

Angioedema Following Spinal Anesthesia with Bupivacaine in a Pregnant Woman Undergoing Caesarian: A Case Report and Review of Potential Etiologies

Alireza Shakeri, Seyed Mohammad Seyed Alshohadaei*

Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

ARTICLE INFO

Article history:

Received 03 February 2025

Revised 24 February 2025

Accepted 08 March 2025

Keywords:

Angioedema;
Spinal anesthesia;
Bupivacaine;
Hypersensitivity;
Pregnancy

ABSTRACT

Spinal anesthesia with bupivacaine is widely used for cesarean sections but can rarely cause angioedema, a rapid swelling of deep tissues that may lead to airway obstruction. This case report presents the occurrence of angioedema in a pregnant woman with postoperative hyper IgE levels following spinal anesthesia. It highlights the intricate interplay between drug sensitivity, immune dysregulation, and the physiological changes associated with pregnancy. We present a case of a 32-year-old woman with post-operative hyper IgE levels who developed angioedema shortly after getting spinal anesthesia with bupivacaine for a cesarean section. It should be noted that the patient had no prior history of allergic reactions, making the case particularly interesting and challenging. This report's goal is to: 1. Report details of the clinical presentation, management, and outcome of this unusual patient; 2. Investigate the potential etiologies of angioedema, with a focus on the relationship between bupivacaine sensitivity, hyper IgE, and other possible factors; and 3. Highlight the challenges in diagnosis and management when facing angioedema in patients with atypical presentations.

Introduction

Spinal anesthesia with bupivacaine is a common and safe method for cesarean sections. It provides many advantages over general anesthesia, including faster recovery times and reduced risk of some complications [1]. However, like any other medical procedure, spinal anesthesia has its risks, and angioedema is one of the rare risks reported [2]. Angioedema is characterized by rapid swelling of the deep layers of the skin and mucous membranes and can lead to life-threatening airway obstruction if not properly recognized and managed [3]. This report presents and discusses an unusual case of angioedema after spinal anesthesia with bupivacaine in a patient with documented postoperative hyper IgE levels, which is not completely discussed in existing literature. This case highlights the

complex relationship between potential drug sensitivities, immune dysregulation, and physiological changes during pregnancy.

Case Report

A 32-year-old woman, gravida 2, para 1, was candidate for an elective cesarean section at 39 weeks gestation due to baby breech presentation and oligohydramnios. Her medical history was unremarkable, with no prior history of allergies, angioedema, or other significant medical conditions. The patient denied taking any medications prior to the procedure. Preoperative laboratory tests, including a complete blood count and coagulation profile, were within normal limits, including normal blood count.

After getting informed consent, spinal anesthesia was done with a standard aseptic technique. The patient

The authors declare no conflicts of interest.

*Corresponding author.

E-mail address: sinsinasin@gmail.com

Copyright © 2025 Tehran University of Medical Sciences. Published by Tehran University of Medical Sciences.



This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International license (<https://creativecommons.org/licenses/by-nc/4.0/>). Noncommercial uses of the work are permitted, provided the original work is properly cited.

received an intrathecal injection of 12.5 mg of 0.5% hyperbaric bupivacaine with no additive. The procedure was uneventful, and the patient achieved adequate anesthesia. Approximately 10 minutes after the spinal injection, the surgical incision had been made, but just before the incision of the uterus, signs of angioedema were observed by the anesthesia team, which was significant facial edema, with pronounced swelling around the eyes, lips, ears, and tongue, symmetrically.

Management

Noting the potential for a rapid airway compromise, we quickly secured the patient's airway. Endotracheal intubation was done with a rapid sequence induction. The patient was preoxygenated with 100% oxygen via a facemask, and intravenous propofol (140 mg) was administered for induction, followed by 100 mg succinylcholine for neuromuscular blockade. A 7 mm endotracheal tube was successfully placed, confirming secured airway access. (Figure 1).

