periods when they had stopped the drug because they did not like its taste. Of the patients regularly taking EACA, patient III.5 was the only one to experience symptoms; on both occasions the rash was transient and symptomless. Patient III.10, who is clinically and immunochemically the least affected, his C4 level being almost normal between attacks, had no symptoms throughout the 12-week trial period.

Trial II. This method of treatment proved less successful than that of continuous therapy. Those in whom the rash appeared before the oedema were asked to take EACA as soon as it appeared. However, as the rash is symptomless and usually confined to the trunk, it was rarely noticed before the oedema appeared. Once the swelling had begun EACA was

of doubtful benefit, even when the dosage was doubled to the level given in trial I, though it was thought that the oedema subsided more quickly than that of the nontreated state. However, as little as one dose taken a few hours before minor trauma prevented oedema occurring in that part. This was shown with one of the children who, during a course of dental treatments, took a solitary dose of 3 g 2 hours before treatment on some days and not on others. When EACA was not taken his dental treatment was always followed by oedema of the mouth and face; this did not occur when he had taken a dose of EACA.

Trial III. As intermittent therapy had proved unsuccessful, the patients were restarted on continuous therapy; however, the dose of EACA was halved, 0.75 g 6-hourly for those under 11 years and 1.5 g 6-hourly for those over 11 years. This regimen kept all but 3 most severely affected patients (II.4, III.4, and III.5) free from attacks. These 3 continued to have intermittent symptoms, albeit much less severe in nature and shorter in duration than previously. With this dose none of the patients experienced unpleasant muscle cramps. However, when the dose was halved again all patients developed attacks. With patients II.4, III.4, and III.5 the attacks were as severe as in the untreated state. The trial was therefore abandoned at this stage and the patients restarted on the previous dosage of 3 g/day and 6 g/day.

Discussion

The prolonged administration of EACA,

*Patient II.6 was withdrawn from the trial because of failure to follow the protocol.

TABLE II
Results of trial I

Patient	Placebo				EACA			
	Rash	Abdominal pain	Vomiting	Oedema	Rash	Abdominal pain	Vomiting	Oedema
III.8	+++	+++++	+++++	++ (face)		+	+	
III.9	++	++	++			+	+	
III.10								
EACA					Placebo			
II.4						+		+++++
III.2						+++++	++	+++++ (limbs and face)
III.3						+++		+++++ (limbs and genitalia)
III.4						++	+	+++++ (limbs and face)
III.5	++				+++++	+++++	+	+++++ (limbs)

Note: Each + represents one attack occurring during each 6-week period. The anatomical site of the oedema is given in brackets.

especially to children, is not without its possible dangers. The theoretical danger that prolonged plasmin inhibition might accelerate the formation of atherosclerosis is a formidable one. This to date has not been shown in adults, who have only been maintained on continuous therapy for some 6 years, but of course children would be expected to take it for a considerably longer period of time. EACA has been shown in animal trials to inhibit growth and weight gain when given to growing rats by McNicol and Douglas (1964), who also found an increase in the serum high density lipoproteins when giving the drug to cholesterol-fed rabbits.

Another potential hazard in childhood is provided by the frequency with which minor trauma occurs, leading in treated cases to the possible formation of haematomata which would resolve extremely slowly.

Side effects were experienced by most of our patients while they were taking 24 g EACA daily, and in 3 of the 4 children taking 12 g EACA daily. They all complained of dizziness, particularly in the early morning, frequently had nausea, and occasionally diarrhoea; these side effects have been well documented in the past (Nilsson, Andersson, and Bjorkmann, 1966). Patient II.4 experienced menorrhagia lasting for 8 days after stopping EACA. All patients experienced muscle aches, which appeared after 5 to 6 days therapy and were particularly painful in the older children and adults, but less severe in the younger patients. The pain disappeared within hours of lowering the dose of EACA. This side effect has previously been recognized by Frank *et al.* (1972) who were able to show raised levels of creatinine phosphokinase during the attacks. This was not shown in the present trial because an attack was never witnessed. (The patients lived approximately 40 miles from the hospital and attended at 2-week intervals during the trial because of transport problems.) At each visit the creatinine phosphokinase, serum aldolase, and lactic dehydrogenase levels were estimated, but were always normal. It is assumed that the high levels of muscle enzymes in the serum returned to normal as rapidly as the symptoms disappeared.

It was therefore decided by the patients themselves that continuous therapy was the most effective, but that the dose required varied with each patient. It appeared that those who were immunologically and clinically more severely affected required higher doses. However, none of the older patients needed more than 12 g/day EACA and none of the children required more than 6 g/day for satisfactory control of symptoms without unpleasant side effects.

Tranexamic acid, which has at least 10 times the

inhibition of plasminogen activator compared with EACA, has been used successfully to control this disease. Sheffer, Austen, and Rosen (1972) described a double-blind trial of therapy with this drug, and found an effective dose to be 1 g daily, which was equivalent to between 18 and 20 g EACA; as described above, none of our patients required as high a dose as this. (Tranexamic acid has recently been made available for hospital use only.)

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