



# CAN'T INTUBATE, CAN'T OXYGENATE: A RARE CASE OF A DIFFICULT AIRWAY DUE TO NONHEREDITARY ANGIOEDEMA

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**SUMMARY** – Angioedema is a form of allergic mediated by histamine and non-allergic mediated by bradykinin and can be lethal if not recognized and treated promptly. This case demonstrates the proper diagnosis of and intervention in rapid onset severe angioedema.

A 68-year-old male came to the emergency department with a complaint of dyspnea that started two hours before. He had type II diabetes, chronic kidney disease and several different antihypertensive medications, including an ACE inhibitor for hypertension. During physical examination, the patient was hypertensive, tachycardic, tachypnoic, and edematous. During his stay in the ED he was treated with a combination of corticosteroids, antihistamines and epinephrine, but the patient's edema and dyspnea worsened and his oxygen saturation started to deteriorate with a progression of skin edema. Intubation was not possible due to the large edema of the tongue, so a tracheotomy was done. An ampule of icatibant was administered and rapid regression of the edema, along with the stabilization of the patient's vital signs, followed after five minutes. The patient was discharged home after five days with a recommendation of discontinuing the ACE inhibitor.

While non-hereditary angioedema is not a rare condition, emergency physicians should be adequately educated about it.

**Key words:** *angioedema, bradykinin, icatibant-B2 bradykinin receptor antagonist*

## Introduction

Hereditary angioedema (HAE) is a rare hereditary disease, an autosomal dominant disorder.<sup>1</sup> It is a form of non-allergic angioedema mediated by bradykinin and can be lethal if not recognized and treated on time. It is defined by a deficiency of functional C1 esterase inhibitor (C1-INH), due to either C1-INH consumption (type 1) or inactivation (type 2).<sup>1</sup> Type 1 is most common, occurring in 85% of patients. It is characterized by decreased production of C1-INH, which results in reduced functional activity to 5-40% of normal value. Type 2 occurs in 15% of cases and C1-INH is

dysfunctional in normal or elevated levels.<sup>1</sup> In addition to hereditary causes, a form of nonhereditary acquired angioedema (AAE) mediated by bradykinin is known.<sup>2</sup> Both HAE and AAE can be life-threatening. AAE is angioedema with normal CI-INH (previously called type 3, or non-type 1, non-type 2 HAE) and a normal complement C4 levels. Specific genetic mutations have been linked to factor XII, plasminogen gene and angiotensin-1 in AAE. Patients with unknown mutations are classified as unknown.<sup>1</sup> A useful test to differentiate AAE from HAE is C1q protein, which is normal in HAE and low in AAE. The management of HAE includes on-demand therapy options like plasma and recombinant C1-INH for intravenous infusion, an ecallantide—an inhibitor of kallikrein administered subcutaneously, and icatibant—a bradykinin  $\beta_2$  receptor antagonist administered subcutaneously.<sup>1</sup>

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Effective agents for long-term prophylaxis are C1-INH enzyme replacement and a monoclonal antibody against kallikrein (lanadelumab, administered subcutaneously).<sup>1</sup> It is typical in angioedema mediated by bradykinin that the classic therapy (antihistamines, corticosteroids and adrenaline) is completely without effect. Clinical features are often associated with elevated bradykinin levels, which lead to increased vascular permeability and the development of angioedema.<sup>3,4</sup> There is increasing data in the literature on the effectiveness of HAE treatment (not only type I and II, but also AAE) related to angioedema caused by drugs for the treatment of hypertension from the ACEI group, such as in the case of our patient.<sup>3,5,6</sup> The number of patients who are taking ACEI therapy to treat hypertension is on the rise. Therefore, it is no surprise that the number of different side effects has doubled in the last decade from 24% to 49%, which is explained by more regular reporting of side effects by doctors and higher awareness of possible side effects in patients.<sup>2,3,4</sup> Regardless of the form and etiology, timely intervention is crucial. This case demonstrates the proper diagnosis and prompt intervention in a scenario of rapid onset angioedema of unknown etiology, presumed to be nonhereditary, induced by angiotensin-converting enzyme inhibitors (ACEI).