Immediately following intubation, the patient was placed on mechanical ventilation. Peak inspiratory pressures were slightly high, ranging from 25 to 30 cm H₂O, showing increased airway resistance likely due to

possible edema. For managing the angioedema, the patient received intravenous dexamethasone (8 mg) and diphenhydramine (50 mg). Intravenous epinephrine was prepared for managing further symptoms, but it was not administered as the patient's symptoms began to mitigate and stabilize with the initial treatment. The patient was transferred to the intensive care unit (ICU) for close monitoring of her respiratory status under mechanical ventilation and hemodynamic stability, and with the following consultations, other tests were ordered. IgE results were reported high (98, normal up to 30), with a normal range of C3, C4, and CH50 levels. Other lab tests were in the normal range. Anti-cardiolipin, anti-dsDNA, anti-CCP, ANA, and anti-b2 microglobulin were not remarkable. It should be noted that the hospital lab does not measure C1 esterase inhibitor, so all we could do was ask to measure the C3, C4, and CH50.

Over the subsequent 24 hours stay in the ICU, the patient's angioedema symptoms gradually disappeared. She was successfully extubated. (Figure 2) The patient's postoperative course was otherwise unremarkable. She was discharged home on postoperative day 5 in good condition, with her healthy newborn.



Figure 1- Rapid onset of facial and airway swelling necessitated intubation shortly after the patient developed pronounced edema around the eyes, lips, ears, and tongue.



Figure 2- The patient immediately after extubation, with residual swelling around the eyes and lips.

Discussion

This case describes the difficult challenges in diagnosing and managing acute angioedema in perioperative settings, especially when a patient shows atypical features during anesthesia and the presence of postoperative hyper IgE levels with no prior history of allergic reactions. The lack of prior allergic symptoms in this patient makes a classic IgE-mediated allergic reaction unlikely, although it could not be impossible.

The elevated IgE levels in this patient suggest careful assessment. Hyper IgE is generally described with serum IgE levels much higher than the normal range and is often associated with parasitic infections, allergies, and some primary immunodeficiency diseases [4]. However, the patient's normal complement levels, specifically normal C4 and C1 esterase inhibitor levels, are unlike the diagnosis of hereditary angioedema (HAE), which is often accompanied by recurrent angioedema attacks and complement abnormalities [5].

For better understanding, angioedema can be categorized into different types [3]:

1. **Hereditary Angioedema (HAE): Type I HAE** is described by low levels of C1-INH,
2. **Type II HAE:** normal or high levels of a dysfunctional C1-INH protein.
3. **Acquired Angioedema:** Similar to hereditary forms, but happens with underlying conditions or medications.
4. **Allergic Angioedema:** Triggered by an allergic substance like food or medications.

With the clinical presentation and laboratory findings, several potential etiologies for this patient's angioedema deserves attention:

1. **Bupivacaine Sensitivity:** Bupivacaine is known generally as a safe drug; severe hypersensitivity reactions, including cases of angioedema, have not been reported [6].
2. **Non-IgE-Mediated Mast Cell Activation:** Angioedema can also happen through non-IgE-mediated mechanisms. Certain drugs, physical stimuli, and even psychological stress can directly activate mast cells and cause the release of histamine and other inflammatory mediators that increase vascular permeability and cause tissue swelling [7]. It's possible that bupivacaine, even in the absence of a true allergic reaction, might have triggered mast cell degranulation in this patient, especially in the setting of pregnancy where physiological changes in vascular tone and permeability are already present [8].
3. **Pregnancy-Related Factors:** The unique pregnancy physiological state is described by profound hormonal and immunological

alterations. As the pregnancy progresses, there's a slow increase in vascular permeability and a shift in the balance of Th1 and Th2 cytokines, which make immune responses. While the exact mechanisms relating pregnancy to an increased risk of angioedema are not fully explained, it should be noted that these physiological changes would have played an important role in this pregnant patient and predisposed her to develop angioedema after exposure to bupivacaine [9-10] (Figure 3).

