

A successful pregnancy and uncomplicated labor with C1INH concentrate prophylaxis in a patient with hereditary angioedema

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ABSTRACT

Patients with hereditary angioedema (HAE) need a special concern during pregnancy. Although, the disease has a relatively benign course during pregnancy, maternal mortality has been reported. We present a HAE patient with recurrent attacks during pregnancy, but uncomplicated labor under C1INH concentrate prophylaxis.

Key words: Hereditary angioedema. Pregnancy.

INTRODUCTION

Hereditary angioedema (HAE) is an autosomal dominant disease characterized by recurrent localized angioedema of the skin or mucosa, caused by a quantitative or qualitative deficiency of the plasma

protein C1 inhibitor (C1INH). The disease has two major subtypes: Type I, accounts for the 85 % of the patients and characterized by low C1 INH levels; and type II by normal (even high) levels, but functionally ineffective C1 INH. In addition, other rare forms of HAE are also described. The prevalence of HAE has been estimated to range from 1:10,000 to 1:100,000 in the general population.

The swelling may affect any part of the body: extremities, face, gastrointestinal tract (severe abdominal attacks mimicking acute abdomen), or upper airway. Laryngeal edema is potentially lethal symptom and accounts for mortality rates as high as 30 %. Antihistamines, corticosteroids, or epinephrine have no significant benefit for the angioedema attacks in HAE^{1,2}.

Patients with HAE need a special concern during pregnancy. Although, the disease has a relatively benign course during pregnancy, maternal mortality has been reported. In this paper, we present a HAE patient with recurrent attacks during pregnancy, but uncomplicated labor under C1INH concentrate prophylaxis.

CASE

Twenty-five-year-old female patient was admitted with episodes of cramp-like abdominal pain and swellings of the extremities without urticaria. Her complaints had been continuing for 12 years. Episodes were usually lasted for 2-3 days and irresponsive to treatment with corticosteroids and antihistamines. She also had a family history of recurrent

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angioedema in parents and grandparents, and a death of a brother due to laryngeal edema. Her laboratory test results were consistent with Type 2 HAE (low serum C4 level, quantitatively normal but functionally defective C1INH). She was followed-up for a month period to make a decision about the nature and frequency of the symptoms. Consequently, prophylactic treatment with danazol started with the diagnosis of HAE.

One-year after diagnosis, she and her husband stated their decision about family planning. She wanted to become pregnant for a second child (She had a 6-year-old girl). They informed again in detail about heredity pattern HAE and genetic consultation offered.

Because of attenuated androgens are contraindicated during pregnancy, danazol treatment was discontinued and she advised to continue contraception within next 8 weeks (to provide wash-out period for danazol).

After conception, the patient discussed with obstetrician: the course of HAE during pregnancy, probable complications, treatment alternatives, management of acute attacks, preferred type of delivery and prophylaxis before delivery were explained.

Up to current literature, the most effective treatment during pregnancy and at time of labor is replacement with C1 INH concentrate¹. But, C1 INH concentrate does not available in our country. C1 INH concentrate was imported (on a named-patient basis) from Germany (Berinert P, Aventis Behring, Germany). A sufficient quantity of C1 INH concentrate was reserved.

She was closely followed-up during pregnancy. Symptom scores were recorded day by day. Fortunately, she did not experience a serious attack. But she was not completely symptom-free, mild to moderate swellings on extremities and abdominal pain, 2 to 3 times a month, were occurred. Attacks were more frequent during second and third trimester of pregnancy. C1 INH concentrate was not used and reserved for delivery and postpartal period..

At term, the labor begun and the patient hospitalized. At the time of amniotic membranes rupture, first dose of Berinert P (500 units) infused within 10 minutes. The second vial reserved for complications, such as edema of genital tract, urethral orifice, episiotomy site, or probable more severe reactions which may trigger by labor stress.

