

Acute Presentation of Undiagnosed Hereditary Angioedema of the Larynx: Averting Death

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Case Report

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Abstract

Hereditary angioedema (HAE) differs from histamine-mediated angioedema in that it is resistant to steroids and antihistamines. Laryngeal attacks of this condition, if not diagnosed timely, carry a mortality rate up to 34%. Rarely, this disease goes undiagnosed until late adulthood and presents a life-threatening episode that poses a management challenge to the emergency physician. We report the case of a 48-year-old man who presented to the emergency department with progressive breathing difficulty two hours after consuming a carbonated drink. Clinical examination revealed supraglottic edema. He did not respond to steroids or antihistamines and required emergency

tracheostomy to secure the airway due to failed intubation. Absence of symptoms such as itching or urticaria and inadequate response to steroids pointed to hereditary angioedema. Low complement factor 4 levels with low C1 esterase inhibitor functionality confirmed the diagnosis. This case report highlights the fact that delayed presentation of HAE can be life threatening and the diagnosis should be considered in all non-atopic adult patients with angioedema.

Keywords: Hereditary angioedema, airway obstruction, tracheotomy, C1 esterase inhibitor, airway management

Introduction

Angioedema is not difficult to diagnose for the emergency physician. Even though it can be life-threatening at times, its management is usually straightforward. Hereditary angioedema (HAE), however, is a rare entity, and relevant history might not be forthcoming in an emergency setting. Airway involvement has the propensity to become life-threatening, because unlike histamine-induced angioedema, HAE does not respond to antihistamines or corticosteroids. Upper airway symptoms are reported in 64-84% of cases (1). The attacks are usually self-limiting, even though the symptoms may take up to 72-120 hours to resolve (2). Patients with unrecognized C1 esterase inhibitor deficiency angioedema (C1-INH-HAE) who develop airway oedema have been reported to have a 15-34% mortality rate (3, 4). Availability of expert airway management teams can be the deciding factor in patient survival in such scenarios.

Case Presentation

A 48-year old gentleman presented to the emergency room with difficulty in breathing two hours after consuming a carbonated drink. He had multiple similar episodes in the past, the first being six years ago. None of these episodes required hospitalization, and symptoms would resolve over a few hours. These episodes were not associated with abdominal pain, the involvement of the extremities or genitalia. There was no history of itching, urticaria, or rash, nor were similar episodes reported among his immediate relatives.

The patient had increased work of breathing, use of accessory muscles of respiration, and a respiratory rate of 32 per minute. There was no edema of the lips or tongue. Fiberoptic laryngoscopy showed significant edema of the supraglottis (Figure 1). Hydrocortisone (200 mg) and chlorpheniramine (20 mg) were administered intravenously to re-

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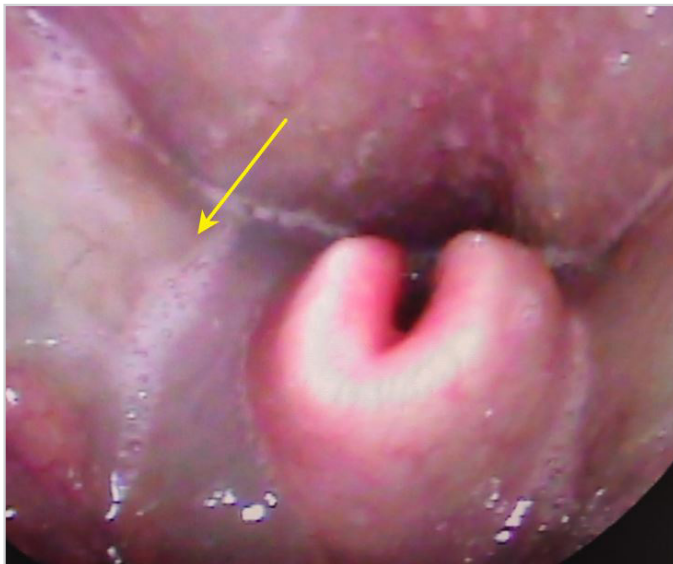


Figure 1. Laryngoscopic image showing significant edema of the aryepiglottic folds (arrow)

