Clinical presentation and diagnosis of hereditary angio-oedema in five families

R. S. WALLS, L. ORDMAN

Summary

The clinical features of 16 patients with deficiency of Cl esterase inhibitor are described. Severity ranged from no symptoms in 2 young subjects to repeated and severe abdominal pain and angio-oedema. Diagnostic techniques are described and the ease with which the diagnosis can be established is emphasized. A functional assay is required in addition to immunological determination of the protein in order to detect a minority of patients who have ineffective inhibitor. Experience of treatment with tranexamic acid is reviewed and its place in management in relation to androgens is discussed.

Hereditary angio-oedema (HAE), caused by deficiency of the inhibitor of the first component of complement (Cl INH), is an uncommon cause of clinical angio-oedema, but it is important to recognize for several reasons: (i) untreated, it carries a high mortality and young people are frequently affected mortality rates of up to 35% have been reported when the respiratory tract is involved; (ii) a definitive diagnosis can be established readily with simple laboratory tests; and (iii) treatment is effective, but differs from that of more common forms of angio-oedema. Osler first described the condition in 1888. He traced it through five generations of a family, spanning more than 100 years, and he firmly established the pattern of inheritance.

Five patients were studied by our clinical immunology unit over a period of 2 years, and investigations of other members of their families revealed a total of 16 affected individuals. We wish to draw attention to this syndrome in South Africa and to assess the various diagnostic procedures available.

Case reports

Case reports of propositi from the five families between them show many characteristics of this disease. Family pedigrees appear in Fig. 1.

Case 1 (Family O, III-1)

The patient presented at the age of 29 with episodes of severe cramping abdominal pain with vomiting since 2 years of age. From the age of 16 years he had had painful, non-itchy swelling of extremities. He attributed the attacks to a variety of foods (although elimination diets had been unsuccessful), and to excitement and anxiety. He often had premonitory symptoms of increased appetite, continual yawning, lethargy or excessive activity. He had never experienced respiratory obstruction. Attacks varied in frequency from two to three per month with intervals of 6 months in between, and lasted up to 10 days. Numerous barium meal examinations had been reported as normal, and recently he had undergone cholecystectomy with removal of gallstones and appendicectomy, but his attacks of abdominal discomfort persisted after the operation.

Prophylactic tranexamic acid was ineffective initially as he took it erratically, but since taking 3 g/d regularly he has been free of symptoms other than occasional mild attacks of non-progressive swelling. On one occasion he omitted to take his medication for 3 days and was admitted to hospital with an acute abdominal crisis.

Fig. 1: Pedigrees of five families presenting with hereditary angio-oedema (HAE).

Case 2 (Family Br, II-4)

The propositus, age 50 years, had suffered from recurrent peripheral, facial and glottic oedema, and periodic attacks of abdominal colic from the age of 2. His symptoms subsided between the ages of 36 and 40 years, but more recently attacks were occurring at 10 - 14-day intervals. Precipitating factors included certain foodstuffs, emotional disturbances, and trauma. Sitting for a long time on a hard bench led to swelling of buttocks and scrotum. He lost several jobs as a result of his illness, and was treated on a number of occasions for addiction to alcohol and to various drugs including pethidine. He had witnessed his mother and several other family members die from laryngeal oedema and he emphasized his need for sedation with alcohol in the face of impending attacks. Prophylactic treatment with tranexamic acid in a dose of 3 g/d was commenced in September 1974, and he was able to return to steady work, although he had intermittent episodes of swelling and abdominal cramps which on each occasion followed omission of his treatment. A barium meal during one episode showed giant gastric rugae and the stacked-coin appearance of small bowel characteristic of mucosal oedema (Fig. 2). Acute attacks were treated by recommencing...
Fig. 2. Barium meal during an acute abdominal attack of HAE in patient 2. Giant gastric rugae and the stacked-coin appearance characteristic of mucosal oedema of the small bowel are clearly seen.

tranyescamic acid. He refused all blood products on religious grounds.

