A Case Report about the Management of Hereditary Angioedema with Normal Complement Levels during Pregnancy

Caso Clínico sobre a Abordagem do Angioedema Hereditário com Complemento Normal Durante a Gravidez

Keywords: Complement C1 Inactivator Proteins/administration & dosage; Hereditary Angioedema Type III; Pregnancy Complications
Palavras-chave: Angioedema HereditárioTipo III; Complicações na Gravidez; Proteínas Inativadoras do Complemento 1/administração e dosagem

Hereditary angioedema (HAE), a rare and underdiagnosed condition characterized by recurrent episodes of mucocutaneous swelling, can lead to poor outcomes.[1,2] *SERPING1* gene mutations dictate quantitative and qualitative changes of serum C1 inhibitor (C1-INH) in HAE type 1 and 2, respectively. Another less prevalent HAE subtype presents with a similar phenotype but normal complement levels (HAE-N) and can arise from different mutations, namely in coagulation factor XII (*FXII*) gene.[3]

During pregnancy, the elevation of estrogen levels may trigger a parallel increase in the number of acute episodes of HAE. Therefore, in order to minimize their frequency/severity, long-term prophylaxis may be required.[2,4] Specific clinical situations may justify prophylaxis – airway involvement, multiple mucocutaneous angioedema episodes per month, multiple severe gastrointestinal/cervicofacial angioedema episodes per year, or if quality of life is compromised.[5] The drugs approved for this effect and considered safe during pregnancy are C1-INH concentrate (first line), tranexamic acid (except during the first trimester) and fresh frozen plasma.[5]

We describe a case where intravenous C1-INH concentrate was safely and effectively used as long-term prophylaxis of HAE episodes in a pregnant woman with HAE-N.

An 18-week pregnant, 24-year-old female with Behcet's disease, presented to the Emergency Department (ED) with isolated periorbital and labial angioedema that started 24 hours earlier, with no identifiable triggers (Fig. 1A). Considering clinical unresponsiveness to hydrocortisone and clemastine, intravenous C1-INH concentrate was administered, with symptom resolution (Fig. 1B). Two weeks later, she developed laryngeal edema following an upper airway tract infection, which was also responsive to C1-INH concentrate. She recalled several angioedema episodes during her adolescence, particularly while on a combined contraceptive pill, throughout a previous pregnancy and since the beginning of the current pregnancy. The patient had no history of respiratory/gastrointestinal complaints or family history of urticaria/angioedema. The laboratory assessment revealed normal C1q, C3, C4 and C1-INH levels, with normal C1-INH function. A genetic study later confirmed a heterozygotic mutation in the *FXII* gene - c.983C>A p. (*Thr328Lys*). Given this finding, it is recommended that first-degree relatives undergo genetic evaluation.

The expected exacerbation during pregnancy and the

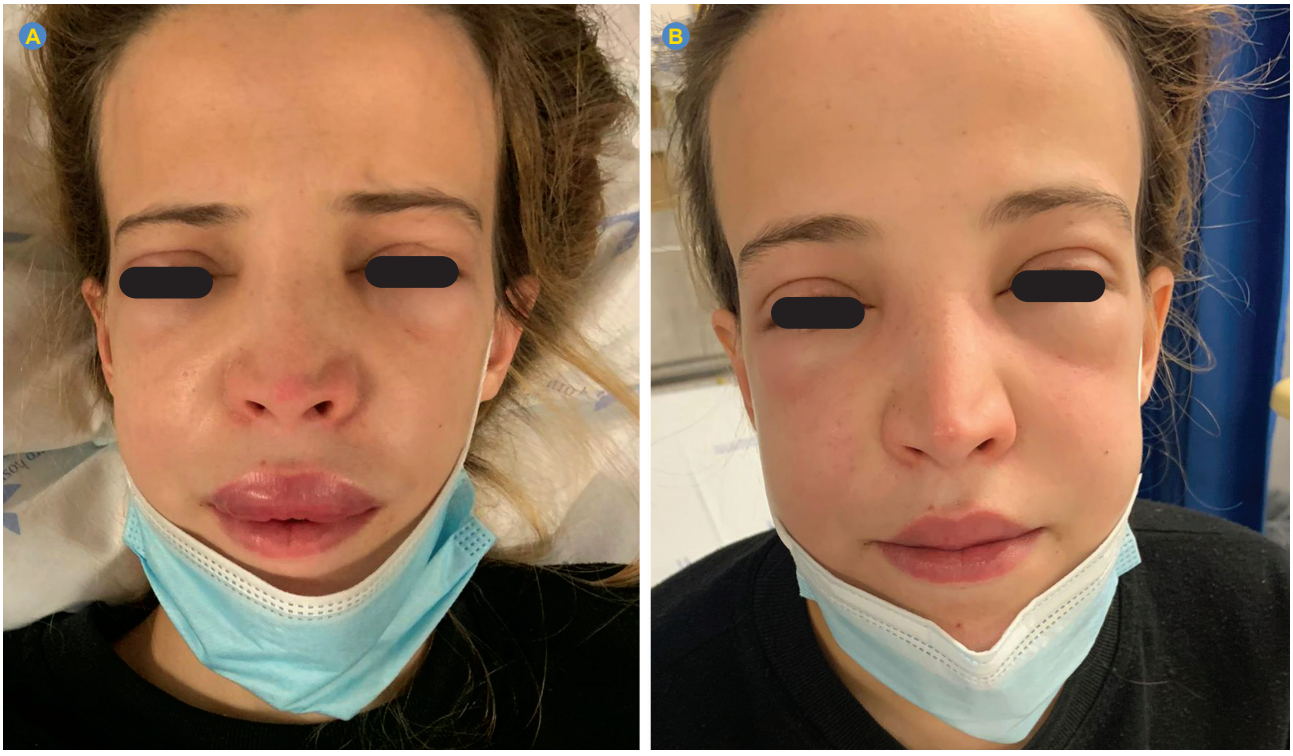

Figure 1 – (A) Initial admission in the emergency department, with periorbital and labial angioedema. The patient's eyes and lips are visibly swollen and inflamed, with no apparent involvement of other areas of the face or body; (B) Angioedema in resolution following administration of intravenous C1-INH concentrate.

recent episode involving the airway prompted the initiation of long-term prophylaxis. Besides being considered a second line agent, the pro-thrombotic risk of Behcet's disease excluded tranexamic acid as an option and, since subcutaneous C1-INH concentrate is not commercially available in Portugal, the intravenous formulation was administered biweekly (20 UI/kg) until the day before delivery. Subsequently, only a few minor episodes of angioedema in the extremities were reported. No short-term prophylaxis was prescribed considering the long-term cumulative protection of prophylaxis. Nevertheless, the concentrate was available for emergencies. She had a vaginal delivery at 36 weeks of gestation, without fetal or maternal complications.

In the reported case, the C1-INH concentrate administered through the intravenous route was effective and safe for the treatment of HAE-N in a pregnant woman, as previously described in a small number of cases in the literature.[4] Future reports may corroborate and reinforce our observations.

A high index of suspicion is crucial to properly identify patients with HAE-N, especially in the ED, as this entity may mimic more common diagnoses, such as allergic angioedema. Prompt referral to a specialist is essential, particularly during pregnancy, where close surveillance by a multidisciplinary team is required.

AWARDS AND PREVIOUS PRESENTATIONS

An abstract about this case report has been presented as an ePoster at the European Academy of Allergy and Clinical Immunology Hybrid Congress, in July 2022. It has not been previously published and it is not under consideration for publication in another journal.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

PATIENT CONSENT

Obtained.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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