The labor process lasted for 5 hours and completed without complication. The baby was healthy and normal in weight and development. After delivery, the patient admitted to intensive care unit and closely observed for 24 hours. Observation period was also uncomplicated and no additional transfusion of

C1 INH concentrate was needed. The patient and her baby discharged on day two. She nursed her baby for 4 months, then prophylactic treatment with danazol re-administered.

DISCUSSION

HAE typically begins in childhood and symptoms increases about the time of puberty. Patients typically continue to experience recurrent attacks of angioedema throughout of their lives. Attacks can be severe and potentially life threatening. The disease negatively affects daily life of the patients as well as their families, often preventing them from leading a productive life.

The treatment consists of long-term prophylaxis, short-term prophylaxis and treatment of acute attacks. HAE attacks usually begin with trauma; even minor. For this reason short-term prophylaxis should be given in all patients who will undergo surgical operations or dental procedures, to avoid potentially catastrophic swelling. Thus, dealing with potential triggers is crucial in general management of HAE. Trauma, infection, drugs (oral contraceptives, ACE inhibitors) or psychological stress may cause acute angioedema attacks^{1,2}.

The fluctuations in sex hormone levels in early adolescence, perimenopausal period, pregnancy or use of oral contraceptives, may precipitate angioedema attacks in HAE. Visy and colleagues showed that, pregnancy is associated with a higher incidence of attacks, but lower angioedema formation, in 36 % and 56 % of patients, respectively³. This means that female patients also need special care during pregnancy and labor. Because hormonal changes, emotional instability and labor trauma are potential triggers that may complicate the pregnancy.

Limitation of drug use in pregnancy is also making the management of HEA difficult. Attenuated androgens (danazol and stanazolol), which are effective for prevent HEA attacks, contraindicated during pregnancy. Furthermore, it should be stopped about 8 weeks before a planned gestation. Another drug used for prophylaxis of HAE is tranexamic acid. Tranexamic acid can crosses the placenta, however there is no direct evidence about its' teratogenic effect, and may be used if necessary. Lastly, fresh-frozen plasma may be an alternative when C1 INH is unavailable but is not acceptable as prophylactic treatment^{1,4}.

Replacement with C1INH concentrate is the most effective treatment of HAE and can be used at any period of pregnancy. In the high-risk patients, it can be given in regular intervals throughout the pregnancy.

However, there is an important question about using of products originate from blood. Does the repetitive infusions safe? Especially viral safety is always a matter of concern. Studies showed that, pasteurized C1INH concentrates appear to be safer than steam-heated ones. Because, enveloped and non-enveloped viruses can be inactivate by pasteurization. In addition to viral safety, a blood product must be safe during infusion. With respect to current knowledge, C1INH concentrates are also safe for allergic/anaphylactic reactions^{1,5,6}.

Another detail: which kind of delivery should be select in patients with HAE? Vaginal delivery appears to be safer. If an operative delivery is undertaken, regional analgesia should be preferred to avoid laryngeal edema due to endotracheal intubation. Whether vaginal or operative, the consequence of an attack during delivery may be potentially serious. In fact, potentially dangerous attacks, even maternal death, have been reported in medical literature. For this reason, C1INH concentrate should be keep available at the time of delivery. Infusion of 500 units C1INH concentrate before expulsive phase of delivery will attain a more reliable labor. A second 500 units of C1INH concentrate should be reserved for postpartum complications¹.

In our case, we did not observe a serious attack except for frequent mild to moderate swellings on extremities and abdominal pain, which were more frequent during second and third trimester of preg-

nancy. Labor completed without complication with C1INH concentrate infusion at pre-expulsive phase of delivery. With respect to our experiences and current literature; 1) Patients with HAE require a close follow-up during pregnancy, even hospitalization if needed, 2) a sufficient amount of C1INH concentrate should provide as early as pregnancy diagnosed, 3) pre-delivery infusion of 500 units of C1INH concentrate will guarantee a safer delivery, 4) postpartum period carries risk for acute attacks, the patient should be observed at least 24 hours after delivery.

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