HEREDITARY ANGIOEDEMA: DIAGNOSIS AND MANAGEMENT

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ABSTRACT

Hereditary angioedema is a rare autosomal dominant disorder due to the deficiency of functionally active C1-inhibitor. It is characterised by recurrent episodes of subcutaneous and mucosal edema. We report a case of hereditary angioedema presenting with the classic features of recurrent swelling of the extremities, abdominal pain and laryngeal edema. Serum complement C3 level was normal but C4 was low. She responded well to danazol and had no further attacks of angioedema.

Keywords: Hereditary angioedema, Clinical features, Diagnosis, Therapy.

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INTRODUCTION

Hereditary angioedema (HAE) is one of the two main groups of C1-inhibitor (C1-INH) deficiency disorders. C1-INH is a regulatory protein of the classical pathway of complement system. Its deficiency results in local increased vascular permeability and edema, the most important being laryngeal edema. The latter event is a medical emergency and it does not respond to the usual therapeutic measures for allergy induced laryngeal edema. Gastrointestinal mucosal edema may mimic acute abdomen resulting in unnecessary surgical intervention. An awareness of this disorder and familiarity with the management of acute attacks is important to doctors particularly at the Accident and Emergency Department, anaesthetists, surgeons and obstetricians and dentists.

We report a patient with the classic features of HAE and the successful use of danazol in controlling her symptoms.

CASE REPORT

LBH, a 32 year old Chinese female, first presented to us in December 1988, with symptoms of recurrent limb swelling, abdominal colic and a recent episode of dysphonia and difficulty in breathing.

Her symptoms started at 11 years of age, when she developed spontaneous swelling of her feet. It was a painless and non-pruritic swelling which resolved spontaneously 2-3 days later. Since then she has had multiple episodes of similar swelling of her hands and feet. On one occasion, her cheeks swelled after dental extraction. She was not bothered by these symptoms as they were mild and infrequent and she had never sought treatment.

During her second pregnancy in early 1988, she experienced her first episode of abdominal colic, vomiting and diarrhoea. These episodes became recurrent after delivery. Extensive investigations including abdominal X-rays (AXR), upper and lower gastrointestinal endoscopy, barium meal studies and serum amylase and urinary diastase were normal. Serum complement C3 level was normal but C4 level was low. She received symptomatic treatment for these episodes. The episodes of limb swelling had also increased in frequency, occurring once every 2-3 weeks.

One week prior to consultation, she woke up from sleep with dysphonia and mild difficulty in breathing. She was seen by an ENT surgeon and was told that her vocal cords were swollen. The dysphonia improved towards the end of the day.

She did not have any history of urticaria or periorbital swelling.

She gave a past history of thyrotoxicosis during her first pregnancy. She was treated with carbimazole. Her recent thyroid function test was normal.

Her father and brother had similar symptoms of episodic limb swelling but they had never sought treatment. Her mother, 2 brothers and a sister are well.

Clinical examination during her first consultation was normal.

A diagnosis of HAE was made on the basis of her personal and family history and the low C4 and normal C3 levels. Long term prophylaxis with danazol was advised in view of the frequency and severity of her symptoms. She declined.

In January 1989, she was admitted for another attack of abdominal pain with vomiting. She had also experienced recurrent limb swelling during the week prior to admission. Clinical examination revealed a soft, tender abdomen with active bowel sounds. Investigations showed C3 level: 103 mg/dl (NR 47-123 mg/dl), C4 level: 8 mg/dl (NR 15-55 mg/dl), CH50 11 Units/ml (NR – 13-

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30 Units/ml), negative ANA, and normal liver function test, serum amylase and urinary diastase and AXR. Her symptoms resolved and she was discharged with danazol 200mg bid.

She responded well to the danazol and the dose was eventually reduced to 100mg eod. She remained asymptomatic. Her serum C4 level rose slightly but was still below normal. She had slight irregularity in her menstrual cycle and decreased menstrual flow whilst on danazol. Liver function test remained normal 4 months after therapy.