Case 3 (Family B-P, II-2)
The patient, aged 45, had suffered since early childhood from recurrent episodes of nausea, vomiting and abdominal pain and swelling at intervals of 4 - 6 weeks. On occasions there was a non-itchy macular rash which preceded or coincided with attacks. He underwent appendicectomy at age 19 for 'chronic appendicitis'; cholecystectomy at age 27 when the bowel was noted to be thickened at operation, tonsillectomy when 29, and complete dental clearance at the age of 32, apparently without ill-effects. Stress was the only precipitating factor noted. Premonitory symptoms were soreness of gums, pain in his hips which prevented him from walking, and a 'scratching' feeling behind the ears. He had been treated with testosterone for acute abdominal cramps from the age of 21 years. Tiredness, lack of sleep and nervous tension brought on intervals of many months, or even years, to only a few days. The propositus had suffered from recurrent attacks of non-itchy swelling of the hands, feet and scrotum and severe abdominal cramps from the age of 21 years. Tiredness, lack of sleep and nervous tension brought on attacks, but there were no prodromata. Tranexamic acid, initially 3 g/d and subsequently reduced to 0,5 g/d, controlled his symptoms, apart from occasional mild swelling of the hands for which he increased the dose.

Case 4 (Family G, II-4)
The propositus had suffered from recurrent attacks of non-itchy swelling of the hands, feet and scrotum and severe abdominal cramps from the age of 21 years. Tiredness, lack of sleep and nervous tension brought on attacks, but there were no prodromata. Tranexamic acid, initially 3 g/d and subsequently reduced to 0,5 g/d, controlled his symptoms, apart from occasional mild swelling of the hands for which he increased the dose.

Case 5 (Family R, I-1)
The patient, aged 49, had swelling of the hands, throat, tongue, face and eyes since the age of 2, with several episodes of respiratory embarrassment more recently. She had been obliged to give up work because of the frequency of attacks which now occurred once to twice a month and lasted 3 days. In addition she had episodes of vomiting and colicky abdominal pain once or twice a month, not necessarily coinciding with the swelling. Attacks were heralded by epigastric distension, watering of the mouth, and a general 'unreal' feeling. They were worse at the time of her periods, although she was free from attacks during pregnancy. There had been no improvement with increasing age. She thought that foods such as vinegar, onion, cabbage and curry precipitated attacks. She underwent a dental clearance without ill-effect.

Methods

Serum from the patients was separated as soon as possible and stored at -20°C. The total haemolytic complement (CH₅₀) was measured by the method of Mayer. C₃ and C₄ were measured by radial immunodiffusion using commercially available antisera (Behringwerke).

C₃ INH assay. C₃ INH was measured by radial immunodiffusion on agarose plates using commercially available antisera (Behringwerke). Functional activity was assessed in two ways:

1. A screening assay was based on a method of Fong et al. Three 0,2 ml aliquots of serum were mixed with 0,8 ml glucose buffer of ionic strength 0,075 (made by mixing complement working buffer with 5% glucose solution 1 : 1). Tubes were incubated for 0, 10 and 20 minutes at 37°C and cooled immediately on ice to prevent further activity. Complement buffer 9 ml was added to bring the serum to a 1 : 50 dilution and the method for CH₅₀ determination was then followed. With reduced CH₅₀ levels, 0,4 ml serum aliquots were mixed with 1,6 ml glucose buffer, and 8 ml complement buffer was added to obtain a final serum dilution of 1 : 25. Normal serum was always used as a control.

2. Inhibition by test serum of the esterase activity of purified C₁. The method has been described fully by Lachman et al. Serum to be tested was incubated with a synthetic substrate of esterase (N-acetyl-l-tyrosine ethyl ester) (ATE; Sigma). Small amounts of activated C₁ (C₁) were added progressively to serum containing C₁ INH and ATE in the reaction chamber of a pHstat titrator at 37°C. Consumption of available C₁ INH was measured by the drop in pH produced by esterase activity of C₁ on the substrate. Values were expressed as a percentage of those obtained for normal controls run at the same time. A large batch of purified C₁ was prepared from fresh plasma and stored at -20°C for up to 12 months. Before use it was activated by dilution with an equal volume of normal saline and incubated at 37°C for 15 minutes.

