Rev Bras Anestesiol. 2020;70(1):48–50

Brazilian Journal of ANESTHESIOLOGY
Revista Brasileira de Anestesiologia

CASE REPORTS

Peri-operative management of a pregnant patient with hereditary angioedema submitted to a cesarean-section: case report

Teresa Maria Ramos Nunes Estevens [a,*], **Angel Serrano** [a,b], **Solange Amaro** [a], **João Ribeiro** [a]

[a] *Hospital Professor Doutor Fernando Fonseca, Serviço de Anestesiologia, Reanimação e Terapêutica da Dor, Amadora, Portugal*
[b] *Clínica de Santo António (CLISA), Unidade Materno-Infantil, Serviço de Anestesiologia, Lusíadas, Amadora, Portugal*

Received 15 April 2019; accepted 26 October 2019
Available online 7 February 2020

KEYWORDS
Hereditary angioedema;
Anesthetic management;
Pregnant patient;
Cesarean section

Abstract Hereditary angioedema is an autosomal dominant disorder, presenting as sudden and recurring episodes of variable severity of subcutaneous and mucosa edema that may occur spontaneously or in response to triggers. There are three knwon types of hereditary angioedema. The disorder is caused by decrease in the plasma level or change in the functional capacity of C1 inhibitor, with increase in bradykinin and in vascular permeability, and consequent edema. Several measures are required in the perioperative period in order to avoid an acute attack. Prophylaxis should be carried out throughout pregnancy before any surgical procedure, before dental procedures, upon airway handling, on patients with previous episodes of angioedema, and when there are significant changes in volemia. The literature is scarce in regard to the association between hereditary angioedema and pregnancy. We describe a successful case of a pregnant patient with type I hereditary angioedema submitted to a C-section.
© 2020 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

PALAVRAS-CHAVE
Angioedema hereditário;
Abordagem anestésica;
Grávida;
Cesariana

Abordagem perioperatória de grávida com angioedema hereditário submetida a cesariana: relato de caso

Resumo O angioedema hereditário é uma doença autossômica dominante que se manifesta por crises súbitas, recorrentes e de gravidade variável de edema subcutâneo e submucoso, que podem ocorrer espontaneamente ou em resposta a gatilhos. São conhecidos três tipos de angioedema hereditário. A doença é condicionada por diminuição do nível plasmático ou alteração da capacidade funcional do inibidor de C1, com aumento da bradicinina e da permeabilidade vascular e consequente edema. Várias medidas devem ser tomadas no período perioperatório de forma a evitar uma crise aguda. A profilaxia deverá ser realizada durante a

* Corresponding author.
E-mail: teresa.estevens@hff.min-saude.pt (T.M. Estevens).

https://doi.org/10.1016/j.bjane.2020.02.010
© 2020 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

gravidez antes de qualquer procedimento cirúrgico, antes de procedimentos dentários, quando existe manuseamento da via aérea, nos doentes com episódios prévios de angioedema e quando há alterações significativas da volemia. A literatura é escassa no que que diz respeito à associação de angioedema hereditário e gravidez. Descrevemos um caso de sucesso de uma grávida com angioedema hereditário tipo I submetida a cesariana.
© 2020 Sociedade Brasileira de Anestesiologia. Publicado por Elsevier Editora Ltda. Este é um artigo Open Access sob uma licença CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Background

Hereditary Angioedema (HAE) is a rare, autosomal dominant inherited disorder characterized by skin and mucosa edema, caused by a deficit of C1 Complement Inhibitor (C1-INH).[1] The latter is a protein responsible for inhibiting C1 and contact system (kallikrein and factor XII), coagulation (factor XI and thrombin), and fibrinolytic (plasmin and tissue plasminogen activator) proteases. The clinical consequences of C1-INH deficit derive from increase in bradykinin, which through its B2 receptor increases vascular permeability, leading to vasodilation and contraction of non-vascular smooth muscle. Presentation of HAE comprises intermittent episodes of skin and/or mucosa edema, involving the upper respiratory tract, skin and gastrointestinal tract. Three types of HAE have been described: in Type I, the most frequent (85% of cases), the mutation leads to inefficient production of C1 inhibiting protein (< 40% of the normal value); in Type II (15% of cases), protein is produced in normal amounts, but is non-functioning (< 50% of normal activity); in Type III, rare, the mutation is unknown, but probably involves factor XII.[2]