4. **Unidentified Triggers or Underlying Conditions:** Despite prior patient evaluation, it could be possible that an unidentified trigger, such as a latent infection, a previously unrecognized drug sensitivity, or an underlying medical condition, caused the angioedema. While the patient rejected using any medications prior to the operation, the possibility of exposure to over-the-counter drugs or herbal supplements could not be entirely precluded. Besides, some underlying conditions, such as mastocytosis or autoimmune disorders, despite the patient's normal history and laboratory findings, could potentially predispose individuals to angioedema.
5. **Idiopathic Angioedema:** In some cases, despite complete investigation, no specific cause for angioedema could be found. This is called idiopathic angioedema. Definitely it is frustrating from a diagnostic perspective, but it's important to identify this possibility when other potential etiologies have been carefully considered and ruled out [11].

Management of Angioedema During Anesthesia

The occurrence of angioedema, particularly bradykinin-mediated forms like HAE, presents challenges during anesthesia. These conditions are not mediated by histamine and are therefore unresponsive to epinephrine or antihistamines [15]. The occurrence of bradykinin-mediated angioedema presents major challenges in anesthesia due to the potential triggers associated with many anesthetic agents. The hereditary form of this condition follows an autosomal dominant inheritance pattern, suggesting that an affected parent has a 50% chance of passing the condition to their offspring. Unlike typical allergic reactions and anaphylactic shocks, this condition is not mediated by histamine. Instead, it affects the complement system and bradykinin, which is why it is unresponsive to epinephrine or antihistamines. The swelling and most affected areas usually disappear spontaneously within 72 hours [16].

Preparedness and Immediate Actions

Planning for the management of bradykinin-mediated angioedema is very important because symptoms may start hours after the triggers. Standard treatments like epinephrine, corticosteroids, and antihistamines are

ineffective. The treatment plan should point to the bradykinin pathway. Confirmation of the diagnosis through proper testing is necessary for targeted treatment. Anesthesiologists who do not have access to specific drugs could administer fresh frozen plasma (FFP) and find it helpful. The primary treatment should address the C1-INH deficiency through the administration of plasma-derived or recombinant C1-INH17. A bradykinin antagonist, such as Icatibant, can be effective [3].

Understanding the Role of C1-INH

Bradykinin-mediated angioedema is primarily caused by a deficiency in C1-INH and can lead to excessive bradykinin and non-pitting edema. (Table 1) illustrates the lab tests that are used to diagnose Type I and Type II HAE. (Figure 4) shows the bradykinin pathway involved

in angioedema. In Type I HAE, the levels of C1-INH (a protein that regulates blood clotting) and C4 (a complement protein involved in the immune system) are both low, which provides the excessive production of bradykinin and causes non-pitting edema. In Type II HAE, C1-INH levels are normal or high, but its function is low, which also causes excess bradykinin production and non-pitting edema [17]. The acquired form of bradykinin-mediated angioedema can be observed in certain diseases and shows the same characteristics as hereditary forms. While angioedema can also be a symptom of allergic reactions, it is not the predominant feature, and these cases often show additional dermatological and hemodynamic symptoms [18] (Figure 5).

