

Clinical Communications

Idiopathic nonhistaminergic angioedema successfully treated with ecallantide, icatibant, and C1 esterase inhibitor replacement

Mark C. Stahl, DO^a, Caitlin K. Harris, DO^b,
Sulaiman Matto, MD^b, and Jonathan A. Bernstein, MD^c

Clinical Implication

- This article reports the first successful treatment of idiopathic nonhistaminergic angioedema with prophylactic C1 esterase inhibitor and affirms other reports of beneficial acute hereditary angioedema therapies.

TO THE EDITOR:

Most immunologically mediated angioedema can be broadly divided into 2 types: histamine mediated and nonhistaminergic, which, for many types, has been demonstrated to be bradykinin mediated. Recent advances have led to a better understanding and more treatment options for bradykinin-mediated forms. Ecallantide, a plasma kallikrein inhibitor, and icatibant, a selective bradykinin β_2 receptor antagonist, have been approved by the US Food and Drug Administration for treatment of acute attacks of hereditary angioedema (HAE). C1 esterase inhibitor (C1INH) replacement therapy exists for both acute and prophylactic treatment of HAE. Use of these medicines outside the realm of HAE has not been well studied. Here we describe a case of idiopathic nonhistaminergic angioedema (INHA) that demonstrated a good response to various HAE treatment options.

A 32-year-old Pacific Islander woman with a medical history of mild asthma and polycystic ovarian syndrome presented to the emergency department (ED) with progressive facial, tongue, and lip swelling. She stated that she had no allergic triggers, concomitant urticaria, or pruritus. She had no family history of similar episodes or unexplained deaths. Two prior angioedema episodes had occurred, one with isolated periorbital swelling bilaterally and another that involved tongue swelling with globus. In the ED, the patient was given diphenhydramine 50 mg, ranitidine, prednisone 60 mg, racemic epinephrine, and two 0.3-mg intramuscular doses of epinephrine; she was observed for a few hours and discharged with an epinephrine autoinjector and oral prednisone after her swelling was noted to be static. Approximately 8 hours later, the patient returned to the ED and was admitted. Despite methylprednisolone 125 mg every 8 hours and diphenhydramine 50 mg every 4 hours intravenously, her symptoms progressively worsened; approximately 24 hours after her initial presentation, the patient had difficulty swallowing and breathing, which required intubation. Her C4, C1INH, and C1INH function levels were normal. Attempting to treat with fresh frozen plasma made the swelling worse. Her swelling abated gradually over 4 days, and no causative etiology could be found. Subsequently, swelling episodes occurred every 6 to 7 days, and the patient required 2 additional intubations over a 3-month period, despite similarly aggressive management with epinephrine, antihistamines, and steroids.

Medical care was delivered through a single hospital that has an ED, intensive care unit, and step-down unit. Laryngeal edema was confirmed by anesthesia via fiber-optic laryngoscopy before each intubation (Figure 1). Laboratory values at each admission were normal (Table 1), and testing for allergic, infectious, rheumatologic, and neoplastic etiologies was negative. Prophylaxis with danazol 200 mg twice daily was ineffective and poorly tolerated. High-dose H1-H2 blockers (fexofenadine 180 mg and ranitidine 150 mg, both twice daily) combined with montelukast proved similarly ineffective. Further prophylactic attempts with progesterin and then with sulfasalazine failed, but tranexamic acid and hydroxychloroquine provided some modest benefit. Treatment of acute attacks of facial, tongue, and laryngeal swelling with ecallantide and icatibant prevented further intubations; if administered within 4 hours of the onset of swelling, she typically responded to these medicines with noticeably reduced swelling within 1 to 2 hours. Approximately 15% of the time she would require a second dose of either one of these medicines within 12 hours. During the early course of her illness, difficulty in obtaining ecallantide led to delays in administration. Although her initial intubation lasted 4 days, her subsequent 2 intubations were shortened to 48 hours and 24 hours due to successively earlier ecallantide administration with each intubation.

