Hereditary angioedema and pregnancy: successful management of recurrent and frequent attacks of angioedema with C1-inhibitor concentrate, danazol and tranexamic acid – a case report

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Summary: Hereditary angioedema (HAE) is a rare but potentially life-threatening condition caused by deficiency of C1 esterase inhibitor. It is characterized by subcutaneous swelling in any part of the skin, gastrointestinal and respiratory tracts. We present the case of a pregnant woman with known HAE that deteriorated during pregnancy with frequent attacks that were managed successfully with danazol, tranexamic acid and regular intravenous administration of C1 esterase inhibitor.

Keywords: hereditary angioedema, pregnancy, C1 esterase inhibitor, C1-INH

INTRODUCTION

Hereditary angioedema (HAE) is a rare autosomal dominant condition caused by impaired transcription or production of non-functional C1 esterase inhibitor. It is characterized by inadvertent activation of the complement system and recurrent subcutaneous swelling in any part of the skin, gastrointestinal and respiratory tracts. It can complicate pregnancy and thus the management should be in a multidisciplinary manner involving close cooperation of the obstetrician, physician, clinical geneticist, immunologist, anaesthetist and neonatologist.

CASE REPORT

We present the case of a 22-year-old primigravida, who was diagnosed with HAE at 17 years of age. Her symptoms outside of pregnancy included infrequent attacks of peripheral oedema, epigastric pain and occasional respiratory symptoms that responded to C1 esterase inhibitor (C1-INH) infusion. Prior to pregnancy, she was on long-term prophylaxis with danazol 200 mg twice a day and tranexamic acid 500 mg twice a day (epsilon-aminocaproic acid). She was diagnosed with personality disorder two years before pregnancy and had a past history of suicidal and self-harm attempts. Her family history was of HAE in her father which had been treated with danazol.

From the first trimester she had multiple admissions with hyperemesis and epigastric pain, which became progressively worse requiring inpatient management from 18 weeks gestation

until after her delivery. At the early stage of pregnancy, it was very difficult to clinically determine whether her symptoms were attributable to flare in her angioedema, hyperemesis gravidarum or mental health issues. She was treated symptomatically with regular antiemetics (including short courses of ondansetron), antacids, oral and parenteral morphine and intravenous C1-INH. Tranexamic acid 500 mg twice daily was continued throughout pregnancy and danazol, which had been stopped on confirmation of the pregnancy, was recommenced after an amniocentesis at 16 weeks gestation confirmed the fetus to be male. Her liver function tests were noted to be deranged at 20 weeks gestation, and this was attributed to drug-induced hepatitis secondary to a course of antibiotics for a urinary tract infection. Her liver function tests made a full recovery over the next few weeks with conservative management.

As the pregnancy progressed, she found it increasingly difficult to cope with her symptoms, experiencing increased frequency of attacks that required C1-INH (1000 IU intravenously) approximately every 3–5 days, and very regular doses of parenteral opiates (about 40–60 mg of morphine per day). Serum C4 levels measured before and after administration of the C1-INH were documented to be low (<30% of normal levels) and normal, pre- and post-C1-INH administration, respectively. Serial growth scans showed appropriate fetal growth and at 32 weeks gestation she was administered prophylactic steroids for fetal lung maturity, in case delivery was required preterm for worsening maternal symptoms.

By 36 weeks gestation her symptoms had significantly worsened and the decision was made for labour to be induced. Her cervix was favourable and induction was performed with artificial rupture of membranes and an oxytocin infusion. A prelabour prophylactic dose of 1000 IU of C1-INH was administered to cover for any exacerbation of her

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angioedema and additional C1-INH concentrate was also made available in the delivery suite. An epidural was sited at the early stages of labour for pain relief. Labour progressed normally and she delivered vaginally a male baby weighing 2370 g. This was on the 25th centile for the gestation at birth. The baby did not show any signs of withdrawal from opiates. Danazol was gradually reduced to the prepregnancy levels following delivery and she was gradually weaned off opiate medications.