### Case report

A 68-year-old adipose (BMI 38kg/m<sup>2</sup>) male came to the emergency department (ED) with a chief complaint of dyspnea that started approximately two hours before. He had a long history of arterial hypertension (8 years), type II diabetes (5 years), chronic kidney disease stage G3b/A3 (2 years) and two separate episodes of dyspnea with facial and oral edema and hoarseness, successfully treated before two and five years with a combination of corticosteroids, antihistamines and epinephrine. He had four different antihypertensive medications in his therapy, including an ACEI -ramipril 5 mg for 8 years. The time of first ACEI intake was 2,920 days. During the physical examination, the patient was hypertensive (blood pressure 180/95mmHg), tachycardic (100/min), tachypnoic, and edematous. No murmurs, gallops, or rubs were auscultated. Abdomen was soft, symmetric, adipose and non-tender without distention. No masses, hepatomegaly, or splenomegaly were noted. No focal defi-



Figure 1. Swollen and enlarged tongue occupying oral cavity.



Figure 2. Whole-body edema.



Figure 3. On the second day of admission, there was no face and body swelling.

cits were appreciated on neurological examination. The initial laboratory results revealed elevated liver enzymes (AST 58 U/L, ALT 63 U/L) glucose (12.5 mmol/L) and creatinine (198umol/L). The chest X-ray showed normal size and shape of the chest wall and the main structures in the chest. He was admitted to the ORL Department with a presumptive diagnosis of

an angioedema. At admission, systemic corticosteroid therapy in high doses (500mg infusion) was started, all previous medications were discontinued and the patient was monitored during the night for signs of clinical recovery. The patient's edema and dyspnea worsened over eight hours and his oxygen saturation started to rapidly deteriorate. Intubation was not possible due to edema of the tongue, so a tracheotomy was performed to secure an airway (Figure 1). Rapid progression of the oedema development and additional therapy was indicated (Figure 2). An ampule of icatibant (B2 bradykinin receptor antagonist) was administered subcutaneously and rapid regression of the edema followed, along with the stabilization of the patient's vital signs. On the second day of the admission, clinical improvement was obvious and there was no face and body swelling (Figure 3). The levels of transaminases began to improve, so the patient was discharged after five days with a recommendation to discontinue the ACEI and other drugs from the Renin-Angiotensin-Aldosterone System (RAAS). The time from the onset of symptoms to settling down of the edema was 34.0 hours. Additional follow-up with an immunologist was included. HAE types I and II were excluded with C1q inhibitor levels within normal range (34.5 mg / dL, normal to 39) and with normal complement level C4 (0.4 g / L).

## Discussion

The unpredictability of HAE is manifested primarily in the emergency department (ER) where patients first appear with various symptoms, including swelling of different parts of the body, allergic nonspecific symptoms, swelling of the tongue and abdomen. Regardless of present-day diagnostic possibilities, if this rare but potentially life-threatening hereditary disease is not considered an option, and most of its symptoms are not timely and adequately recognized, the patient is not referred for further treatment.<sup>1</sup> Acquired angioedema can occur with various lymphoproliferative diseases, as well as with the use of therapeutic drugs for hypertension, especially from the group of ACE inhibitors, as in our case.<sup>1,3</sup>

According to a 2015 study by Bas *et al.*, patients who had induced angioedema while taking ACEI, if treated with bradykinin inhibitor icatibant, had a three-times faster recovery and felt five times better

than with a standard glucocorticosteroid and antihistamine therapy.<sup>5</sup> According to Nosbaum *et al.*, there were 76 patients (60.5% men; middle-aged,  $64.4 \pm 13.7$  years) with angioedema provoked by ACEI treatment registered in France from 2008 to 2013.<sup>6</sup> All of them had normal levels of C1 inhibitors, and other possible causes of angioedema were ruled out. Angioedema (AE) was located on the tongue (49.3%), larynx (22.7%), abdomen (5.6%), and extremities (4.0%). The average time of ACEI intake was 589 days (1 to 5,400).<sup>6</sup> Of the 76 patients, 20 (26.3%) received icatibant. Since 58.3% of the patients were treated in the ICU, the efficiency of icatibant was obvious and there were no deaths. The average time from the onset of symptoms to the settling of the edema was ( $36.0 \pm 12.0$  hours), which is longer than in the Bas *et al.* study and can be explained by more intensive symptomatology of patients in the Nosbaum *et al.* study.<sup>5,6</sup>

