ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Short-term prophylactic use of C1 inhibitor and C4 normalization in a patient with hereditary angioedema: a case report

Profilaxia de curto prazo com inibidor de C1 e normalização do C4 em paciente com angioedema hereditário: relato de caso

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ABSTRACT

Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent episodes of subcutaneous or submucosal edema, which are often debilitating. While HAE attacks are generally unpredictable, they can sometimes be triggered by factors such as dental or medical procedures (including surgery), trauma, or stress. In this report, we present the case of a patient with type 1 HAE who required the extraction of her third molars. Human plasma-derived C1 inhibitor administered 2 hours prior to the extraction prevented angioedema attacks during and after the procedure. Additionally, normalization of C4 levels was observed following the administration of the medication.

Keywords: Hereditary angioedema, complement C4, tooth extraction, complement C1 inhibitor protein.

RESUMO

O angioedema hereditário (AEH) é uma doença genética rara, caracterizada por episódios recorrentes de edema subcutâneo ou submucoso, frequentemente incapacitantes. As crises de AEH são geralmente imprevisíveis, embora possam ser desencadeadas por fatores como procedimentos dentários ou médicos (incluindo cirurgias), traumas ou estresse. Neste relato, descrevemos o caso de uma paciente com AEH tipo 1 que necessitou de exodontia dos terceiros molares. Foi administrado o inibidor de C1 derivado de plasma humano duas horas antes do procedimento, prevenindo o surgimento de crises de angioedema durante e após a extração. Além disso, observou-se a normalização dos níveis de C4 após a aplicação da medicação.

Descritores: Angioedema hereditário, complemento C4, extração dentária, proteína inibidora do complemento C1.

Introduction

Hereditary angioedema (HAE) is a rare genetic disease that manifests with recurrent and disabling episodes of subcutaneous or submucosal edema.[1-2] HAE can be considered a syndrome caused by different defects, being classically associated with C1 inhibitor (C1-INH) deficiency, although it can also result from other changes that, in general, promote an increased concentration of bradykinin in blood vessels, leading to greater vascular permeability.[3] Several subtypes of HAE

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are now recognized and have been genetically identified, with their classification considering both genotypes and endotypes.[4-5]

C1-INH plays an essential role in the regulation of different biological systems.[6] It acts by inhibiting key components of the complement system (C1r and C1s), the contact system (factor XII and kallikrein), coagulation (factor XI and thrombin), and the fibrinolytic system (tissue plasminogen activator and fibrinolysin). Thus, C1-INH modulates the formation of vasoactive peptides, principally bradykinin. Proper regulation of bradykinin is crucial in angioedema prevention.[7-8]

HAE attacks are usually unpredictable, although they can be triggered by factors such as dental or medical procedures (including surgery), trauma, or stress. A preventive treatment plan for patients who will experience such situations can reduce the risk of HAE attacks.[1-2]

Recommendations include short-term prophylaxis for patients with HAE prior to invasive medical procedures, especially those involving the upper airway or digestive tract.[1,9] After tooth extraction, more than a third of patients who did not receive short-term prophylactic treatment prior to the procedure have an angioedema attack, 75% of which occur in the first 24 hours.[10] The first-choice medication for prophylaxis is human plasma-derived C1-INH (pdC1-INH).[1,9]

We report the case of a patient with type 1 HAE who underwent tooth extraction and received short-term prophylaxis with pdC1-INH. We measured complement component C4 as a biomarker of the action and efficacy of pdC1-INH.

Case report

A female patient, 41 years of age, who was born and raised in São Paulo and worked in administration, presented with angioedema attacks in the extremities and intense abdominal pain since 1 year of age. She was diagnosed with HAE at the age of 10, with decreased C4 levels. The attacks intensified at 23 years of age, with multiple visits to the emergency room due to abdominal attacks. The attacks usually arose spontaneously or were associated with trauma. At the age of 29, she was tested for C1-INH and C1q, with results of 6 mg/dL (reference value: 21 to 38 mg/dL) and 14 mg/dL (reference value: 10 to 25 mg/dL), respectively, confirming a diagnosis of type 1 HAE. She has a brother who was also diagnosed with type 1 HAE, and her father died from glottic edema, probably related to undiagnosed HAE.

