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Case Report

Life-threatening laryngeal oedema in a pregnant woman with hereditary angioedema

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Hereditary angioedema is an unusual condition that has been associated with a high mortality rate during acute attacks. The disease is felt to have a benign course in pregnancy, but some reports indicate a worsening of attacks in pregnant women. A case of a pregnant woman with known hereditary angioedema presenting with life-threatening laryngeal oedema is reported, and is followed by a discussion of the disease, its links with sex hormones and a review of the literature.

CASE REPORT A 26-year-old primigravidum woman, pregnant at 25 weeks gestation, was admitted with a two-hour history of a sensation of swelling in her neck. She and her sister had been diagnosed as having type I hereditary angioedema four years previously through family screening following the discovery of a similar diagnosis in her mother. This diagnosis was made on the basis of serum analysis revealing decreased levels of C1 inhibitor (<0.04 g/1; normal range 0.28-0.50 g/l), functional C1 inhibitor (7% of normal levels) and C4, the fourth component of complement (<0.06 g/1; normal range 0.2-0.5 g/1) and normal levels of C3, the third component of complement (1.03 g/1; normal range 0.5-1.2 g/l). Her health prior to her pregnancy had been good with only three short-lived episodes of angioedema affecting her hands alone and one episode of facial swelling following a dental procedure. Since becoming pregnant, there had been an increase in the frequency and duration of the angioedematous episodes, with swelling in her arms, legs and shoulder occurring, on average, once per week.

She was not dyspnoeic and had no foot or arm swelling; her sole complaint was the swelling sensation in her neck which was giving rise to some difficulty in swallowing. On examination she appeared comfortable; her temperature was 36.2° C, with a heart rate of 96 beats per minute, blood pressure of 108/58 mmHg and oxygen saturations of 98% on room air. Cardiovascular and respiratory examinations were normal and abdominal examination was consistent with pregnancy of 25 weeks gestation. There was no evidence of swelling in her throat, neck or peripheries.

She was treated with 200 mg of hydrocortisone and 10 mg of chlorpheniramine intravenously and admitted for observation.

Three hours later she felt that her breathing had become more difficult. Examination of her oropharynx revealed swelling of the soft palate with the vocal cords moving and the airway intact. Observations and clinical examination otherwise were still normal.

A further three hours later she developed respiratory distress with stridor. Examination revealed pharyngeal swelling with the vocal cords viewed only with difficulty. She received one unit of fresh frozen plasma with some improvement of her symptoms and signs and was then given 2000 units of C1 inhibitor concentrate, which led to complete resolution within 30 minutes.

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She had no further problems while in hospital and was discharged five days later on tranexamic acid. The rest of the pregnancy was uneventful. The delivery was vaginal and uncomplicated with prophylactic administration of C1 inhibitor concentrate 1000 units on the day of delivery and the following two days. A healthy male infant was born. To date he has not been screened for hereditary angioedema.

DISCUSSION

Hereditary angioedema (HAE) is an unusual condition characterised by recurrent episodes of localised, well-circumscribed, non-pitting oedema. It may affect any part of the body, but more commonly involves the extremities, trunk, face, throat and the abdominal viscera where it causes pain. Involvement of the larynx is particularly dangerous, with a high mortality rate.[1,2] More recent clinical observations include symptoms of urinary tract infection in women, an increase in spontaneous abortions and premature labour, and more frequently reported heartburn and rheumatic complaints.[3]

The hereditary nature of the disease was first described by Osler in 1888,[4] and it is transmitted in a Mendelian autosomal dominant manner.[5] Investigation of the biochemical abnormality underlying HAE began with the identification and characterisation of C1-inhibitor.[6] C1-inhibitor is an $\alpha 2$ globulin that blocks the esterolytic activity of the first component of the classical component pathway.[7] It also has inhibitory actions on the fibrinolytic and kallikrein-kinin systems.[8] Subsequently a deficiency of this serum protein in individuals with HAE was discovered.[9] There are two forms of HAE, type I in which there is both absent or decreased C1-inhibitor antigenic levels and decreased functional activity, and type II, in which a dysfunctional protein is produced leading to normal C1-inhibitor antigenic levels but markedly reduced functional activity.[10] Both forms have decreased levels of the fourth component of complement. In acute attacks of HAE, the deficiency of C1-inhibitor allows unrestricted activation of the complement, fibrinolytic and kallikrein-kinin systems with increased generation of plasmin[11] and bradykinin[12] which causes localised oedema through enhanced vascular permeability and extravasation of fluid.[13]

