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Traumatic Angioedema as a Complication of a Hyponatremic-Induced Seizure

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Abstract

Angioedema is a known side effect of angiotensin-converting enzyme inhibitors (ACE-I). However, trauma precipitating angioedema is a rare event. We detail a case of trauma-induced angioedema in a patient taking an ACE-I. Specifically, a patient presented to the emergency department (ED) having suffered a seizure from symptomatic hyponatremia; later, the patient precipitously developed angioedema requiring nasotracheal intubation. Herein, the mechanisms and treatments for angioedema are discussed. Acute angioedema is important to the emergency medicine physician because quick recognition, regardless of its precipitant can stave off untoward complications, possible respiratory failure and airway emergencies.

Keywords

Angioedema, Airway Emergency, ACE-I, Hyponatremia

1. Introduction

Angioedema—a potentially life-threatening condition—is caused by two distinct mechanisms: mast cell degranulation and subsequent histamine release or activation of the kallikrine-kinin cascade [1]. Multiple precipitants of angioedema have been described. For example, food and medications may trigger a reaction caused by immunoglobulin E-mediated hypersensitivity, which can manifest on a continuum from acute urticaria to a generalized life-threatening anaphylactic reaction [2]. Hereditary angioedema (HAE) is an autosomal dominant disease caused by low levels of the plasma protein C1 inhibitor and bradykinin release [3]. Angiotensin-converting enzyme inhibitors (ACE-I) are commonly encountered precipitants for acquired angioedema that also trigger bradykinin release [4]. A less common etiology for activation of the kallikrine-kinin axis and subsequent angioedema

is trauma [5], which is highlighted in this case report. Specifically, a patient with symptomatic hyponatremia and taking ACE-I suffered a seizure and later facial trauma, leading to life-threatening oral and airway angioedema. Astute recognition of the development of angioedema—via medications, trauma or otherwise—by the emergency physician can help guide emergent treatment and avoid unfavorable outcomes.

2. Case Presentation

A 74-year-old Caucasian female presented to the emergency department via emergency medical services after having a generalized tonic-clonic seizure witnessed by her husband. The patient was post-ictal upon arrival. Her past medical history included hypertension, hyperlipidemia, type-2 diabetes mellitus, and osteoarthritis. Over the preceding weeks, she had been struggling with persistent hypertension and hyponatremia. Her primary-care physician had started her on chlorthalidone and was adjusting her metoprolol dose while maintaining her long-standing dose of lisinopril.

Upon presentation, the patient's vital signs were as follows: blood pressure of 156/59 mm/Hg, heart rate of 96 bpm, and respirations of 14 breaths per minute. Her temperature was 37˚C, blood sugar was 96 mg/dL and she had a Glasgow coma score of 14 as the patient was slow to respond to questions. Her head and neck exam was significant for an abrasion on the right side of her tongue with associated swelling and blood seen at the corners of her mouth. The rest of the exam was unremarkable: no focal deficits were noted, heart, lung and abdominal exam were normal, as was an examination of her skin and extremities. Laboratory studies were significant for a serum sodium of 123 mg/dL, a lactate of 4.8 mg/dL, and an elevated white blood cell count of $13.9 \times 10^3/\mu L$.

Shortly after our initial evaluation, the patient's tongue swelling worsened, and the patient's mental condition rapidly declined, portending hypoxia stemming from progressing angioedema. The decision was made to secure the patient's airway utilizing nasotracheal intubation. Targeting a presumptive histamine-driven pathway, the patient received 0.3 mg of 1:1000 epinephrine intramuscularly, 125 mg of methylprednisolone, 50 mg of diphenhydramine, and 20 mg of famotidine via intravenous injection. This provided limited effect. Addressing a bradykinin-driven cause, one gram of intravenous tranexamic acid was given. In preparation for intubation, she was pretreated per standard methods (pre-oxygenation through a face mask, glycopyrrolate to reduce secretions, and nebulized lidocaine and etomidate for comfort and sedation, respectively) and an awake first-pass nasotracheal intubation was successfully completed; the patient was admitted to the intensive care unit with a secure airway.

The patient was extubated on day two of her admission. Her low sodium level was slowly corrected with fluid restriction and the patient's electroencephalogram showed no epileptic activity. Advanced imaging found an 11 mm meningioma, although not a seizure focus. Chlorthalidone and lisinopril were both discontinued in

favor of losartan. She was instructed to stop taking lisinopril and other ACE-I drugs, given appropriate follow-up with her primary physician, and safely discharged from the hospital.

