Tranexamic Acid Plus Bemiparin Sodium as Long-Term Prophylaxis in a Patient With FXII-HAE During Pregnancy: A Case Report

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Hereditary angioedema (HAE) is characterized by recurrent attacks of severe swelling with involvement of multiple organs. The attacks are induced by genetic mutations that result in increased bradykinin levels. In particular, patients with a mutation in the *F12* gene (FXII-HAE) experience worsening of symptoms under hyperestrogenic conditions, such as pregnancy, oral contraceptive intake, and in vitro fertilization [1-3]. Therapy for HAE is limited during pregnancy, delivery, and postpartum [1,3,4], with plasma-derived C1-inhibitor concentrate (pdC1-INH) being the approach of choice during these periods [3,4].

We report the course and management of repeated angioedema attacks during pregnancy in a 32-year-old woman with FXII-HAE.

The patient had been diagnosed with FXII-HAE at the age of 27, with normal C1-INH levels and function and a single missense mutation in the *F12* gene (c.1032C>A). The diagnosis was made in 2013, during her first pregnancy, owing to a severe attack of facial angioedema (previously reported by Gomez-Traseira [5]). She had previously experienced angioedema attacks after starting a combined oral contraceptive pill (Yasmin, drospirenone 3 mg/ethinylestradiol 0.0 mg).

Her second pregnancy was marked by recurrent episodes of facial angioedema starting during the third week of gestation. The patient went on sick leave in the seventh week of gestation and was followed up in the high-risk pregnancy outpatient clinic of our center. During the first trimester, she experienced 3 episodes of facial angioedema (at weeks 3, 5, and 7 of gestation) that required treatment with intravenous pdC1INH (Berinert, CSL-Behring) in the emergency department. Sometimes she needed 2 or 3 doses of intravenous pdC1INH 1500 IU to resolve the attack.

Given the increased frequency of angioedema attacks, most of which affected the face, and the poor response to high doses of intravenous pdC1INH, we decided to initiate long-term prophylaxis with tranexamic acid (TXA) because of its previously reported usefulness [2,3] and the lack of efficacy of pdC1INH in the treatment of acute attacks in this case. The patient was evaluated by a hematologist to assess hypercoagulable states before initiating treatment with TXA. As pregnancy itself is a physiological prothrombotic state, the assessment was not performed, and the hematologist recommended concomitant treatment with anticoagulants. At 11 weeks of gestation, we initiated long-term prophylaxis with tranexamic acid 500 mg every 8 hours and subcutaneous bemiparin sodium 7500 IU daily. Hematologic monitoring was performed every 5 weeks.

The patient was asymptomatic for 5 months immediately after starting oral long-term prophylaxis with TXA and bemiparin sodium. She experienced only 2 mild facial attacks during the third trimester. One of these was treated with intravenous pdC1INH (1500 IU), and the response was acceptable.

A cesarean delivery was scheduled because of a prior cesarean due to cephalopelvic disproportion [5] at the 39th week of gestation. The patient discontinued TXA the night before the delivery, and short-term prophylaxis with intravenous pdC1INH (1500 IU) was administered before the procedure. The patient also underwent tubal ligation for contraceptive purposes. No complications were reported during pregnancy, cesarean delivery, or postpartum.

The patient gave birth to a healthy girl (3.5 kg, length 50 cm, and Apgar score of 10 at minutes 1 and 5). An *F12* gene mutation was ruled out in the newborn. The patient breastfed her child for 4 months. TXA was not reinitiated, and the patient continued treatment with subcutaneous bemiparin sodium for 6 weeks after delivery. No new HAE attacks were recorded, and the child did not present any drug-related abnormalities. The child is now 18 months old and healthy.

Tranexamic acid was shown to be helpful for preventing FXII-HAE attacks during pregnancy [2,3,6], although there are no reported cases of its association with a heparin as long-term prophylaxis. TXA could be effective for prevention and remission of HAE attacks, because it inhibits activation of FXII owing to its antiplasmin activity and, therefore, the contact activation system [7]. Despite the theoretical increased risk of thrombotic events due to TXA, there are no reported increased risks of thromboembolic events, including myocardial infarction and stroke [1]. Bemiparin sodium is a second-generation low-molecular-weight heparin (LMWH) that is widely used as a thromboprophylactic agent and for clot prevention during hemodialysis. Evidence for the efficacy of heparin to control angioedema attacks in patients with C1-INH-HAE is discordant. A case series of 30 patients with C1-INH-HAE treated with nadroparin, another LMWH, as on-demand therapy and short-term prophylaxis was effective in adults and children, even during pregnancy and postpartum [8]. Enoxaparin, also an LMWH, proved to be safe

and effective in a pregnant woman with C1-INH-HAE and heterozygous mutations in the *MTHFR* gene [9]. However, a double-blind placebo-controlled trial involving 24 patients with C1-INH-HAE failed to attenuate the average intensity of attacks with injected or inhaled calcium heparin as long-term prophylaxis [10].

In the present case, we were able to manage the angioedema attacks during pregnancy using TXA plus bemiparin sodium with no adverse effects. This case demonstrates the importance of individualized treatment during pregnancy in patients with HAE. Consensus on long-term prophylaxis for FXII-HAE is lacking, and clinical trials with FXII-HAE are needed. We expect that future studies will clarify the effectiveness and safety of TXA combined with heparin for patients with FXII-HAE during pregnancy.

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Conflicts of Interest

Dr D. Loli-Ausejo has received funding to attend conferences/educational events from CSL Behring and Shire (a Takeda company) and is/has been a clinical trial/registry subinvestigator for Shire.

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Dr R. Cabañas has received funding to attend conferences/educational events from CSL Behring and Shire and is/has been a clinical trial/registry subinvestigator for Biocryst, Novartis, Shire, and CSL-Behring.

Dr A. Entrala has received funding to attend conferences/educational events from CSL Behring and Shire and is/has been a clinical trial/registry subinvestigator for Biocryst, Novartis, and Shire.

Dr T. Caballero has received research grant support and/or speaker/consultancy fees from BioCryst, CSL Behring, Merck, Novartis, Octapharma, Pharming, and Shire and funding to attend conferences/educational events from CSL Behring, Novartis, and Shire. She is/has been a clinical trial/registry investigator for Biocryst, CSL Behring, Novartis, Pharming, and Shire and is a researcher in the IdiPAZ program for promotion of research activities.

Dr M. Gutiérrez-Albariño and Dr N. Martínez-Sánchez declare that they have no conflicts of interest.

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