Case report

We describe the case of a 34 year-old primigravida with Type I HAE diagnosed at the age of 19. After recurring episodes of abdominal pain, she was submitted to exploratory laparotomy in 2002 due to suspected appendicitis. In 2004, she presented a sudden episode of face and upper and lower extremity edema without identifiable precipitating factors, having been referred to an immune-allergy consult at the time, when the diagnosis was established, and medication with danazol 100 mg/day was initiated. In 2009, the patient was submitted to an uneventful maxillo-facial surgery for tooth extraction after prophylactic treatment with C1-INH. Anthropometric data were 78 kg weight, 1.70 m height, Body Mass Index of 27 $kg.m^{-2}$. No other routine medication was in use and there were no other associated conditions, except for known allergy to shrimp. No family history of HAE.

Test labs showed C1-INH with very low values (< 0.060) (normal: 0.210–0.390 $g.L^{-1}$), with functional activity after danazol reaching 57% (normal > 68%; low < 40%). The C4 value was low (0.02 to 0.07 $g.L^{-1}$), even out of attacks (normal: 0.1 to 0.40 $g.L^{-1}$). Treatment with danazol was discontinued upon medical advice before becoming pregnant and during pregnancy there were two episodes of extremity edema, with improvement after treatment with C1-INH concentrate.

Elective C-section was proposed because of breech presentation and oligohydramnios at 39 weeks of pregnancy. After careful pre-anesthetic assessment and in compliance with the protocol proposed by the patient's attending physician, she was medicated prophylactically one hour before the C-section with a slow (2–3 minutes) Intravenous (IV) bolus administration of 500 U of C1-INH concentrate. Additionally, she received a bolus administration of 1 g of tranexamic acid followed by infusion of 1 g during a 6-hour period. Patient's blood was typed pre-operatively and two units of frozen fresh plasma were reserved. Icatibant, a bradykinin receptor antagonist, was made available for administration in the event of an acute attack.

Upon arrival to the operating theater, standard monitoring was installed and peripheral venous access was inserted. The neuraxial blockade was chosen, using a combined spinal-epidural technique, with a median approach at the L3-L4 level, with an intrathecal injection of 10 mg of 0.5% bupivacaine, and the sensory block reaching the T10 dermatome. The surgical procedure lasted 40 minutes. The patient remained hemodynamically stable, presenting estimated blood loss of 500 mL during the uneventful intraoperative period. For antibiotic prophylaxis 2 g of cefazolin was administered.

The patient remained 24 hours at the Intensive Care Unit for post-operative recovery, during which another 500 U of C1 inhibitor concentrate were administered. For analgesia, she remained with an epidural infusion using a Drug Infusion Balloon (DIB) with 0.1% ropivacaine at 5 cc/h, and medicated with 1 g IV of paracetamol 6/6 hours and 100 mg of tramadol 8/8 hours as rescue medication. The patient was discharged from hospital after 72 hours, without pain or exacerbation of her disease.

Discussion

There have been few reports on HAE progress during pregnancy, delivery and puerperium. Our case also includes the C-section perioperative management of the patient. One of the potential triggers of HAE attacks is anesthetic and surgical trauma. Moreover, during the progression of the disorder, hormonal factors seem to present a particular importance in triggering and worsening episodes in women, with a considerable variation in frequency according to life phase: childhood, puberty, menstruation, pregnancy and

menopause. Estrogen plays an important role in the synthesis of several genes and proteins, namely of the coagulation cascade and of the bradykinin-kallikrein system, increasing the synthesis of bradykinin and kallikrein and, consequently, vascular permeability. Thus, there is an increased consumption of C1-INH due to estrogen action.[3]

The management of an elective surgery for a patient presenting HAE, should include the following measures to prevent angioedema[2]:

a) Administer androgen derivatives such as danazol, up to 5 to 7 days before surgery;
b) Administer anxiolytic pre-medication (short acting benzodiazepines or opioid on the eve of surgery and at entry to operation theater);
c) Use recombinant C1-INH factor (10–20 $U.kg^{-1}$) prophylactically, 30 to 60 minutes before surgical procedure;
d) Use tranexamic acid (1 g bolus followed by 1 g perfusion in 6 hours), optional as double prophylaxis treatment;
e) Choose the locoregional anesthetic technique over general anesthesia;
f) Have medication available for treatment of severe acute episodes, such as recombinant C1-INH factor (500–1000 U), bradykinin receptor antagonists (icatibant 30 mg SC) or, if the medication is not available, fresh frozen plasma (10 $mL.kg^{-1}$ or one to two units);
g) Promote appropriate analgesic control and post-operative surveillance.

