ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Icatibant in a pregnant woman with HAE-FXII: a case report

Uso do icatibanto em gestante com AEH-FXII: relato de caso

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ABSTRACT

Hereditary angioedema (HAE) due to pathogenic variants in the factor XII gene (HAE-FXII) is the most common type of HAE with normal C1 inhibitor (HAE-nC1INH). HAE-FXII is highly influenced by estrogen exposure. Patients with this condition tend to experience worsening of angioedema-related symptoms during periods of elevated estrogen, such as pregnancy. Currently, there is no approved treatment for HAE-FXII, and during pregnancy management can be even more challenging, since first-line drugs are not always available. We report the case of a pregnant woman with HAE-FXII who received a single dose of icatibant during an upper airway angioedema attack in the third trimester, with a favorable outcome for the patient and fetus.

Keywords: Hereditary angioedema, bradykinin B2 receptor antagonists, pregnancy, factor XII.

RESUMO

O angioedema hereditário (AEH) por variantes patogênicas no gene que codifica o Fator XII da coagulação (AEHFXII) é o tipo mais comum de AEH com inibidor de C1 normal (AEH-nC1NH). O AEH-FXII é altamente influenciado pela exposição ao estrogênio. Pacientes com esta condição tendem a ter piora do angioedema em períodos de elevação deste hormônio, como na gestação. Atualmente, não há tratamentos específicos aprovados para o manejo do AEH-FXII, e durante a gravidez o tratamento pode ser ainda mais desafiador, visto que os medicamentos recomendados como primeira linha nem sempre estão disponíveis. Neste relato, descrevemos o caso de uma gestante portadora de AEH-FXII que recebeu icatibanto em dose única durante crise de angioedema de vias aéreas superiores no terceiro trimestre, com desfecho favorável para a paciente e para o feto.

Descritores: Angioedema hereditário, antagonistas de receptor B2 da bradicinina, gravidez, fator XII.

Introduction

Hereditary angioedema (HAE) is a rare autosomal dominantly inherited genetic disease that manifests as recurrent and unpredictable attacks of AE in subcutaneous tissue and mucous membranes. Gastrointestinal tract involvement leads to attacks of intense abdominal pain and can result in unnecessary surgical interventions. Death by asphyxia due to upper airway edema is the most feared event, and more than 60% of patients with HAE have reported report ≥ 1 laryngeal AE event. Variants in SERPING1, the gene that encodes C1-INH inhibitor (C1-INH), result in HAE with C1-INH deficiency (HAE-C1INH), which can be type 1 when the defect is quantitative or type 2 when it is functional. HAE with normal C1-INH (HAE-nC1INH)

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is associated with variants in other genes; 7 types are currently described. No genetic defects have been identified in some patients with HAE, so in carriers the cause is unknown. HAE-nC1INH is considered rarer than HAE-C1INH, with the most common cause being variants in the F12 gene. HAE-FXII also has an autosomal dominant inheritance pattern.[1-3]

C1-INH inhibits the contact and kallikrein-kinin systems at different points. The absence or dysfunction of this inhibitor results in a cascade of uninhibited activation and final release of bradykinin (BK). The release of BK results in increased vascular permeability and AE through binding to its B2 receptor (BDKRB2). Activation of the contact and kallikrein-kinin systems is initiated by converting activated factor 12 (FXII) to its active form, FXIIa. FXIIa cleaves prekallikrein into kallikrein, which induces the release of BK from high molecular weight kininogen. In HAE-FXII, FXII is more sensitive to activation by plasmin. In addition to HAE-FXII, other forms of HAE-nC1INH are also mediated by BK, but some forms of HAE-nC1INH are due to increased vascular fragility, as is the case of HAE-nC1INH due to a variant in the angiopoietin-1 gene.[1,2,4]

Short- and long-term prophylaxis and effective treatments for flare-ups are only approved for patients with HAE-C1INH. In Brazil, the first-line drugs for flare-ups are BDKRB2 inhibitor, subcutaneous icatibant, and intravenous human plasma-derived C1-INH concentrate (pdC1-INH), while fresh frozen plasma is a second-line therapy that should only be used intravenously when first-line therapies are unavailable. Intravenous pdC1-INH is the first-line option for short-term prophylaxis, while the second-line options are attenuated androgens, such as danazol and oxandrolone. Although difficult to access, the first-line options for long-term prophylaxis are intravenous pdC1-INH, subcutaneous pdC1-INH, subcutaneous lanadelumab, and oral berotralstat, the latter 2 being kallikrein inhibitors. Due to the limited availability of first-line therapies for flare prophylaxis, attenuated androgens and tranexamic acid, which are second-line options, are still commonly used.[2,5-7]