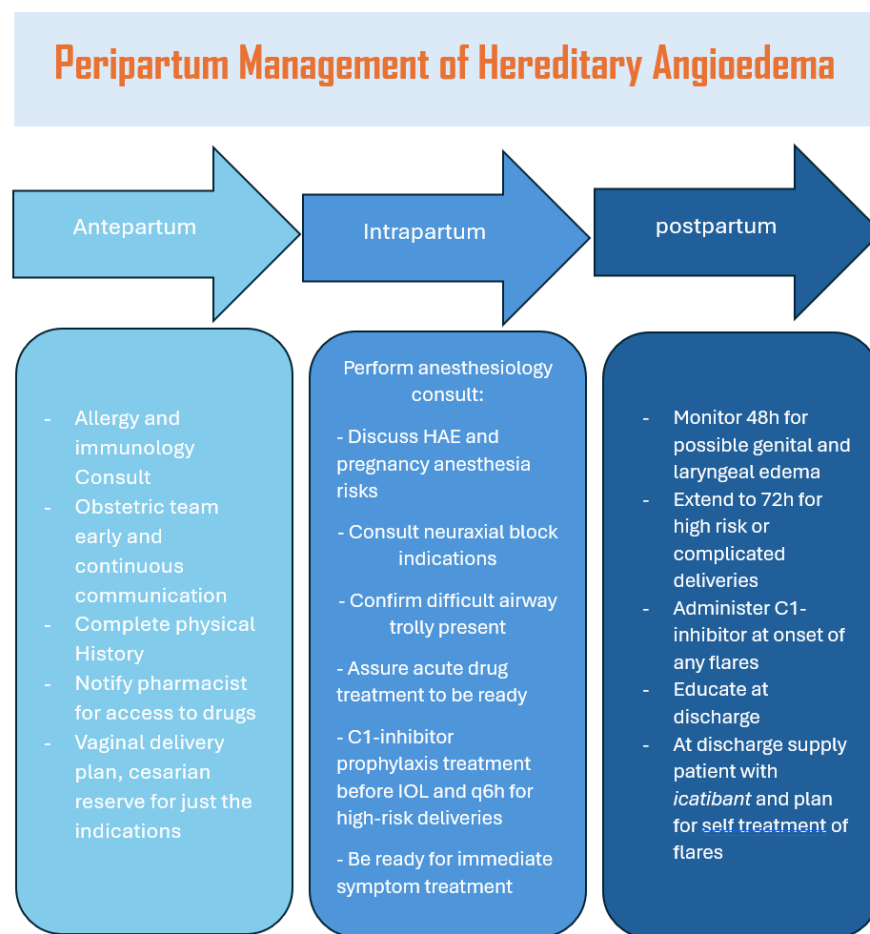


Figure 3- Key anesthetic considerations for peripartum management of hereditary angioedema (Adapted from Caballero et al., 2012; Betschel et al., 2019; Maurer et al., 2018) [12-14].

Table 1- Lab tests in Type 1 and Type 2 hereditary Angioedema

Tests to confirm HAE Types I and II		
Lab test	Type I	Type II
C4 concentration	Low	Low
C1-INH concentration	Low	Normal/High
C1- INH function	Low	Low