3. Discussion

Angiotensin-converting enzyme inhibitor-induced angioedema (ACE-I) presents itself as swelling without urticaria in the head and neck regions [4]. Problems arise when significant swelling involves the tongue and the upper airways, leading to signs of airway obstruction; this is manifested by hoarseness, inability to manage secretions or swallow saliva, increased work of breathing and stridor *en route* to airway collapse. The presence of urticaria leans more toward an allergic cause via mast cell degranulation and histamine release and thus can help guide treatment [6]. However, the treatments for type I hypersensitivity reactions are not effective e.g., steroids and antihistamines nor recommended for ACE-I angioedema because the mechanism of action is different [7].

The general causes of angioedema have been discussed in detail previously [8] [9]. Medications are common causes and chief among these are ACE-I, which can induce significant angioedema in a spontaneous and potentially life-threatening manner. Trauma itself is less often noted to be a cause of angioedema. Key to this discussion is the prevalence of ACE-I induced angioedema in the United States, which is 0.1% - 0.3% for people using ACE-I for blood pressure management [6]. Cases of angioedema triggered by facial trauma have been reported for patients taking ACE-I and rarely, angiotensin receptor blocking agents, which underscores two points regarding our assessment of traumatic angioedema [10]-[13]. First, minor trauma (say simply using a bag-mask-valve) in this patient population can trigger angioedema and second, disruption of the renin-angiotensin axis for targeted blood-pressure control seems to put patients at greater risk for angioedema relative to other blood pressure control modalities, e.g., β-blockers. Specifically, ACE-I blocks the conversion of angiotensin II from angiotensin I, thus inhibiting vasoconstriction by the renin-angiotensin axis. However, ACE-I also inhibits the degradation of bradykinin into metabolic inactive components (**Figure 1**) and it is this pathway which leads to localized accumulation of bradykinin and increased adverse reactions in a select population. Overall, ~2% of people on ACE-I will experience some adverse reaction over their lifetime. ACE-I prevents the breakdown of bradykinin, leading to localized accumulation [14].

Regarding injury-induced angioedema, trauma accelerates the clotting cascade, including Factor XIIa, plasminogen, and kallekrine to produce bradykinin-mediated swelling [10]-[13] (demonstrated by pathway 1). Patients taking ACE-I have an increase in relative bradykinin and this can produce massive responses from traumatic injury.

The major consequence of angioedema, as described here, is life-threatening airway obstruction. Swelling of lips and face can be seemingly benign and necessitates close observation. However, swelling of tongue and soft tissues of the neck

including the vocal cords can be life-threatening [10]. The larynx represents the narrowest part of the upper airway and the bottleneck for most of the difficult airways encountered in the emergency department [15]. Mucosal swelling in the pharynx region reduces the reduction of the airway lumen and thus the success of first-pass intubation. Because of this risk, an airway should be established immediately with little hesitation before swelling progresses to complete obstruction of the airway lumen, which is likely to require a surgical airway.