Approximately 1 year after initial presentation, the patient presented to the ED with face and tongue swelling after self-administering icatibant at home. Ecallantide was administered in the ED and resulted in anaphylaxis (flushing; difficulty breathing, with oxygen saturation in the mid 80% range; hypotension) approximately 5 minutes after administration. After this event, additional acute therapeutic options were considered, and, on subsequent admission, C1INH (Berinert, CSL Behring; King Of Prussia, Pa) was administered at 20 U/kg, which improved her facial, tongue, and hand swelling within 2 hours. Given this response, a trial of prophylaxis with C1INH (Cinryze, Viropharma; Exton, Pa) was initiated at 1000 U every Monday and Friday. Before initiating C1INH prophylaxis, the patient was using icatibant 5 to 7 times per month and spent 5 days in the hospital in addition to 7 ED visits during the preceding 4 months. For 6 months after initiation of prophylaxis, she had used icatibant an average of 1.5 times per month and was hospitalized for 2 days due to issues unrelated to her illness. She was able to stop the tranexamic acid and hydroxychloroquine as well.

HAE types I/II are characterized as recurrent episodes of hand, face, and abdominal swelling, with a quantitative or qualitative deficiency in C1INH. Frequent laryngeal attacks with this condition are uncommon. Patients with type III HAE, now referred to as HAE with normal complement with or without a genetic mutation,¹ have exacerbations associated with estrogens. Because this patient had no family history of angioedema and normal complement levels, she would be more accurately described as having INHA based on her lack of response to antihistamines, corticosteroids, and epinephrine. The underlying mechanism of this condition is poorly understood, but bradykinin is suspected as a possible mediator. Therapeutic options for acute attacks in patients with this condition have previously been limited, although several case reports of the use of ecallantide^{2,3} and icatibant^{4,5} appear in the literature. Prophylactic options have

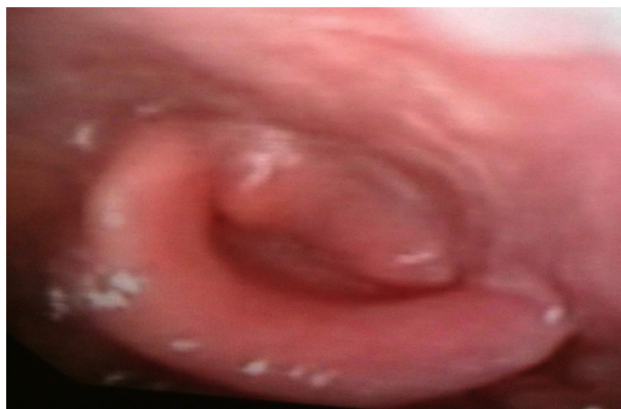


FIGURE 1. Edema of the epiglottis and arytenoids before intubation.

TABLE I. Patient's laboratory values

Test	Value	Reference range
C4 (mg/dL)	26-47	11-41
C1 inhibitor (mg/dL)	12-21	11-26
C1 inhibitor function (%)	95-100	>68 (normal)
Factor XII gene mutation	Negative	Negative
C1q (mg/dL)	6.4-9.2	5.0-8.6
Tryptase (ng/mL)	1-5	2-10
IgG (mg/dL)	1150	700-1600
IgM (mg/dL)	76.6	40-230
IgA (mg/dL)	164	70-400
IgE (IU/mL)	19.3	0-100

similarly been limited, but some investigators have recommended using tranexamic acid.^{6,7}

This patient with INHA was initially successfully treated with icatibant and ecallantide, which suggests a bradykinin-mediated process. The mechanism that explains why this patient would benefit from C1INH in lieu of her having normal C1INH function is unclear but could involve its multiple regulatory functions in the contact, complement, and fibrinolytic pathways. For HAE III, Bork et al⁸ described 7 patients treated with C1INH for more than 63 attacks, with 6 reporting very or moderately effective responses. A similar response may be present in patients with INHA, and future research may demonstrate that INHA and HAE with normal C1INH share specific physiological mechanisms that will help to further classify these patients.

To our knowledge, this is the first case report of INHA treated with prophylactic C1INH replacement. Further studies into INHA are needed, but, if more traditional and less expensive therapies have been exhausted, we believe that treating similar patients with these HAE-specific medications should be considered and may be beneficial.

^aAllergy/Immunology, Wright-Patterson Medical Center, Wright-Patterson Air Force Base, Ohio

^bBoonshoft School of Medicine, Department of Medicine, Wright State University, Dayton, Ohio

^cDivision of Immunology/Allergy Section, Department of Internal Medicine, University of Cincinnati, Cincinnati, Ohio

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Corresponding author: Mark C. Stahl, DO, Division of Allergy, Department of Medicine, Allergy, Wright-Patterson Medical Center, 4881 Sugar Maple Dr, Wright-Patterson AFB, OH 45433. E-mail: docstahl@yahoo.com.

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