MAYO CLINIC

CASE REPORT

Hereditary Angioedema Attack in Utero and Treatment of the Mother and Fetus

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Abstract

Hereditary angioedema (HAE), an inherited deficiency of functional C1 esterase inhibitor (C1-INH), is characterized by unpredictable recurrent episodes of painful and often disabling swelling in subcutaneous and/or submucosal tissues. We report the case of a 23-year-old woman with type I HAE who had abdominal, facial, and peripheral attacks throughout her first pregnancy. A facial HAE attack occurred at week 38 of her pregnancy, and symptoms improved after self-administration of 50 U/kg of recombinant human C1-INH (total dose, 3500 U), but soon after she had an unusual abdominal sensation. Ultrasonography detected fetal lower lip swelling (~3 times the normal size) and limb swelling. Physical examination of the mother found cervical dilatation, indicating the final stages of labor. Two hours after treatment of her HAE attack, she spontaneously delivered a healthy male infant. Photographs taken within 2 minutes of delivery revealed resolution of the infant's facial edema, and the limb edema was resolved within 30 minutes. By 10 minutes postdelivery, the mother's facial attack had almost completely resolved. Ten months after birth, genetic analysis confirmed that the infant had type I HAE. This is the first documented case of an HAE attack in utero. Treatment of the mother with recombinant human C1-INH was effective for the maternal and fetal attacks, with resolution within approximately 2 to 2.5 hours for both patients.

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Hereditary angioedema (HAE) is an inherited deficiency of functional C1 esterase inhibitor (C1-INH) characterized by unpredictable recurrent episodes of painful and often disabling swelling in subcutaneous and/or submucosal tissues.[1] Hereditary angioedema is a rare condition with an estimated prevalence between 1:10,000 and 1:150,000.[2] Compared with men, women are more likely to have severe HAE attacks, and their attacks occur more often.[3-5] Fluctuations in sex hormone levels during puberty, menstruation, and pregnancy are believed to play a role in the occurrence of HAE attacks in women.[6,7] In fact, female sex hormones have been found to affect the kallikrein-kinin pathway by increasing the synthesis of bradykinin, a key mediator in HAE.[8]

Changes in hormone levels during pregnancy and a fetus with HAE have the potential to affect the frequency and severity of HAE attacks.[7,9,10] It has been found that abdominal HAE attacks are more frequent during pregnancy.[9,10] Although some data indicate a higher frequency of attacks in the first trimester,[9] other data point toward increased attack frequency in the second and third trimesters.[10] Severity may also vary by trimester.[9] Interestingly, a retrospective analysis of 118 pregnancies revealed that the presence of a fetus with HAE, determined after birth, increased the number of attacks the mother had during the third trimester of pregnancy.[9] However, no effect was observed in a smaller observational study of 35 pregnancies.[10] In addition, administration of certain medications during pregnancy can complicate the medical management of HAE.[7]

Recombinant human C1-INH (rhC1-INH, Ruconest, Pharming Americas B.V.) is indicated in multiple countries for the treatment of acute attacks in adolescents and adults with HAE, with several studies reporting that rhC1-INH is efficacious and well tolerated across various age ranges.[11-14] Two studies reported that rhC1-INH treatment of HAE attacks during pregnancy (n=17 women) was generally safe and well tolerated; all women delivered infants at full term without complications.[15,16] In this report, we describe the first documented case

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of an HAE attack in utero and successful treatment of the mother and fetus.

CASE REPORT

A woman with a family history of type I HAE started having clinical symptoms at 12 years of age and was diagnosed with type I HAE in 2015 at the age of 21 years. In 2015, the patient had 19 HAE attacks (peripheral [n=7], facial [n=5], and abdominal [n=7]); in 2016, she had 14 HAE attacks (skin [n=3], facial [n=1], abdominal [n=9], and laryngeal [n=1]). The patient received acute treatment for the HAE attacks and was not taking long-term prophylaxis. Subsequently, at 23 years of age, she was pregnant with her first child. During pregnancy, she had 30 HAE attacks (abdominal [n=12], facial [n=10], and peripheral [n=8]) that were distributed across the first (abdominal [n=4], facial [n=3], and peripheral [n=2]), second (abdominal [n=3], facial [n=4], and peripheral [n=2]), and third (abdominal [n=5], facial [n=3], and peripheral [n=4]) trimesters.

At week 38 of pregnancy, she had a facial HAE attack that started in the lower lip and quickly spread over the face (Figure 1). The HAE attack was treated with self-administered rhC1-INH 50 U/kg (total dose, 3500 U), with patient-reported clinical symptom improvement apparent within 15 minutes. Ten minutes after this observation, she felt an unusual abdominal sensation (ie, discomfort), distinct from previous experiences of abdominal HAE attacks, and was concerned about the fetus' health. The patient did not have nausea; abdominal pain, typically felt when she had an abdominal HAE attack; or bloating. She was subsequently advised to travel to the hospital for an examination. At the hospital, ultrasonography was performed transabdominally with the Voluson E8 Expert (3 to 5 MHz transabdominal probe) ultrasound system (GE Healthcare) by a single trained operator. Ultrasonography detected lower lip swelling (~3 times normal size [5 mm vs 1.5 mm]) (Figure 2) and limb swelling (observed; not documented with image) in the fetus. All other anatomical assessments of the fetus were normal; the forehead measured 3 mm, and a finger measured 1.8 mm. Physical examination of the mother revealed cervical dilatation, indicating the final stages of labor.