DISCUSSION

C1-INH is a regulatory protein synthesised by hepatocytes, circulating human monocytes and fibroblasts (1). It inhibits C1 and its subcomponents C1s and C1r, factors XIIa and XIa, plasma kallikrein and plasmin (2, 3). C1-INH deficiency results in local events of increased vascular permeability. There are two possible mechanisms for the production of edema:

(1) physiologically occurring activation of Hageman factor generates plasmin which in the presence of C1 (easily activated in the absence of C1-INH), C2 and C4, leads to the generation of a C2 kinin responsible for the increased vascular permeability,
(2) increased activation of kallikrein (which is normally modulated by C1-INH) results in the formation of bradykinin, a vasoactive peptide.

There are two main groups of C1-INH deficiency disorders: acquired and inherited forms. The hereditary form (HAE) was first reported to be dominantly inherited by Crowder and Crowder in 1917 (4). Two main variants of HAE are recognised, type I and type II HAE (5). In type I HAE, both the antigenic and functional C1-INH levels are low (about 10-30% of normal). Persons with the type II variant have normal or upper normal antigenic levels of C1-INH but low functional activity of the protein. About 15% of patients have the type II variant.

Patients with HAE frequently have onset of their symptoms during childhood as distinct from the acquired form which has a late onset (6). These episodes however seldom become severe until the time of puberty. Attacks are usually spontaneous although in some they may be induced by emotional stress or physical trauma (particularly dental manipulation) (6, 7). Many women have increased attacks while on estrogen – containing oral contraceptive pills and during menstrual period. On the other hand, pregnancy often has a favourable influence and complications are rare (6, 7).

Subcutaneous swelling of HAE is non-pitting, non-erythematous, non-pruritic and painless. The edema usually lasts for 24 to 72 hours but could range from 4 hours to 1 week (6). Extremities, trunk and face can be affected. Patients often reported "tingling" or "tightness" at the site of the edema one half to several hours before the swelling actually occurred. Gastrointestinal symptoms include crampy abdominal pain, bloating, nausea and vomiting and later watery diarrhoea as the attack terminates. These symptoms may mimic an acute abdomen. Occasionally, hypotension occurs because of extravascular fluid loss into the gut lumen. A recent report of abdominal pain as the only life-long manifestation of HAE in multiple members of a family stresses the importance of recognising this disorder in its various forms (8). The most dangerous event in HAE is laryngeal edema which accounted for approximately 30% of deaths in undiagnosed patients (9). Airway compromise is usually preceeded by a change in the tone of voice and difficulty in swallowing secretions (6).

The association of HAE with autoimmune diseases has been reported and include systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, scleroderma and thyroiditis (6, 10).

The diagnosis of HAE is relatively easy when classical symptoms and a positive family history are present. When patients present with laryngeal edema, allergic angioedema must be considered. Characteristics of the latter are urticarial rashes and the almost constant involvement of eyelids or lips.

Clinical diagnosis of HAE can be confirmed by the findings of low levels of C4 or C1-INH or both. The primary deficiency in C1-INH leads to increased activation of C1. Activated C1 consumes its substrates C4 and C2 which are both low during acute attacks as well as during asymptomatic periods. Complement C3 is normal although there is increased turnover of this component. Total hemolytic complement (CH50) measurement is unreliable in diagnosing the disease because it is often normal in HAE and reduced in a host of other disorders. Normal C1-INH level in the presence of low C4 suggests type II, variant of HAE and the functional activity of C1-INH should be done. A low functional C1-INH activity confirms the diagnosis. Complement C1 level is useful in differentiating HAE from acquired C1-INH deficiency. It is almost undetectable in the acquired form of C1-INH deficiency even in between attacks.

Therapy of HAE can be divided into three phases:

(1) treatment of acute episodes of life threatening upper respiratory tract obstruction and/or incapacitating abdominal colic,
(2) short term therapy to prevent anticipated attacks and
(3) long term prophylaxis of episodic self-limited attacks.