She began treatment with aminocaproic acid in childhood. In 2006, at the age of 23, oxandrolone 5 mg/day was introduced, and episodes of abdominal pain and angioedema in the extremities continued. In 2014, it was decided to replace oxandrolone with danazol 200 mg/day, which resulted in good clinical control. However, in 2016, the patient decided to return to oxandrolone 5 mg/day due to personal preference, presenting only sporadic attacks of angioedema in the extremities. In 2021, she returned to danazol 200 mg/day because it was freely available through the Brazilian Unified Health System. During pregnancy, also in 2021, the attacks worsened, with weekly episodes of angioedema in the extremities, leading to the introduction of tranexamic acid. Currently, the patient is taking a combination of danazol 200 mg/day and tranexamic acid 500 mg/day, with good control of the disease.

The patient was admitted by the oral and maxillofacial surgery team in 2024 for third molar extraction. Her immunology team chose to continue danazol (200 mg/day) and tranexamic acid (500 mg/day), in addition to pre-procedure prophylaxis with pdC1-INH 20 U/kg, administered intravenously. Weighing 78 kg, the patient received 3 vials of the medication (total 1500 U) 2 hours before surgery. No angioedema crisis occurred during or after the procedure.

Complement component C4 levels were measured before and after pdC1-INH was administered. Prior to administration, the patient's C4 levels were low – 14.4 mg/dL (reference value: 15-57 mg/dL). Approximately 11 hours after application, the C4 levels returned to normal – 19.7 mg/dL.

Discussion

HAE, a rare condition that is still poorly understood, is underdiagnosed by many health care professionals. The long interval between

symptom onset and diagnosis, as well as limited access to therapy, increases the risk of death from laryngeal angioedema and disease-related morbidity, negatively impacting the quality of life of patients and their families. Patients with HAE generally see numerous physicians before correct diagnosis, and many of these patients are misdiagnosed. Health care professionals must be aware of the clinical presentation of HAE and the appropriate laboratory screening tests. In addition, allergy and immunology specialists should remain up-to-date on the diagnosis and management of patients with HAE.[11]

We reported the case of a patient with type 1 HAE who required extensive dental surgery and used pdC1-INH as pre-procedure prophylaxis, with no episodes during or after the intervention. Exogenous C1-INH acts on the same targets as endogenous C1-INH, and administration results in higher plasma levels of this protein. The increased level helps regulate systems that interact in a cascade to produce bradykinin during HAE episodes.[12]

Pharmacokinetic studies have demonstrated that exogenous C1-INH results in increased plasma concentrations and functional activity of C1-INH, increased C4 levels, and reduced cleaved high molecular weight kininogen, a marker of bradykinin production.[13-14] In the present case, prior to the procedure, the patient had reduced C4 levels. After using the medication, this parameter normalized, even 11 hours after application, which can be explained by the prolonged half-life of pdC1-INH, which is greater than 30 hours.[15]

C4 measurement before and after pdC1-INH administration may be a useful strategy to determine the optimal dose of pre-procedure medication. There is no consensus in the literature on the most appropriate dose of pdC1-INH for prophylaxis, although a dose of 1000 U or 20 U/kg (both intravenously) may be used for all patients.[1] In this context, assessing C4 levels can serve as an auxiliary parameter in defining the best therapeutic approach.

Short-term prophylaxis is recommended prior to medical, surgical, or dental procedures for patients with HAE, with pdC1-INH considered the first-line medication.[1] In Brazil, the National Health Surveillance Agency has approved 2 forms of pdC1-INH: Berinert® and Cinryze®. Although Berinert® has already been incorporated into the Brazilian Unified Health System, its availability in care centers is still limited. As an alternative for these patients, fresh frozen plasma can be administered before the procedures or the maintenance dose of tranexamic acid or danazol can be doubled 5 days before to 5 days after the procedure. However, these strategies may be less effective, reinforcing the need for adequate access to first-line treatment.[9]

Therefore, individualized therapy, including the possible use of C4 level as a parameter for adjusting the pdC1-INH dose, may contribute to more effective and safe treatment for patients with HAE who are undergoing medical and dental surgical procedures. Recognizing the importance of short-term prophylaxis and improved clinical management of HAE by health professionals are fundamental steps for reducing the morbidity and mortality associated with the disease. Future studies should evaluate the relevance of C4 as a biomarker to monitor adequate plasma C1-INH concentrations.

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