Two hours after she had administered rhC1-INH treatment, a healthy male infant (Apgar score, 8-9) was delivered spontaneously. Photographs taken within 2 minutes of delivery revealed resolution of the infant's facial edema (Figure 3). Of note, the circumference of the infant's right thigh was 25 mm larger than that of the left thigh, but the edema completely resolved within 30 minutes of delivery. When the mother was examined 10 minutes postdelivery, the facial attack had almost completely resolved. She did not have any additional acute HAE attacks within 72 hours. The parental medical history revealed no underlying comorbidities or diseases that might cause fetal edema other than HAE. Ten months after birth, blood from the infant was collected. Genomic DNA was purified from the sample for genotyping by using a QIAamp DNA Blood Mini Kit (Qiagen) in adherence to manufacturer's instructions. The detection of *SERPING1* mutations in the promoter, the noncoding exon 1, the 7 coding exons, and the exon-intron boundaries was performed as previously described.[17] Mutations were identified by comparing with the *SERPING1* reference sequence in GenBank (GenBank accession number X54486.1). The genetic analysis confirmed that the infant had type I HAE.

DISCUSSION

This is the first documented case of an HAE attack in a fetus. Treatment of the mother with rhC1-INH was effective for both maternal and fetal attacks, which occurred almost simultaneously, with resolution within approximately 2 to 2.5 hours for both patients. For the mother, the number of HAE attacks during pregnancy was higher than before pregnancy, which is consistent with data from other studies.[7,9,10] For this mother, the attack occurred during labor, which is uncommon, as published studies have reported that less than 10% of attacks in pregnant women occurred during labor/delivery.[7,9] Of note, the woman's HAE attacks were distributed across the 3 trimesters of her pregnancy. This observation differs from a report from a retrospective study, indicating that patients (n=84 pregnancies ending in delivery) are statistically significantly more likely to have a higher number of attacks in the third trimester when the fetus is

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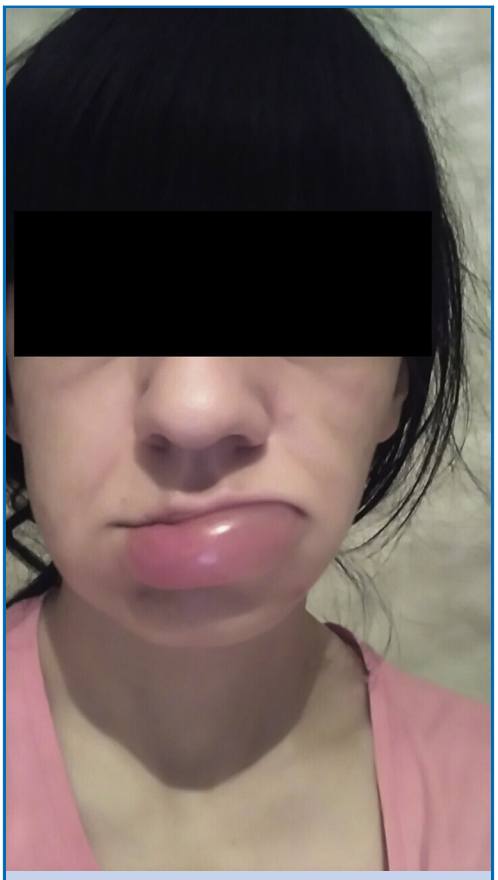

FIGURE 1. Photograph of the swollen lip of the mother during the acute facial hereditary angioedema attack.

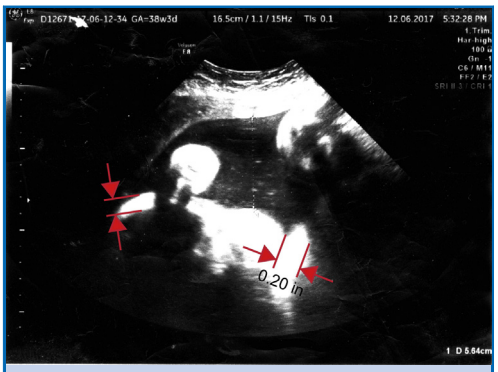

FIGURE 2. Ultrasound imaging of the fetus in utero 107 minutes after the acute facial hereditary angioedema attack in the mother.

determined to have HAE than patients carrying a fetus that does not have HAE (P=.04).[9] However, in a smaller observational study of 35 pregnancies, a fetus with HAE did not affect the attack frequency in the mother, but these mothers had lower levels of functional C1-INH activity than did mothers in whom the fetus tested negative for HAE.[10] The potential mechanism by which a fetus with HAE affects clinical symptoms in a mother with HAE is unclear, and future research is needed.