Results

Clinical features (Table I)

Sixteen individuals were identified in five families, two of which were Coloured and three White. There were 10 males and 6 females. Ages varied from 4 to 74 years, but onset of the condition was usually in childhood, often as early as 2 years of age. In 2 patients many years separated the onset of abdominal cramps and of painful swelling of extremities or throat. There were no deaths in this group of patients but in several families other relatives had died from acute laryngeal oedema. Frequency of attacks was variable even in the same individuals, with intervals of many months, or even years, to only a few days. Attacks usually lasted 3 - 4 days, but in 1 patient 7 - 10 days elapsed before symptoms subsided. Two patients noted a
TABLE I. CLINICAL FEATURES IN 16 PATIENTS

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodromata</td>
<td>5</td>
</tr>
<tr>
<td>Peripheral swelling</td>
<td>11</td>
</tr>
<tr>
<td>Facial/throat swelling</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory obstruction</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
</tr>
<tr>
<td>Nausea and/or vomiting</td>
<td>8</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
</tr>
<tr>
<td>No symptoms</td>
<td>2</td>
</tr>
</tbody>
</table>

diminution of symptoms with increasing age, but 1 was still having severe episodes requiring hospitalization at the age of 74.

Five patients described prodromata which warned them of impending attacks. These included symptoms of hunger, yawning, lethargy or excessive activity, watering of the mouth, epigastric swelling, sore gums, scratchy feelings, and other strange sensations, particularly in the area which subsequently swelled.

Two affected individuals were identified by laboratory testing of family members, but were asymptomatic at the time. One was 4 years and the other 13 years old. Other subjects had clinical features characteristic of the syndrome. Swellings usually involved an extremity and were tense and painful, but not itchy. Swelling around the throat was experienced by 6 patients, but only 2 had respiratory difficulty at any time. In 13 patients abdominal pain mimicked an acute abdominal emergency. It was frequently associated with nausea and vomiting, and prior knowledge of the diagnosis helped to save them from unnecessary surgery. Two had undergone abdominal surgery for diagnoses such as cholecystitis, adhesions and appendicitis in the past, but the symptoms had persisted postoperatively. Two patients complained of a blotchy, erythematous rash which sometimes preceded and sometimes accompanied attacks. It was non-itchy and did not have the features of urticaria. One patient had been addicted to several drugs, including pethidine and alcohol.

Some patients were able to identify factors which they felt were responsible for precipitating attacks (Table II). Foods which were frequently incriminated included cabbage, beans, onion, curry, vinegar, various fruits and eggs, but their elimination from the diet had no effect on frequency of attacks. Trauma, especially blunt pressure, produced swelling at the site of contact. Two patients had swelling of buttocks and genitalia after sitting for prolonged periods on hard benches. Anxiety and stress, including lack of sleep, were felt by some patients to be precipitating factors.

TABLE II. FACTORS CONSIDERED BY PATIENTS TO BE RESPONSIBLE FOR PRECIPITATING ATTACKS OF HAE

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foods</td>
<td>4</td>
</tr>
<tr>
<td>Trauma</td>
<td>3</td>
</tr>
<tr>
<td>Anxiety and stress</td>
<td>3</td>
</tr>
<tr>
<td>Undetermined</td>
<td>6</td>
</tr>
<tr>
<td>Not recorded</td>
<td>2</td>
</tr>
</tbody>
</table>

Laboratory diagnosis (Table III)