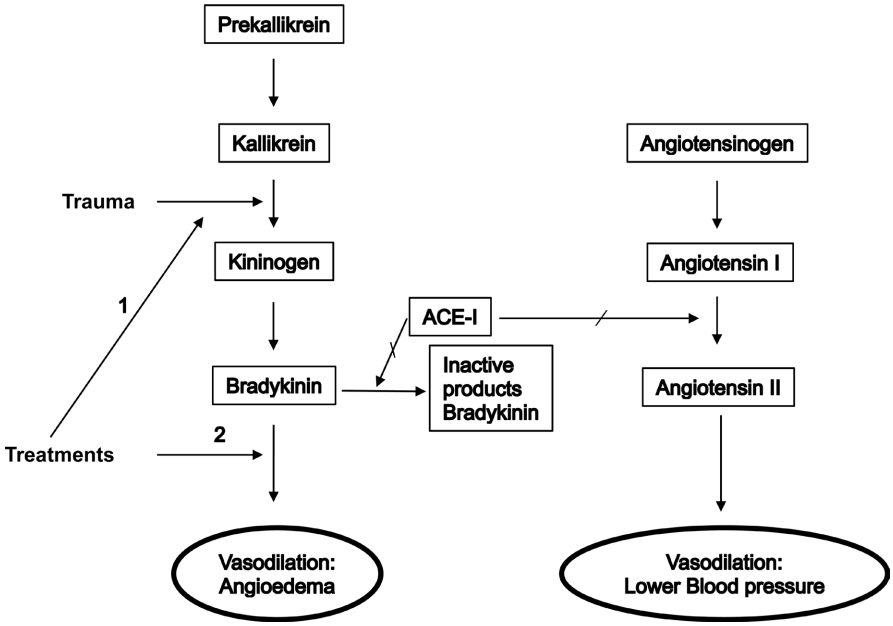

Figure 1. Kallikrein-Bradykinin axis showing activation of bradykinin from ACE-I as well as treatments pathways 1 and 2 (see text). ACE-I blocks production of angiotensin II from angiotensin I as well as degradation of bradykinin.

Several signs and symptoms indicate edema in the upper airway, such as increased respiratory rate, use of accessory muscles of respiration, and even stridor. As oxygen saturation will deteriorate only in the later stages of respiratory failure, it is dangerous to rely on a good oxygen-saturation value alone; end-tidal CO_2 is a more sensitive indicator of impending respiratory collapse and should be used as an adjunct in monitoring all patients with any airway concerns [15]. In case a patient has signs of impaired breathing due to laryngeal edema (as confirmed with laryngoscopy), intubation might be necessary. In milder cases, admitting a patient for close observation and repeating the laryngoscopy after several hours can be sufficient.

Alternative to other causes of angioedema (histamine or hereditary), the treatments for bradykinin-induced angioedema target the upstream molecules in the production pathway. Tranexamic acid (TXA) can reduce plasmin creation and activation of Factor XII (**Figure 1**, pathway 1). Plasma is a treatment option that theoretically contains the anti-bradykinin molecules that are deficient in ACE-I medicated angioedema patients [16]. Other pharmacological treatments developed

for treatment of hereditary angioedema have been studied for acquired angioedema (**Figure 1**, pathway 2). The logic here is that the mechanism for both pathways leads to similar outcomes; thus proven treatments for HAE might theoretically work for ACE-I induced angioedema by targeting bradykinin generation.

Icatibant is a C1-esterase inhibitor for HAE and works by blocking bradykinin at its receptor thus decreasing vasodilation and vascular permeability but has largely been shown to be ineffective for ACE-I angioedema [17]. Ecallantide is a kallikrein inhibitor effective for HAE but has no clinically proven effectiveness on ACE-I angioedema in several blinded placebo-controlled studies [18]. We also note, no blinded placebo-controlled studies exist showing the efficacy of fresh frozen plasma or TXA over placebo; much of the literature regarding both of these generic treatments is in the form of retrospective studies or case studies and case series [16].

4. Conclusions

Reports of bradykinin-induced angioedema precipitated by trauma are rare and to our knowledge, this is the first report of angioedema secondary to direct airway trauma caused by a hyponatremic seizure and necessitating intubation. The traumatic incident was due to a seizure from acute-on-chronic hyponatremia. Other cases of direct injury typically involve perioperative trauma induced by intubation, head and neck surgery, carotid endarterectomy, for example, as the cause of ACE inhibitor-related angioedema. Our patient deteriorated rapidly, requiring quick action to secure the patient's airway. This recognition and proper treatment targeting bradykinin-induced angioedema led to improvement over the first 24 hours.

Understanding and recognition of the overlap of disease processes and the targeted therapies available can make a meaningful difference in patient outcomes. We note importantly, angioedema can occur via a number of inciting events [19] [20], which underscores the importance of its early recognition. As in the case above, suspected causes must be identified early to initiate targeted therapies. ACE-I-induced angioedema can occur even in patients who have taken the medication for several years. This was true of our hyponatremic patient. In addition to rash and other common side effects, we reaffirm previously published assertions that angioedema risk should be thoroughly discussed with patients prior to selecting ACE-I medications. Following a triggered incident of angioedema, patients should start alternative anti-hypertensive medications. As seen in this case, the patient was prescribed losartan. Angiotensin receptor blockers do carry a small risk of angioedema recurrence, but the incidence is still quite low overall [21]. Therapy choices should be decided through shared decision-making.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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