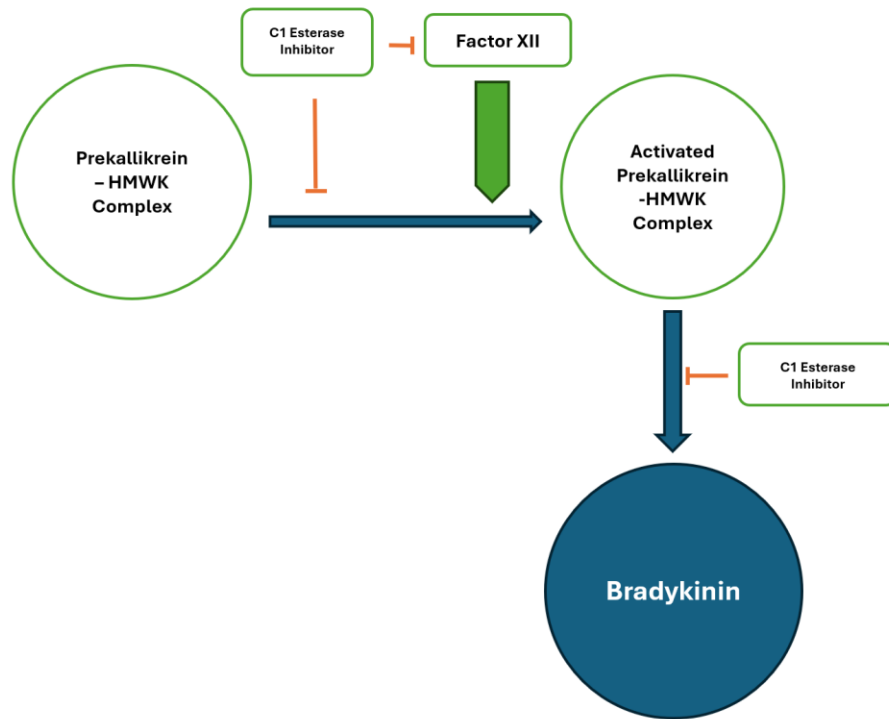


Figure 4- Bradykinin pathway Angioedema.

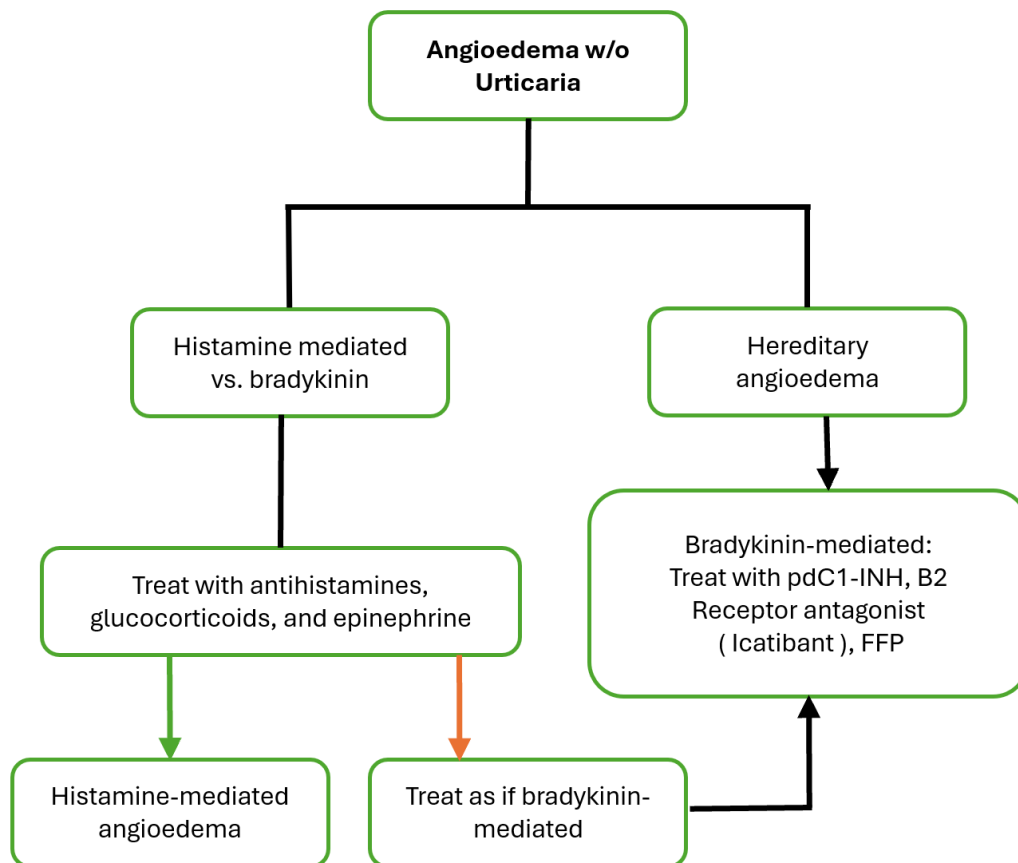


Figure 5- Angioedema Treatment

Conclusion

To summarize, the management of bradykinin-mediated angioedema during anesthesia requires prompt identification and targeted intervention. Typically, there is a window of three to four hours from the onset of symptoms to full manifestation. During this period, patients may experience severe respiratory distress and facial edema post-surgery. Immediate action, including the administration of at least two units of FFP, is recommended to reduce the acute symptoms.