No specific treatments have been approved for HAE-FXII, and current therapeutic strategies are based on treatments that have been shown to be effective in patients with HAE-C1INH.[8] HAE-FXII treatment also includes discontinuation of potential triggers, such as estrogen-containing contraceptives, hormone replacement therapy, and angiotensin-converting enzyme inhibitors.[9,10]

Proper pregnancy planning in patients with HAE is important to minimize risk to the mother and fetus. During pregnancy, changes in the severity and frequency of attacks are unpredictable and may decrease or increase. In patients with HAE-FXII, symptoms tend to worsen under hyperestrogenism conditions, such as pregnancy. Angioedema attacks in pregnant women mainly affect the abdomen and extremities. Airway attacks are less frequent, but should be treated urgently, preferably with pdC1-INH.[11,12]

Although the safety of icatibant therapy during pregnancy is unknown, it can be used in pregnant women when pdC1-INH is unavailable or when the action of pdC1-INH is doubtful for a given patient. For ethical reasons, there have been no randomized controlled studies on these drugs for HAE attacks during pregnancy. However, several observational studies have found that icatibant is safe and efficacious for treating attacks during pregnancy. Therefore, until more data are available, icatibant is not recommended as a first-line option during pregnancy, but it can be considered when first-line medication is unavailable or when the benefits outweigh the risks.[13-15]

Case report

A female patient had frequent attacks of severe abdominal pain since childhood, which worsened at 22 years of age. In addition to the abdominal manifestations, she had AE of the extremities and face. Initially, the episodes recurred every 2 to 3 months, either in association with trauma or spontaneously. Increasing symptom severity coincided with the beginning of combined contraceptive use. At the age of 24, she was diagnosed with HAE-FXII. Laboratory tests at the time revealed normal C4 and C1-INH values (Table 1), and genetic testing found the pathogenic variant in exon 9 of the F12 gene, p.Thr328Lys (c.983C>A) in heterozygosis. Although there was no family history, the asymptomatic father is a carrier of the same variant.

When HAE-FXII was diagnosed, the use of combined contraceptives containing estrogen was suspended and, as the patient had no desire to become pregnant at the time, she continued using contraceptives containing only progesterone. The patient then remained completely asymptomatic for approximately 10 years.

Intending to become pregnant, she discontinued contraception and had her first pregnancy at 34

years of age. At 12 weeks of gestation, the attacks resumed and increased in severity and frequency over time. Because access to pdC1-INH was denied, prophylactic treatment with tranexamic acid 500 mg/day was indicated, with partial and unsatisfactory symptom control. Doses > 500 mg/day were not tolerated due to gastric symptoms.

Table 1
Results of initial laboratory tests

	Results	Reference values
C4	29 mg/dL	10-40 mg/dL
C1-INH	28 mg/dL	21-29 mg/dL

At 30 weeks of gestation, the patient had an attack of oropharyngeal AE (Figure 1) with no other associated symptoms. Due to the risk of progression and potential obstruction of the upper airways, as well as the unavailability of pdC1-INH, the first-line treatment during pregnancy, it was decided to use subcutaneous icatibant 30 mg, to which the patient consented after the risks and benefits were explained. Icatibant was selected because it had been available since diagnosis prior to the pregnancy. The drug was administered approximately 4 hours after attack onset. Improvement was reported after 2 hours, and complete resolution occurred after 10 hours. There were no immediate or late adverse events, either local or systemic. Delivery occurred after 35 weeks and 2 days of gestation due to bleeding secondary to placenta previa, which was diagnosed at the beginning of pregnancy. The delivery and postpartum period were uneventful for both the mother and the newborn.