Radial immunodiffusion of complement components indicated that all affected individuals had depressed levels of C4, but only 9 of the 16 had reduced levels of CHs0. 5 had reduced levels of C3. C1-InH was absent in all patients. Sera from affected subjects showed a marked drop in CHs0 after incubation in hypotonic electrolyte solution. No complement activity could be demonstrated after 20 minutes of incubation in most cases (Fig. 3). In 2 patients the initial CHs0 was too low to measure. The functional assay of C1-INH using ATE as substrate, was reduced in patients to less than 30% of control values. The degree of abnormality in laboratory tests showed no correlation with severity of the clinical syndrome. Unaffected family members had normal C4 levels, 5 had C3 levels below the normal range and 1 had slightly reduced CHs0. C1-INH was shown to be present by radial immunodiffusion and by both functional assays in unaffected family members, except for 2 in whom biochemical parameters were consistent with hereditary angio-oedema yet who were so far asymptomatic. These 2 individuals have been included as 'patients'.

Management

Five patients were given tranexamic acid in doses varying from 0.5 to 3 g/d as prophylaxis. A further 2 patients warrant treatment because of frequency or severity of symptoms and respiratory difficulty, but treatment was refused. In 7 affected individuals symptoms were not of sufficient severity to warrant the risk of prolonged prophylactic treatment, and 2 were asymptomatic. Four of the 5 treated patients showed dramatic improvement. A number were conscious of an impending attack occasionally but the symptoms usually subsided without development of swelling. When attacks did occur they were mild and the swelling remained localized, for example to a finger. They were of slower evolution and persisted for longer than usual. Three patients presented with acute abdominal pain and vomiting after ceasing or reducing the dose of tranexamic acid. One was transfused with 2 units of fresh frozen plasma and was discharged 12 hours later with complete resolution of clinical signs. The second patient was treated with intravenous fluids and nasogastric suction, and his symptoms settled in 3 days. In
TABLE III. COMPLEMENT STUDIES IN PATIENTS AND UNAFFECTED FAMILY MEMBERS

<table>
<thead>
<tr>
<th>Patients (N = 16)</th>
<th>Unaffected family (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± 1 SD</td>
</tr>
<tr>
<td>Serum complement</td>
<td></td>
</tr>
<tr>
<td>C3 (mg/dl)</td>
<td>120 ± 36</td>
</tr>
<tr>
<td>C4 (mg/dl)</td>
<td>8 ± 4</td>
</tr>
<tr>
<td>CH₄₆₀ remaining after 20 min. incubation (% pre-incubation value)</td>
<td>127 ± 72</td>
</tr>
<tr>
<td>Esterase activity (% normal control)</td>
<td>17 ± 9</td>
</tr>
</tbody>
</table>

* 0 in 11 patients, <40 in 3 patients. Pre-incubation CH₄₆₀ too low to measure in 2 patients.

Discussion

Identification of 16 patients with HAE over a 2-year period through casual referral indicates that the condition may not be uncommon in South Africa. HAE is not limited to Whites, as was previously suggested. Two Coloured families are described in this report, and subsequent reviews have described cases in Blacks. The family studies in this report again indicate the autosomal dominant inheritance of the condition. The biochemical basis of HAE was first described independently by Landerman et al. and by Donaldson and Evans (Fig. 4). Affected patients lack a α₂-neuraminoglycoprotein, present in small quantities in normal serum, which is a potent inhibitor of C1 and other esterases including plasmin, kallikrein, activated Hageman factor, serum permeability factor, activated plasma thromboplastin antecedent (PTA), and the conversion of PTA to activated PTA. During attacks of HAE, C1-INH appears in the serum of patients, and C4 and C2, the natural substrates of C1, are reduced. It is thought that the increased capillary permeability results from production of C2 kinin from uninhibited C1 activation. A kinin-like peptide has been isolated from the plasma of patients with angio-oedema, which can produce typical attacks in patients with HAE, but not in normal people or in patients with complement deficiency, suggesting that complement components beyond C2 are not required in the reaction. Complement activation occurs spontaneously or is induced by trauma which exposes negatively charged surfaces in the form of collagen, thereby activating Hageman factor and inducing complement activation through plasmin. It is not clear what terminates attacks. Patients become progressively more refractory to intradermal injections of C1 during an acute episode and this refractoriness lasts for 2 - 4 days. This may indicate exhaustion of substrate, or end-organ unresponsiveness. The disease has been associated with systemic lupus erythematosus and scleroderma, and a syndrome clinically indistinguishable from HAE has been reported in lymphoma. IgE-mediated mechanisms are not involved in the pathogenesis of this condition and these patients did not have allergic manifestations.