The C1 inhibitor gene is located on chromosome 11 (p.11.2-q-13), where mutations in the structural gene region are responsible for HAE.[14] A particular region of the gene contains direct repeats of the triplet CAA, making it susceptible to mutation.[15] There is considerable genetic heterogeneity in the disease, with a number of mutations described.[16-20]

The initial presentation of HAE is typically early in life, with over 50% having their first attack in the first decade of life.[8,21,22] It affects a wide diversity of ethnic groups.[21] The most common precipitants of an acute attack are trauma, emotion,[1] insect stings and food.[2]

HAE appears to follow a benign course in pregnancy.[8,21] However, case reports have described an increase in the incidence and severity of attacks,[23-25] while labial oedema caused by vaginal delivery has been the first clinical presentation of the disease.[26] Indeed, vaginal delivery leading to perineal oedema and hypovolaemia has caused maternal mortality.[27] Caution is advised in making a diagnosis of HAE in pregnancy, as levels of C1 inhibitor may be decreased in normal pregnant women, returning to normal levels after delivery.[28]

The role of oestrogen in HAE has been debated. An increase in attacks has been reported during menstruation,[8,22] with oral contraceptives causing greater frequency and severity of attacks.[2,8,29] The mean values of both C1 inhibitor activity and antigen titres are significantly decreased in normal women using oral contraceptives compared to non-users.[29] Familial, oestrogen-linked angioedema attacks not caused by C1 inhibitor deficiency have also been described.[30]

The treatment of HAE has been traditionally divided into three groups i.e. treatment of acute attacks, long-term prophylaxis and short-term prophylaxis. Attempted therapy with adrenaline, antihistaminic agents or corticosteroids has no role or benefit in patients with HAE.[8] The mainstay of the treatment of acute episodes of HAE is replacement therapy, successfully used in the therapy of other serum protein deficiencies such as haemophilia and hypogammaglobulinaemia. Infusion of fresh frozen plasma has been shown to be beneficial,[31] although concerns exist that it may theoretically worsen the attack.[32] C1 inhibitor concentrate has also been shown to be safe and effective in the resolution of acute episodes.[33] Given in doses of 500 to 1000 units intravenously, oedema begins to resolve within 30 minutes to two hours of injection, with complete remission within 24 hours.[32]

Agents effective in long-term prophylaxis include attenuated androgens and antifibrinolytics. The main androgen used is danazol, which has been shown to decrease the severity and frequency of attacks, with biochemical assays of C1 inhibitor and C4 returning to normal levels.[34-36] The doses used should be the minimum needed to control attacks, as significant dose-related adverse reactions have been reported, including weight gain, myalgia, headaches, microscopic haematuria, altered liver function tests, anxiety, altered libido, alopecia, dizziness and nausea.[38, 39] Danazol also has virilizing effects on a female foetus if used in pregnancy.[37] Stanozolol is another androgen with a similar efficacy and side effect profile.[40] Two antifibrinolytic agents, ε-aminocaproic acid and transexamic acid are reported to assist in the control of HAE, but have a number of serious side effects including muscle necrosis and a potential thrombotic tendency.[41, 42] Fresh frozen plasma has also been used for long-term prophylaxis in a pregnant woman with HAE.[43]

Short-term prophylaxis is important in individuals with known HAE who are undergoing procedures which can potentially precipitate an attack, including surgery, dental work or labour. Attenuated androgens may be used in pregnancy,[44] but there is the potential risk of virilization of a female foetus, and this risk has been cited, at least in part, as an indication for termination of pregnancy in a woman with HAE.[45] Fresh frozen plasma[46] and C1 inhibitor concentrate[22, 47] have both been advocated for short-term prophylaxis in these situations.

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