By focusing on the bradykinin pathway and addressing the C1-INH deficiency, anesthesiologists can successfully manage this challenging condition and ensure patient safety and optimal outcomes.

References

- [1] Stewart J, Gasanova I, Joshi GP. Spinal anesthesia for ambulatory surgery: current controversies and concerns. *Curr Opin Anaesthesiol*. 2020;33(6):746-52.
- [2] Volk T. [Complications of spinal anesthesia and how to avoid them]. *Anesthesiol Intensivmed Notfallmed Schmerzther*. 2010;45(3):188-95.
- [3] Misra L, Khurmi N, Trentman TL. Angioedema: Classification, management and emerging therapies for the perioperative physician. *Indian J Anaesth*. 2016;60(8):534-41.
- [4] Pate MB, Smith JK, Chi DS, Krishnaswamy G. Regulation and dysregulation of immunoglobulin E: a molecular and clinical perspective. *Clin Mol Allergy*. 2010;8(1):3.
- [5] Sinnathamby ES, Issa PP, Roberts L, Norwood H, Malone K, Vemulapalli H, et al. Hereditary Angioedema: Diagnosis, Clinical Implications, and Pathophysiology. *Adv Ther*. 2023;40(3):814-27.
- [6] Cohen B, Glosser L, Saab R, Walters M, Salih A, Zafeer-Khan M, et al. Incidence of adverse events attributable to bupivacaine liposome injectable suspension or plain bupivacaine for postoperative pain in pediatric surgical patients: A retrospective matched cohort analysis. *Paediatr Anaesth*. 2019;29(2):169-74.
- [7] Kalambay J, Ghazanfar H, Martes Pena KA, Munshi RA, Zhang G, Patel JY. Pathogenesis of Drug Induced Non-Allergic Angioedema: A Review of Unusual Etiologies. *Cureus*. 2017;9(8):e1598.
- [8] Gangakhedkar GR, Kulkarni AP. Physiological Changes in Pregnancy. *Indian J Crit Care Med*. 2021;25(Suppl 3):S189-s92.
- [9] Abu-Raya B, Michalski C, Sadarangani M, Lavoie PM. Maternal Immunological Adaptation During Normal Pregnancy. *Front Immunol*. 2020;11:575197.
- [10] Chair, II, Binkley KE, Betschel SD. Hereditary Angioedema in Pregnancy. *Obstet Gynecol Surv*. 2021;76(9):566-74.
- [11] Jackson CW, Pratt CM, Rupprecht CP, Pattanaik D, Krishnaswamy G. Mastocytosis and Mast Cell Activation Disorders: Clearing the Air. *Int J Mol Sci*. 2021;22(20).
- [12] Caballero T, Farkas H, Bouillet L, Bowen T, Gompel A, Fagerberg C, et al. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. *J Allergy Clin Immunol*. 2012;129(2):308-20.
- [13] Betschel S, Badiou J, Binkley K, Borici-Mazi R, Hébert J, Kanani A, et al. The International/Canadian Hereditary Angioedema Guideline. *Allergy Asthma Clin Immunol*. 2019;15:72.
- [14] Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. *Allergy*. 2018;73(8):1575-96.
- [15] Zeerleder S, Levi M. Hereditary and acquired C1-inhibitor-dependent angioedema: from pathophysiology to treatment. *Ann Med*. 2016;48(4):256-67.
- [16] Valerieva A, Nedeva D, Yordanova V, Petkova E, Staevska M. Therapeutic management of hereditary angioedema: past, present, and future. *Balkan Med J*. 2021;38(2):89-103.
- [17] Smolinska S, Antolín-Amérigo D, Popescu FD. Bradykinin Metabolism and Drug-Induced Angioedema. *Int J Mol Sci*. 2023;24(14).
- [18] Macy E. Practical Management of New-Onset Urticaria and Angioedema Presenting in Primary Care, Urgent Care, and the Emergency Department. *Perm J*. 2021;25.