Discussion

Pregnant women with HAE may experience a significant worsening in disease frequency and severity. Exposure to estrogen, whether endogenous or exogenous, influences patients with HAE-C1INH types I and II, as well as carriers of HAE-FXII, but this relationship is not yet fully understood. HAE-FXII was once considered estrogen-dependent, since some patients with pathogenic variants in F12 only begin to have clinical manifestations when exposed to this hormone, such as during pregnancy or when using estrogen-containing contraceptives. This hormone can act during several stages of the activation cascades of the contact and kallikrein-kinin systems, both at the genomic level and through several endothelial membrane receptors. Its effects include stimulating the release of certain cytokines and the heat shock protein Hsp90, which can act on endothelial cells, leading to the conversion of prekallikrein into kallikrein, with subsequent cleavage of HMWK and BK release. Kallikrein also activates FXII, both directly and by inducing the degradation of plasminogen into plasmin and consequent activation by the latter. Estrogen can increase the expression of the BK receptor B2, in addition to intervening in the activity of the angiotensin-converting enzyme, reducing the degradation of BK.[1,16]

Although the therapy of choice for AE attacks during pregnancy is pdC1-INH,[7] we decided to use icatibant in this patient due to the severity of the crisis and the location of the AE in the oropharynx, including potential progression and upper airway obstruction. The first-line medication was also unavailable at the time.

Icatibant is classified as category C due to adverse events in animal studies,[13] including premature birth, abortion, fetal death, and pre-implantation loss, with

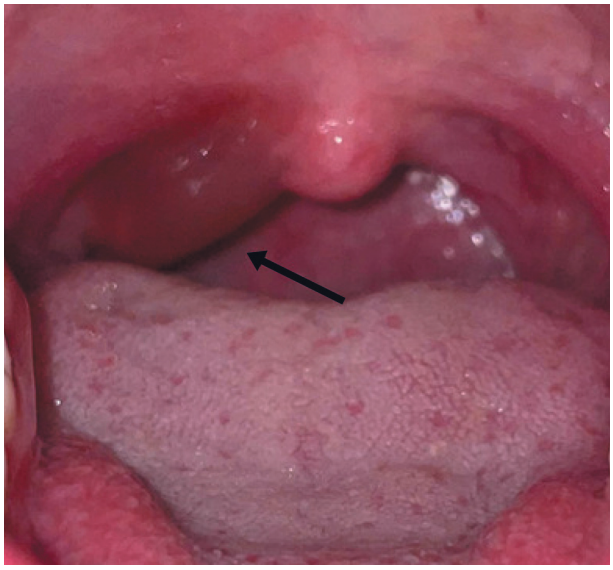

Figure 1
Oropharyngeal hereditary angioedema during pregnancy, which was treated with icatibant

no evidence of teratogenicity. Observational studies in humans have reported preterm births in pregnant women who received icatibant during HAE attacks, with no other adverse events reported. However, the dataset is too small to draw conclusions about the relationship between icatibant and increased incidence of prematurity.[14] One concern related to icatibant use during pregnancy is the fact that human decidual cells express BDKRB2 receptors and the effects of inhibition of these receptors, even during transient periods, are still unknown.[15] Although some observational studies have reported preterm births among women using icatibant, in the present case the preterm birth could not be attributed to medication, since this outcome was secondary to complications of placenta previa, which was diagnosed during the first trimester of pregnancy.

No drugs have been approved for HAE-FXII due to a lack of solid clinical trial data. Treatment for these patients is based on well-established clinical experience with HAE-C1INH. Discontinuing exogenous estrogen is the first step for women with suspected HAE-FXII, prior to any other therapies. Because the drugs used for crisis or prophylaxis in HAE-C1INH, such as icatibant, pdC1-INH (intravenous and subcutaneous), tranexamic acid, injectable lanadelumab and, more recently, oral berotralstat, directly or indirectly modulate bradykinin metabolism, they may be useful in patients with HAE-FXII. Of note, tranexamic acid is more effective for prophylaxis in HAE-FXII than HAE-C1INH.[17]

All forms of HAE significantly affect the quality of life, education, and professional performance of patients. Difficulty in early diagnosis is often associated with multiple emergency room visits, misdiagnosis, unnecessary surgical interventions, and increased anxiety and depression, resulting in greater mortality risk.[3,17] Some studies have estimated that the delay in diagnosing HAE varies between 14-18 years in Brazil. Both a lack of knowledge by physicians and difficulty accessing screening and diagnostic tests contribute to this delay. Coordinated effort to increase awareness of HAE is urgently needed among health professionals (whether specialists or non-specialists) and the general public.[7,18]

Conclusions

No targeted treatment for HAE-FXII has been developed. Current therapies are based on treatment for HAE-C1INH. Despite the unavailability of controlled studies on icatibant during pregnancy, this drug has been described as effective and safe in these patients. In the various reports to date, there has been no evidence of adverse effects to the patient or fetus. Therefore, this drug may be considered when the first-line option is unavailable, after the risks and benefits have been discussed with the patient.

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