The resolution of the fetal HAE attack via rhC1-INH treatment of the mother during labor is intriguing. Multiple changes occur within the placental barrier as pregnancy advances, which may influence permeation of molecules from the maternal to the fetal circulation.[18,19] As the pregnancy progresses, the placental barrier becomes thinner (50-100 μm in the first trimester vs 4-5 μm at term) and the surface area increases (total syncytiotrophoblast surface area, 5 m^2 at 28 weeks vs 11-14 m^2 at term).[19-21] In addition, there may be differences in expression and cellular distribution of placental transporter proteins in early- vs late-stage pregnancy.[22] Another possible explanation for the resolution of the fetal HAE attack is that as the mother had self-administered rhC1-INH before feeling the clinical onset of labor, and labor appeared to have begun before the fetal HAE attack, rhC1-INH may have entered the fetal circulation with the rupture of the amniotic sac and disruption of the placenta.

In this report, treatment of the mother with 3500 U of rhC1-INH administered in 1 dose resolved facial HAE attacks in both the mother and the fetus. Additional safety and efficacy data from women with HAE

FIGURE 3. Photograph of the newborn 2 minutes after birth and 2 hours after the mother received recombinant human C1 esterase inhibitor.

who had attacks during pregnancy that were successfully treated with rhC1-INH (2 studies: n=14 women and n=3 women) have been published recently.[15,16] In these studies, all women delivered infants at full term without complications, and the treatment was generally safe and well tolerated. Further supportive information has come from treatment with plasma-derived C1-INH products during pregnancy for acute HAE attacks[9,23,24] and HAE prophylaxis[25,26] and short-term perinatal prophylaxis.[9,25] Although no controlled studies have been conducted comparing HAE treatment regimens during pregnancy, international guidelines recommend C1-INH concentrate as first-line treatment for acute HAE attacks during pregnancy on the basis of its safety profile.[27] However, the US Food and Drug Administration and the European Medicines Agency labeling recommends that C1-INH concentrates only be used during pregnancy if clearly needed (ie, benefits outweigh risks). In this case, the treating physician followed these recommendations as the facial HAE attack experienced by both the mother and the fetus had the potential risk of laryngeal involvement.

It is unknown whether rhC1-INH (a 68-kDa protein) can passively cross the fetoplacental barrier, and no active transport of C1-INH protein across this barrier has been documented to date.[28,29] However, the present findings suggest that active transport across the placental barrier should not be ruled out. The favorable safety profile of C1-INH concentrate (ie, plasma-derived C1-INH and rhC1-INH) documented during pregnancy (ie, off-label use)[15,23] is not merely explained by the assumption that the molecule may not actively pass the fetoplacental barrier. Endogenous C1-INH is expressed in the maternal liver and extrahepatically, including the placenta.[30] In addition, C1-INH protein has been detected in the fetal liver as early as 11 weeks of gestation.[31] With both the mother and the fetus exposed to endogenous C1-INH, the intermittent exposure to rhC1-INH is unlikely to constitute a safety concern.

Offspring of a patient with HAE have a 50% chance of inheriting HAE through autosomal dominant genetic inheritance.[27] Prenatal diagnosis of HAE is rarely requested,[32] but may be conducted using chorionic villous sampling or amniocentesis.[29] It should be assumed that asymptomatic infants with a family history of HAE have the condition until it is ruled out or confirmed via testing.[29] Expert consensus recommends that diagnosis of HAE be made as soon as possible for an infant, ideally to have a treatment plan in place for clinical symptoms of HAE.[29] In a report of 2 newborns, erythema marginatum, a frequently reported prodromal symptom, was an early manifestation of HAE.[33] However, it is important to note that erythema marginatum does not occur in all HAE attacks. The complement system of an infant generally achieves adult maturity level between 6 and 36 months of age,[34] and the concentration of C1-INH in the umbilical cord blood of healthy infants is approximately two-thirds of normal adult values.[28] Because of these factors, for infants less than 12 months of age, HAE diagnosis by biochemical testing potentially could be inaccurate, so it is recommended that any diagnosis be confirmed with further testing after the infant reaches 12 months of age.[29,35] Compared with biochemical testing, DNA analysis is less sensitive to sample handling issues and is specific when a family mutation is known.[35]

CONCLUSION

This report documents the occurrence of an HAE attack in utero that resolved after treatment of the mother's HAE attack. Ultrasonographers and neonatologists should consider the possibility of HAE in utero and immediately after birth when considering possible causes of fetal or neonatal edema. These data reinforce that it is imperative that newborns be tested as soon as possible if fetal edema via ultrasound is observed, particularly in those with a family history of HAE.

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Abbreviations and Acronyms: **C1-INH** = C1 esterase inhibitor; **HAE** = hereditary angioedema; **rhC1-INH** = recombinant human C1 esterase inhibitor

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