

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, which are induced by genetic mutations that result in increased bradykinin levels. Patients with a mutation in the *F12* gene (FXII-HAE) specifically show worsening of symptoms under hyperestrogenic conditions, such as pregnancy, oral contraceptive intake or *in vitro* fertilization [1-3]. Therapy for HAE is limited during pregnancy, delivery, and postpartum [1,3,4] being plasma-derived C1-INH concentrate (pdC1-INH), the election treatment recommended during these periods [3,4].

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

The patient had been diagnosed of FXII-HAE at the age of 27, with normal levels and function of C1-INH and a single missense mutation in the *F12* gene (c.1032C>A). The diagnosis was made in 2013, during her first pregnancy, due to a severe facial angioedema attack (previously published by Gomez-Traseira [5]). She had previously suffered from several angioedema attacks after starting a combined oral contraceptive pill (Yasmin[®], drospirenone 3mg/ ethinylestradiol 0.03mg).

Her second pregnancy was marked by recurrent episodes of facial angioedema since the 3rd week-of-gestation. She was on sickness leave since the 7th week-of-gestation and was followed up in the high-risk pregnancy outpatient consultation of our center. During the first trimester of pregnancy the patient presented three episodes (at 3rd, 5th and 7th weeks-of-gestation) of facial angioedema that required treatment with intravenous (IV) pdC1INH (Berinert[®], CSL-Behring, Marburg, Germany) at the emergency department. Sometimes she needed two or three doses of IV pdC1INH 1,500 IU to resolve the attack.

As there was an increase in the frequency of angioedema attacks, most of them located in the face, and a poor response to high doses of IV pdC1INH we decided to initiate long term prophylaxis (LTP). We initiated LTP 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 patient. The patient was evaluated by a hematologist to assess a hypercoagulable state before initiating treatment with TXA. As pregnancy itself is a physiological prothrombotic state, the assessment was not performed, and the haematologist recommended anticoagulant co-treatment. At 11 weeks-of-gestation, we initiated LTP with tranexamic acid 500 mg every 8 hours and subcutaneous (SC) bemparin sodium 7,500 IU daily. Hematologic controls were performed every five weeks.

The patient was asymptomatic for 5 months immediately after starting oral LTP with TXA and bemparin sodium, having had just 2 mild facial attacks during the third trimester of pregnancy, and treating only one of them with IV 1,500 IU of pdC1INH with acceptable response.

A caesarean delivery was scheduled because of a prior caesarean due to cephalopelvic disproportion [5] at 39th week-of-gestation. She discontinued TXA the night before the

delivery and short-term prophylaxis (STP) with IV pdC1INH (1,500 IU) was administered before caesarean section. A tubal ligation was also performed for contraceptive purpose.

A healthy female baby was born (the birth weight was 3.5 kg, length 50 cm and Apgar score was 10 at 1st and 5th minute). An *F12* gene mutation was discarded in the newborn. The patient breastfed her child for 4 months. TXA was not reinitiated and our patient continued the treatment with SC bemiparin sodium for 6 weeks after the delivery. There were no new HAE attacks and no complications were reported during pregnancy, caesarean section and postpartum period. The child did not present any drug-related abnormalities. Currently the child is 18 months old and healthy.

Tranexamic acid was shown to be helpful for preventing FXII-HAE attacks during pregnancy [2,3,6], but 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 due to its anti-plasmin activity and therefore the contact system activation [7]. Despite the fact of an increased theoretical risk of thrombotic events due the use of TXA, there are not reported increased risks of thromboembolic events, including myocardial infarction and stroke [1]. Bemiparin sodium is a second-generation low-molecular-weight heparin (LMWH) widely used as a thromboprophylactic agent and for cloth prevention during hemodialysis. There has been discordant evidence about the efficacy of heparin treatment to control angioedema attacks in patients with C1-INH-HAE. A case series of 30 patients with C1-INH-HAE treated with nadroparin, another LMWH, as on-demand therapy and short-term prophylaxis showed efficacy in adults and children even during pregnancy and postpartum periods [8]. Enoxaparin, a different LMWH, proved to be safe and effective in a pregnant woman with C1-INH-HAE and heterozygous *MTHFR* (methylene

tetrahydrofolate reductase) gene mutations [9]. However, a double-blind and placebo-controlled trial with 24 patients with C1-INH-HAE failed to attenuate average intensity of attacks with injected or inhaled calcium heparin as long-term prophylaxis [10].

In our patient, a successful management of the angioedema attacks during pregnancy was carried out with TXA plus bemiparin sodium without any side effects being observed. This case demonstrates the importance of an individualized treatment during pregnancy in patients with HAE. There is currently a lack of consensus on LTP for FXII-HAE and clinical trials on FXII-HAE are needed. We expect that future studies can help to clarify the effectiveness and safety of TXA associated with heparin for patients with FXII-HAE during pregnancy.

Conflicts of interest

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

Dr I. Hernández-Martin has received funding to attend conferences/educational events from CSL Behring and Shire (a Takeda company); is/has been a clinical trial/registry sub-investigator for Shire.

Dr R. Cabañas has received funding to attend conferences/educational events from CSL Behring and Shire (a Takeda company); is/has been a clinical trial/registry sub-investigator for Shire and CSL-Behring; and is a researcher from the IdiPAZ program for promoting research activities.

Dr A. Entrala has received funding to attend conferences/educational events from CSL Behring and Shire (a Takeda company); is/has been a clinical trial/registry sub-

investigator for Shire and CSL-Behring; and is a researcher from the IdiPAZ program for promoting research activities.

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

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

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