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Management of hereditary angioedema type I and homozygous *MTHFR* mutation during pregnancy

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Abstract

Hereditary angioedema (HAE) is an autosomal dominant disease, characterized by edema attacks resulting from quantitative and/or functional deficiency of the C1 inhibitor (C1-INH), which acts in controlling the complement, coagulation, fibrinolysis, and contact systems. The exacerbation of these systems results in decreased circulating levels of kallikrein and conversion of bradykinin. In addition, thrombophilia is related to the deficiency of methylenetetrahydrofolate reductase (*MTHFR*) enzyme, causing an increase in homocysteine, accumulation of atheromatous plaques, and arterial and venous thrombosis. The association of these conditions in related systems brings greater clinical risks to the patient. We report a female patient, aged 23 years, with HAE and homozygous *MTHFR* mutation, G2A1, carrier of HAE with crises since early childhood. The first pregnancy terminated with abortion due to gestational sac detachment. In the second pregnancy, at 5.1 weeks, she had bleeding and partial detachment of gestational sac. Thrombophilia tests confirmed homozygosity for the *MTHFR* enzyme. At the beginning of gestation, she had attacks of angioedema treated with fresh plasma, and at one occasion, she received treatment with a plasma-derived C1-INH esterase. During breastfeeding, she received prophylaxis with plasma-derived C1-INHdp. The course of HAE during pregnancy worsened. There are studies that discuss the occurrence of abortion due to attacks of angioedema. The patient's disease was associated with a homozygous *MTHFR* mutation, which probably caused the miscarriage. The control of both clinical situations is important for the success of pregnancy, so a combined action plan between obstetricians and HAE treatment specialists is essential.

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Introduction

Hereditary angioedema (HAE) is a rare disease with an approximate prevalence of 1:50,000.¹ Inheritance is autosomal dominant and there is a quantitative (type 1) and/or functional (type 2) impairment of the C1 esterase inhibitor (C1-INH). C1-INH acts in several pathways: complement, fibrinolytic, coagulation, and contact systems. HAE generally manifests in the first decade of life and is characterized by abdominal symptoms and episodes of angioedema on the face, genitalia, extremities, urinary tract, and upper airways.¹ Another form of HAE with normal C1-INH was described and had similar clinical features to HAE, mainly affecting women after puberty. However, it was related to high levels of estrogen.²

Pregnancy influences the course of HAE in different ways: it may aggravate or have no effect on edematous attacks. We previously showed increasing number of attacks during the second trimester³ of pregnancy, while others reported worsening at the third trimester.^{4,5} During this period, high levels of progesterone reach a plateau, and simultaneously an increase in the concentration of estrogen and placental prolactogenic hormones is visible, resulting in a greater frequency of edema attacks.⁶ The recommended treatment for acute episodes during pregnancy is the infusion of C1-INH concentrate; however, when this concentrate is not available, fresh frozen plasma is administered.⁷ Long-term prophylaxis should be considered according to four variables analyzed: frequency and severity of attacks, impact on the quality of life, and availability of drugs for therapy. On account of this if long-term prophylaxis is indicated, it should be introduced as soon as possible.

During gestation, thrombophilia becomes a relevant factor due to the tendency for hypercoagulability related to the elevation of procoagulant factors and, consequently, the possibility of obstetric complications.⁸ In addition, thrombophilia could be related to the deficiency of the methylenetetrahydrofolate reductase (*MTHFR*) enzyme responsible for the conversion of 5,1-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which assists in the methylation of homocysteine into methionine. *MTHFR* deficiency interferes with this conversion, causes plasma homocysteine accumulation, and predisposes to atheroma plaques and arterial and venous thromboses.⁹

C1-INH also controls the activation of Factor XII. Thus, the association of HAE-C1-INH and thrombophilia can result in vascular complications during pregnancy. A recent report on HAE pregnancy associated with heterozygous *MTHFR* mutation has shown the enhancement of attacks and seven abortions preceding a successful pregnancy.⁸ We report management of a patient during gestation period with HAE type I and the homozygous *MTHFR* mutation.

Case Report

A 23-year-old female with HAE type 1 reported recurrent episodes of angioedema affecting the face and respiratory difficulty since infancy. The first miscarriage due to gestational sac detachment lead to the investigation of thrombophilia. During the second gestation, at 5.1 weeks, there was bleeding and partial detachment of the gestational sac with no harm to the embryo. At this time, oral progesterone

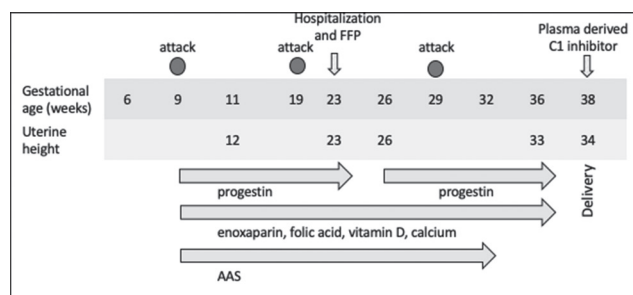


Figure 1 Treatment medications for the patient and uterine height over time.

