

Hereditary angioedema

HAE, hereditary angioneurotic oedema, HANE, C1 esterase inhibitor deficiency

The condition is caused by a mutation of the gene that inhibits the activation of the C1 component of complement. It is at gene locus 11q11-q13.1 and the protein is called C1-INH.

The underlying problem is low or low functioning levels of the inhibitor of C1, the first component of the complement cascade. The protein is also an inhibitor of kallikrein that splits kininogen to release bradykinin. The result is subcutaneous and submucosal oedema.

Epidemiology: It is inherited as an autosomal dominant that is not manifest until the second decade of life but affects the rest of life. It can affect all races with an incidence between 1 in 50,000 and 1 in 150,000. Males and females are equally affected.

OMIM recognises a type I and type II. Type I has low antigenic and functional levels of the protein at 35% of normal or less, but type II has normal or elevated levels but mutation impairs its function. About 85% of cases are type I and 15% type II but clinically they are identical.

Risk factors: Attacks may be precipitated by trauma, especially dental trauma, anxiety and stress. In pregnancy it may be better or worse.

History:

- There is usually a family history although spontaneous mutations do occur
- Symptoms are intermittent and may affect skin, abdominal organs or the upper airways
- Skin of the face, hands, arms, legs, genitals, and buttocks tends to be swollen rather than itchy
- Stomach, intestines and bladder may be affected causing pain, nausea, vomiting and diarrhoea. Incorrect diagnosis may lead to laparotomy
- Oedema of the larynx or other part of the airways can be fatal

Examination:

- Affected skin and mucous membranes are swollen but it does not look inflammatory
- The oedema may be preceded by mild urticaria and erythema

Investigations:

- Usually routine blood tests are normal although white count may be elevated with abdominal complications
- C1-INH level is low in type I HAE. C1-INH level is normal or elevated but function is abnormal in type II HAE. C4 and C2 levels are low whilst C1q level is normal in both
- Plain abdominal x-ray, usually with erect and supine, may show features of ileus
- Ultrasound may show fluid in the abdomen during an attack

- Biopsy of an affected part may show subcutaneous or submucosal oedema without inflammatory cell infiltrate

Associated conditions: Many other diseases, especially autoimmune diseases or those related to the immune system have been described in this condition. As many as 2% of patients with HAE may have systemic lupus erythematosus. Less commonly associations are other autoimmune disorders, glomerulonephritis, rheumatoid arthritis, thyroid disease, Sjogren's syndrome, and pernicious anaemia.

Differential diagnosis:

- Acquired angioedema can be due to autoantibodies against the C1-INH protein²
- Drug eruption, especially ACE inhibitor induced angioedema
- Chronic urticaria
- Angioedema due to acquired C1 inhibitor deficiency has been associated with benign or malignant B-cell lymphoproliferative disorders such as chronic lymphocytic leukaemia, multiple myeloma, or cryoglobulinaemia and is due not to defective synthesis but to markedly increased catabolism of the C1 inhibitor protein.

Management: In the acute attack, unnecessary procedures such as laparotomy for abdominal pain, must be avoided if the diagnosis is sure. Fluid loss into tissues may be such that intravenous replacement is required. In severe cases it may be necessary to give C1-INH concentrate if commercial preparations are available or else fresh frozen plasma must suffice. Steroids, antihistamines and adrenaline are not useful in the acute attack. Laryngeal oedema may even necessitate intubation.

If attacks are frequent and troublesome, prophylaxis is required. Both danazol and stanazolol can be used and it is not necessary to achieve normal levels of C1-INH. LFTs should be monitored as should blood pressure as hypertension may develop. Women are concerned about virilising effects of both these drugs although it is less marked with danazol. The aim is to give the minimum effective dose. They both have androgenic effects and must be stopped in the presence of prostatic carcinoma or before pregnancy. In pregnancy alternatives are epsilon amino caproic acid and tranexemic acid.

Largely because of the risk of laryngeal oedema, sufferers should wear a *Medic-Alert* bracelet or the like to warn medical staff in case of an attack.

Prognosis: This is usually good with adequate control of attacks.