Acute attacks of HAE respond to intravenous C1-INH plasma concentrate within 15-10 minutes (11). It is the treatment of choice in laryngeal edema, negating the need for intubation or tracheostomy. Unfortunately, it is not readily available. If there is no contraindication to a plasmin inhibitor, intravenous epsilon aminocaproic acid may be used when C1-INH is not available. This drug decreases the propagation of swelling. However it may not be effective as late as 48 hours from the onset of therapy. Fresh frozen plasma is not recommended during acute attacks as it may worsen the edema since additional substrates are supplied to the complement system (12). Typically attacks of angioedema became increasingly severe for about $1^1/_2$ days and then slowly resolve. Thus a patient with partial airway obstruction 3 days into an attack is in less danger than one having symptoms for only 3 or 4 hours. All patients with symptoms of upper airway edema should be hospitalised and evaluated by an ear, nose and throat specialist and indirect laryngoscopy performed. If the swelling is increasing, intubation should be done by a skilled anaesthetist with the full awareness that failure of this technique will necessitate emergency tracheostomy. Abdominal symptoms respond to supportive therapy. Patients with severe abdominal pain may be treated with narcotic agents. Subcutaneous edema although inconvenient, usually does not require treatment.

When edema is anticipated, as in dental manipulation, surgery or endoscopy, patients may be started on oral

suppressive therapy (attenuated androgens or antifibrinolytic agents) 2-3 weeks prior to the procedure. These do not completely prevent an attack and fresh frozen plasma is often given on the day before the procedure (6, 12). Intravenous C1-INH concentrate, if available, is the treatment of choice.

Long term preventive therapy is not required for all patients with HAE. Attacks in most patients are probably mild or infrequent so that they do not require long term treatment. It is considered when the frequency of attacks is at least once a month and interferes with daily activities. Two classes of drugs are available, antifibrinolytic agents and attenuated androgens. The antifibrinolytic agents epsilon aminocaproic acid (EACA) and its analogue tranexamic acid decrease the frequency of attacks (13, 14). Their mechanism of action is not clearly understood. They block the activation and enzymatic function of plasmin. Plasmin can activate C1 and it is believed that the anti-plasmin activity may explain their therapeutic effectiveness. They are contraindicated in situations where there is a predisposition to thrombosis. The principal adverse effects are muscle toxicity with muscle pain and/or elevated serum level of creatine phosphokinase and aldolase. EACA is the drug of choice if therapy is required in a child as it does not affect gonadal development.

Attenuated androgens are far more effective. They act by increasing the serum level of C1-INH in all phenotypes of the disease. Studies in animal showed that androgenic steroids augment protein synthesis by increasing mRNA level through reduction of its cytoplasmic degradation more than through enhancement of gene transcription. In patients with HAE, low doses of attenuated androgens can keep the patient free of symptoms without significantly affecting C1-INH level. Often the increase in the levels of C4 and C2 is variable. The two preparations commonly used are danazol and stanozolol (15-17). Danazol is preferred in female patients as it is less virilising. The most common adverse reactions are hepatic dysfunction, menstrual irregularity or amenorrhoea, hirsuitism and fluid retention leading to weight gain. Attenuated androgens have been reported to induce peliosis hepatis a life-threatening complication in patients after long term therapy with high doses (18). Thus, minimal effective doses are advised. Liver function tests should be carried out every 6-12 months. Contraindication to androgen derivatives are the presence of liver disease, pregnancy and children. Ideally, patients on these drugs should avoid conception so as to avoid possible teratogenic effects (19).

In conclusion, our patient demonstrates the varied presentations of HAE. Early diagnosis allows institution of appropriate therapy and long term prophylaxis which can significantly reduce morbidity. Familiarity with short term therapy and management of acute attacks reduces mortality from upper airway obstruction.

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