(200 mg/day) was introduced. The obstetrician requested evaluation for thrombophilia and a homozygous mutation of *MTHFR* gene was identified. The following drugs were introduced: enoxaparin (40 mg/day, subcutaneously, after the 11th week of gestation), aspirin (100 mg/day up to 32 weeks of gestation), folic acid (5 mg/day), calcium carbonate (500 mg), and Vitamin D. Moreover, the patient used progestins for an 8-week period starting at week 9 of pregnancy, and again from week 26 to week 36 (Figure 1). No prophylactic therapy for HAE was used during the pregnancy. Attacks occurred at 9th, 19th, and 29th week of pregnancy and were treated with fresh frozen plasma in one episode due to unavailability of C1-INH concentrate at that time. Mild attacks were not treated but followed up closely. The pregnancy evolved without further complication and with an adequate progression of uterine height. A cesarean section was performed at 38.2 weeks of gestation after prophylaxis with plasma-derived esterase C1-INH (pdC1-INH; 1000 IU). The patient was discharged after 48 h and prescribed noxaparin (40 mg) until the 15th day of puerperium. The attacks restarted at every 5 days during puerperium and breastfeeding. Then, this time, prophylaxis with plasma-derived esterase C1-INH was introduced at every 7 days. After this, the child's development was within normal limits. The patient's sister also had HAE and heterozygous polymorphism for *MTHFR* (A1298C); she got pregnant just after the patient, with frequent HAE attacks but no other complication: her tests did not show thrombophilia and heparin was not prescribed. Furthermore, she had access to plasma-derived C1-INH that was prescribed for prophylaxis during the entire gestation. No family history of thrombosis was found. Their parents were asymptomatic and had never been tested for C1-INH deficiency.

DISCUSSION

Appropriate monitoring is required during pregnancy of women with HAE, especially because of its unpredictable course and, as in the discussed case, aggravated by the previous report of abortion and gestational sac detachment, conducting to investigation of thrombophilia. Angioedema attacks affect the same sites in both pregnant and non-pregnant women, with the exception of abdominal attacks, which are prevalent during this period. Differential diagnosis of HAE attacks and uterine contractions could be difficult in this situation. Abdominal symptoms were not relevant to our patient; nonetheless, three severe attacks with involvement

Table 1 Parameters of hereditary angioedema and thrombophilia determined in the patient.

Parameters	Results	Reference values
C3 (mg/dL)	87	86-160
C4 (mg/dL)	5	17-45
C1-INH functional (%)	25	>50%
Variant C677T	Wild type	No mutation
Variant A1298C	Homozygous	No polymorphism
	for A1298C	
Homocysteine (μmol/L)	3.5	4.44-13.56

of upper airway were reported. No attacks occurred at the third trimester but they recurred after delivery. Our patient delivered through a cesarean section, even though it was not a mandatory procedure for HAE patients. In fact, the type of delivery has not been associated with higher chance of edema attacks. Even so, prophylaxis with C1-INH concentrate was available and infused.⁷

Folic acid was prescribed for its important role in fetal development and the metabolism of homocysteine, which is recognized as an independent risk factor for deep venous thrombosis.¹⁰ It is important to note that the *MTHFR A1298C* mutation is located in the domain that regulates the MTHFR enzyme and is characterized by the alteration of glutamate to alanine, decreasing the enzymatic activity.¹¹ Such a mutation, in both homozygosis (CC) and heterozygosis (AC), has no association with the elevation of plasma homocysteine or the reduction of folic acid in plasma.^{11,12} Notwithstanding, the analyzed patient presented suggestive events compatible with thrombotic episodes even with normal plasma homocysteine values. Wild type 677CC and homozygous 1298CC genotypes have been found with 0.088 frequency.¹³

Low-molecular weight heparin, enoxaparin, was introduced to our patient at week 11 of gestation, just after the homozygous mutation of *MTHFR* was identified. Nevertheless, nadroparin has been reported as an option for the treatment of attacks in patients with HAE.¹⁴ However, its efficacy on HAE attacks is still controversial.^{15,16}

Conclusion

In this case, it is relevant to discuss the influence of abdominal attacks as a complicating factor during pregnancy. Although no higher frequency of abortions has been reported in literature, restricted information is available.⁷ A combined plan of action between obstetricians and specialists is essential to treat HAE.

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