DISCUSSION

HAE is a rare genetic disease that is caused by mutations on the C1 esterase inhibitor gene.¹ It is an autosomal dominant disorder and the incidence in the general population is estimated between 1 in 10,000 and 1 in 150,000.² There is usually a family history, although in approximately 10–25% of cases the disease is caused by spontaneous mutations. In HAE type 1 there is a deficiency in the amount of C1-INH protein in the plasma, which is the result of only one functioning gene, whereas in HAE type 2 the circulating C1-INH concentrate is normal or high but not fully functional.³ C1-INH is the main regulator of the early activation steps of the classical complement pathway. This protein is produced by the liver and also by activated macrophages and other cell types.⁴ In the absence of C1-INH, the classical complement pathway can be excessively or inappropriately activated and lead to the production of anaphylactic, chemotactic and vasoactive peptides (C2Bb, C3a, C5a) that increase capillary permeability and cause subcutaneous and submucosal oedema. The onset of the disease is usually during adolescence and it presents with episodic oedema of the upper and lower extremities, the face, the vulva, upper respiratory airways and the gastrointestinal tract. Laryngeal oedema is life-threatening and accounts for the majority of deaths in patients with the condition. Gastrointestinal tract involvement leads to stomach and bowel submucosal oedema with abdominal pain, vomiting and diarrhoea. The attacks last 4–5 days and then gradually resolve. Serum C4 level is a good screening test for C1-INH deficiency as the serum C4 is invariably low in untreated HAE (C4 <30% of mean normal level).⁵

Long-term treatment of HAE with anti-fibrinolytic agents such as tranexamic acid and androgens such as danazol reduce the frequency of attacks and achieve good control of the disease. Antifibrinolytic agents inhibit plasminogen activation with consequent sparing of C1-INH usage and attenuated androgens increase the hepatic production of C1 inhibitor protein. Acute attacks are managed with intravenous C1-INH concentrate. Alternatively when this is not available, the use of intravenous fresh frozen plasma has been used effectively.^{6,7} Corticosteroids and antihistamines have no effect in limiting the severity of attacks in HAE and should not be used.

Insults that can trigger an attack of the disease include major or minor trauma, physical and emotional stress, menstruation, oestrogens and pregnancy. The course of HAE during pregnancy is unpredictable and controversial. In some patients the frequency of attacks increases⁸ as was the case in our patient or decrease in frequency and intensity during the second and third trimester.⁹ In others the attacks may only present with localised perineal and vulval oedema.¹⁰ If feasible, prophylactic drugs should be stopped during pregnancy or before conception. Androgens are contraindicated in pregnancy when

the fetus is female.¹¹ Tranexamic acid may be used with caution. Although tranexamic acid crosses the placenta, there are no data to suggest that it is teratogenic. Severe attacks during pregnancy may require regular C1-INH replacement therapy. Even though the presence of HAE does not affect the progress of pregnancy itself, frequent attacks have been associated with preterm labour and stillbirth.¹²

When disease onset occurs during pregnancy the differential diagnosis can be challenging due to overlap of symptoms with those of early pregnancy such as morning sickness. In our case even though the diagnosis of HAE was already established, the frequency of attacks made it difficult to distinguish between flare-ups and other causes of upper gastrointestinal symptoms and her care required close cooperation of obstetricians, geneticists, immunologists and gastroenterologists. During the second half of pregnancy, our patient received regular opiates and antiemetics for symptomatic relief and needed regular intravenous C1-INH administered at the onset of acute attacks. The patient herself was very good in assessing her own symptoms and requesting C1-INH before the establishment of the attack. However, it was difficult to assess the abdominal pain objectively and at that time it was questioned whether she indeed experienced HAE attacks or whether the pain was secondary to a developing drug-seeking behaviour. Although serum levels of complement have been used predominantly as a diagnostic test for HAE,^{5,13} in our case it was used to monitor flare-up of the disease and avoid over administration of C1-INH and opiates. Serum levels of factors C3 and C4 were measured before and after administration of the C1-INH and confirmed a significant drop below the lower normal range consistent with an acute attack approximately every 4–5 days that correlated in timing with the onset of patient's symptoms and the request for C1-INH.

Intravenous C1-INH has also been used as a prophylaxis before elective surgery, endotracheal intubation and during labour. A safe obstetric approach would be to administer a pre-delivery infusion of 500–1000 IU C1-INH concentrate. During labour, endotracheal intubation can trigger severe acute laryngeal oedema and every effort should be made for regional anaesthesia whenever feasible.¹³ In our case, a single dose of 1000 IU of intravenous C1-INH was administered on admission to labour ward. She had a quick labour without any acute attacks or localized perineal oedema and did not require further C1-INH.

She was followed up for six months postdelivery. During that time the frequency of angioedema attacks and the need for C1-INH and opiate medication gradually returned to the prepregnancy status, thus confirming the triggering effect of pregnancy in exacerbating disease in this patient. She was counselled about future contraception and the likelihood of the same disease pattern in a further pregnancy. For contraceptive purposes, progesterone-only methods including the minipill, depo-provera or implantable Etonogestrel are offered, as combined oestrogen–progesterone preparations may exacerbate symptoms in HAE patients and should be avoided.

CONFLICTING INTERESTS

There is no conflict of interest and no other declarations that should be disclosed.

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