Dental extractions and other forms of blunt trauma to the face are particularly dangerous in these patients because of the risk of precipitating swelling in the vicinity of the airway, and it has been suggested that patients undergoing dental surgery should be given prophylactic tranexamic acid. Four of our patients had undergone dental extraction before the diagnosis was made, but fortunately suffered no ill-effects. Attacks of abdominal pain are frequently accompanied by rigidity, guarding and rebound tenderness, and mimic acute surgical conditions. Patients may be subjected to unnecessary operations if the diagnosis is not made. Two of our patients underwent multiple abdominal operations before the diagnosis was established. A number of patients become addicted to narcotics because of the frequency and severity of their symptoms. One of our patients was addicted to pethidine and alcohol, but considerable improvement in this aspect followed the institution of effective therapy. The danger of addiction should be borne in mind when treating these patients, particularly for acute abdominal emergencies.

![Fig. 4. Diagram to show activation of first component of complement and generation of C2 kinin in HAE. Sites of activation of C1 INH are shown in broken lines.](image-url)
The diagnosis can be established readily in the laboratory with relatively simple techniques. All our patients had low serum C4 levels, in keeping with other experience. About 15% of kindred have normal levels of C1 INH protein identifiable by immunological techniques, but lacking in functional activity, and at least four separate phenotypes of HAE have now been reported. It is important, therefore, to use a functional assay to avoid missing the diagnosis.

Linkage with HLA antigens has been demonstrated with deficiencies of complement components C2, C4 and C8, but studies in four families have failed to show HLA association in HAE. Genes coding for Clr, C3 and C6 are likewise not linked with HLA haplotypes.

Effective management of HAE is possible, since steps can be taken to reverse the biochemical consequences and even correct the underlying defect. In 1969 Pickering et al. described the treatment of an acute attack of HAE in 2 patients with fresh frozen plasma as a source of Cl- INH. Improvement was prompt and coincided with a rise in C4 and C1 INH levels. One of our patients, who had an acute surgical abdomen, was given 4 units of fresh frozen plasma, recovered promptly and was discharged from hospital within 12 hours. There is a theoretical danger that fresh frozen plasma may supply substrate for Cl, thereby perpetuating or aggravating the attack, and for this reason partially purified Cl INH has been used more recently. Prophylactic treatment is indicated for patients with recurrent abdominal pain or laryngeal obstruction or whose symptoms are sufficiently frequent or severe. Patients with mild and infrequent symptoms probably do not need prophylaxis except when dental or facial surgery is to be undertaken. The antifibrinolytic agents ε-aminocaproic acid (EACA) and its analogue, tranexamic acid, have been shown in double-blind trials to be effective in reducing the number and severity of acute attacks. These agents inhibit plasmin activation of Cl. In addition, high concentrations of EACA directly inhibit Cl activation. Tranexamic acid has been reported to be at least ten times more potent than EACA in inhibiting plasminogen activation, so that a smaller dose is necessary and reported side-effects are less. In one series pruritus ani developed in 1 patient and mild abdominal discomfort and diarrhoea in another, but thrombosis seems to be rare. Four of our patients tolerated tranexamic acid without side-effects. One patient complained of abdominal discomfort and diarrhoea in another.

Whether it will replace tranexamic acid in the long-term management of HAE remains to be seen. It is probably best avoided in children and premenopausal women, and tranexamic acid is still the drug of choice before dental surgery.

We wish to thank the following physicians for referring their patients to us: Drs P. R. Barnard, D. Burns, H. Hecht, J. Levenstein and L. Vogelpoel; Dr H. S. Myers for the radiological investigations; and Dr H. R. Sanders, Medical Superintendent of Groote Schuur Hospital, for permission to publish.

REFERENCES