Especially in the case of this patient, drugs used for long-term prophylaxis, such as danazol, were discontinued before pregnancy due to risk of teratogenesis and virilization of female fetus.[1] Pre-anesthetic medication becomes important for these patients to decrease the levels of stress and anxiety, possible attack triggers. However, as the patient was pregnant, opioids or benzodiazepines were not indicated due to risk of placental transfer to the fetus. Prophylactic C1-INH was given in the perioperative period, as recommended. Prophylaxis is not totally effective to prevent attacks, so rescue doses of C1-INH concentrate at the hospital pharmacy and icatibant, a selective antagonist bradykinin Type 2 receptor competitor, administered during acute episodes, should be made available for the patient in the initial 24 hours. During emergencies, and when the medication is not available, fresh frozen plasma can be administered. Occasionally, when C1-INH concentrate is not available, antifibrinolytics, such as tranexamic acid, can be used.[2] Despite little evidence regarding efficacy, Sheffer et al. have shown some benefit in short-term prophylactic treatment. Specifically, for our patient it was administered concomitantly, as C-sections have major hemorrhagic potential, and abrupt changes in volemia can trigger episodes.[4]

Whenever possible, the anesthesiologist should prefer locoregional anesthesia techniques, instead of general anesthesia, to avoid airway manipulation, which could be a major episode trigger, explaining the choice for the combined spinal-epidural technique. Still, devices to manage a difficult airway should be available. There do not seem be contraindications to anesthesia drugs. Although the literature suggests that there is a subjacent pathophysiological mechanism to the angioedema caused by mast cell degranulation induced by opiates, using opioids has not proven to be contraindicated for patients with HAE, even when the neuraxial route is used.[5] However, we chose multimodal analgesia by epidural DIB with local anesthetic associated with intravenous analgesia, using opioids only as rescue therapy. Angiotensin Converting Enzyme (ACE) inhibitors are not recommended because they catabolize bradykinin. Non-steroid anti-inflammatory drugs should be avoided, given they inhibit prostaglandin synthesis, leading to skin mast cell degranulation and possibly triggering angioedema.[6]

Due to the risk of post-operative angioedema episodes, these patients should remain in a permanent surveillance unit during the initial 24–36 hours, under the care of personnel trained in airway management.

In conclusion, although a rare disorder, anesthesiologists should be familiar with the pathophysiology of HAE, as proper planning of anesthetic and surgical procedures is essential. In our case, appropriate crucial care and preventive measures were put in place, and contributed to the positive outcome for a patient with a diagnosis of HAE submitted to C-section.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Tavares M, Gonçalo M, Pais M, et al. Angioedema hereditário e gravidez — um caso clinico. Acta Obstet Ginecol Port. 2013;7:143–5.
2. Rodrigues C, Adrego T, Vieira H. Abordagem perioperatória de doentes com angioedema hereditário. Rev Soc Port Anestesiol. 2018;27:70–7.
3. Bouillet L. Hereditary angioedema in women. Allergy Asthma Clin Immunol. 2010;6:17.
4. Horiuchi T, Hide M, Yamashita K, et al. The use of tranexamic acid for on-demand and prophylactic treatment of hereditary angioedema — a systematic review. J Cutan Immunol Allergy. 2018;1:126–38.
5. Maynard A, Burger C, Schlesinger J. Angioedema: perioperative management. SAGE Open Med Case Rep. 2017;5:1–4.
6. Conceição L, Martinho H, Azenha M. Abordagem anestésica de doente com hereditary angioedema proposto para cirurgia electiva. Rev Soc Port Anestesiol. 2013;22:20–3.