The patient in question had previously manifested on two occasions Quincke's edema, which led to his hospitalization at ORL, where he was administered a supportive classic corticosteroid therapy in high doses of 500 mg (iv), after which his symptoms ceased. However, when the patient was hospitalized for the third time there was no clinical response to corticosteroid therapy and due to worsening clinical condition and progressive edema with inability to intubate, he was tracheotomized and administered with icatibant, to which he promptly responded and withdrawal of the edema occurred, as in other studies.<sup>5,6</sup> Mild cases of ACEI-AE may respond to antihistamine or corticosteroid therapy, but moderate to severe cases do not. Withdrawal of ACEI is the key to managing this condition.<sup>6,7</sup>

Medical experts in the ER have to be educated on the appropriate management of angioedema.<sup>7-9</sup> Angioedema may be primarily manifested by recurrent episodes of Quincke's edema (as in our patient), but also by edema of subcutaneous tissue, edema of the mucous membranes of the upper respiratory tract and the gastrointestinal tract, with great variability in occurrence, usually without urticaria, rash or itching.<sup>10,11</sup>

In our first study in Croatia we analyzed the frequency and treatment of bradykinin-induced angioedema as a cause for emergency treatment. Bradykinin-induced AE was the leading cause in the investigated group (31.5%).<sup>11</sup> Angioedema resulting from bradykinin-induced AE (AAE and HAE) was the

main reason for emergency arrivals of patients.<sup>11</sup> Our previously study confirmed a poor response to glucocorticoid, antihistamine and epinephrine treatment in severe AE, and the need for new therapeutic options to improve the resolution of AE. Advances in the treatment of HAE and case reports of patients with ACEI-AE treated with C1-INH concentrate or bradykinin receptor antagonist show that they may be a safe and efficacious therapeutic option.<sup>11</sup>

In conclusion, emergency physicians should be adequately educated on when to suspect nonhereditary angioedema, and how to manage the rapid onset of airway obstruction it causes in the most severe cases. Emergency departments should also be equipped with the medications used in its management.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

The authors state that this manuscript has not been published previously and is not currently being assessed for publication by any journal other than the *Acta Clinica Croatica*. The authors disclose that they did not receive any financial support for the study. No proprietary interest is involved in the study.

### Consent

Informed consent was obtained from the patient for the publication of this case report and the accompanying images.

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## Sažetak

RIJEDAK SLUČAJ OTEŽANOG DIŠNOG PUTA ZBOG STEČENOG ANGIOEDEMA  
- BEZ MOGUĆNOSTI INTUBACIJE I OKSIGENACIJE*Đ. Delalić, V. Borčić i I. Prkačin*

Angioedem može biti posredovan histaminom te se radi o alergijskom, no može biti posredovan bradikininom te se radi o nealergijskom angioedemu. Ukoliko se ne prepozna ili liječi pravovremeno može biti smrtonosan. U ovome radu prikazujemo slučaj pravovremene dijagnoze i intervencije nealergijskog angioedema 68-godišnjeg muškarca koji je došao u hitnu službu sa simptomima dispneje koja je započela dva sata ranije. Od pridruženih bolesti liječio se zbog šećerne bolesti, kronične bubrežne bolesti i hipertenzije zbog čega je godinama uzimao lijek iz skupine ACE-inhibitora. Na fizičkom pregledu pacijent je bio hipertenzivan, tahikardan, tahidispnoičan i edematozan ne samo u području lica i tijela. Tijekom boravka u Hitnoj službi liječen je kombinacijom kortikosteroida, antihistamina i epinefrina, no edem i dispneja su progredirali kroz nekoliko sati, a zasićenost kisikom počela se pogoršavati. Intubacija nije bila moguća zbog izrazitog otoka jezika, stoga se pristupilo traheotomiji radi očuvanja dišnog puta. Obzirom na i dalje oticanje jezika i tijela postavljena je sumnja na bradikinski angioedem te je primijenjena ampula icatibanta nakon čega se prati promptna regresija edema jezika i tijela, sa stabiliziranjem vitalnih znakova pacijenta. Pacijent je otpušten kući peti dan s preporukom isključenja ACE inhibitora. Liječnici u hitnim službama trebaju biti upoznati s mogućnostima dodatnog liječenja nealergijskog angioedema.

Ključne riječi: *angioedema, bradykinin, icatibant-antagonist B2 bradikinskog receptora*