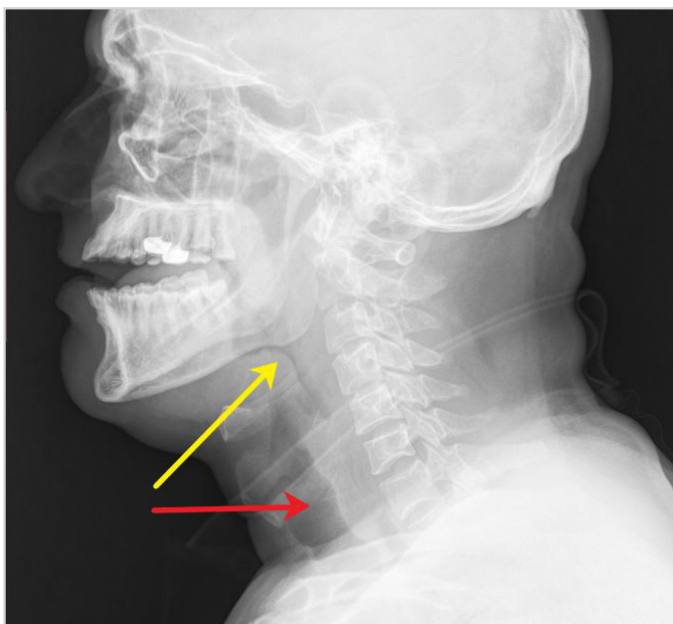


Figure 2. Lateral radiograph of the neck showing edema and narrowing of the supraglottic airway (yellow arrow) with a normal subglottis and trachea (red arrow)

duce the edema. The clinical picture was of angioedema with self-limiting similar past episodes. A lateral neck radiograph was obtained, which ruled out subglottic involvement (Figure 2). Since the patient did not respond to steroids and antihistamines,

Main Points

- All angioedema is not histamine-mediated and might not respond to antihistamines or steroids.
- Emergency teams should have excellent airway management skills and specialist back up.
- Evaluate non-atopic patients with angioedema for hereditary angioedema.
- Screening of relatives might be useful in early detection.

we suspected a non-atopic nature of the disease, such as HAE. Oxygen saturation showed a decreasing trend despite humidified oxygen at 5 L/hr along with nebulized adrenaline, mandating invasive airway management. Trial of intubation with tracheotomy was planned as backup, and the patient was shifted to the operation room. Fiber-optic bronchoscopy guided intubation was attempted but failed as the patient could not tolerate the procedure. A tracheotomy was done under local anesthesia in sitting posture while mask ventilating.

Later, he was investigated for C1 esterase inhibitor (C1-INH) and complement factor 4 (C4) levels. The results were available only a couple of days later and showed C1-INH function level of 8% (normal >68%) and a C4 level of 0.07 g/L (normal: 0.14-0.54 g/L) (5).

The principal differential diagnosis was acquired angioedema (AAE). AAE can be a manifestation of underlying malignancies, especially lymphoproliferative disorders. Our patient, however, had no clinical features suggestive of this. The vast majority of HAE presents in the second decade, and report recurrent abdominal pain. AAE presents from the fourth decade onward and abdominal symptoms are rare. Both the age of onset, and the lack of abdominal pain were not in favor of HAE. However, the patient's daughter had recurrent episodes of abdominal pain for which she was hospitalized at the age of nine. Based on the presence of ascites, she was empirically prescribed antitubercular therapy at the time. Yet she continued to have intermittent symptoms. This prompted us for further investigation. Her functional C1-INH levels were 23% (normal >68%), and C4 levels were 0.07 g/L (normal: 0.14-0.54 g/L) which confirmed that we were, indeed, dealing with a case of HAE.

We did not have immediate access to C1 esterase concentrates. The airway edema subsided over the next 24 hours, and the patient was decannulated 48 hours post tracheotomy and discharged. The need for prophylactic treatment to prevent future episodes was explained. Informed consent was obtained from the patient for the publication of this report.

Discussion

Hereditary angioedema is a rare entity. Airway involvement in HAE has the propensity to become life-threatening because, unlike histamine-induced angioedema, it does not respond to antihistamines or corticosteroids. Depending upon the levels of C1-INH function, HAE is classified into three types: HAE-1 in which there is an absolute deficiency of C1-INH, HAE-2 in which only functional deficit is present, and HAE-3 where the defect is due to other mutations (6, 7).

HAE should be considered when a patient presents with recurrent angioedema without urticaria and with a family history of similar attacks. A certain grade of suspicion bears crucial significance for correct diagnosis and treatment (3). Once a clinical diagnosis of angioedema is made, tests to determine the concen-

trations of C4 and C1-INH and the latter's functional activity should be done. HAE due to C1 esterase deficiency can be diagnosed with 98% specificity when serum C4 levels are subnormal and there is low activity of C1-INH (5, 8).

The primary differential diagnosis to be excluded is AAE, which can be secondary to hematologic malignancy (9). Patients who present at an advanced age need to be investigated to rule out AAE (9, 10). The presence of B-symptoms, clinical examination, peripheral blood morphology, and immunoglobulin levels may be useful on a case to case basis (10).

The recommended medical treatment for acute episodes includes C1-INH concentrates and antagonists of bradykinin receptors (4). Newer drugs and formulations, including subcutaneous C1-INH, oral kallikrein inhibitors, and gene therapy have also been described (3). However, it has to be borne in mind that these drugs might take up to 30 minutes to act, and hence if the patient presents in distress, management of the airway might require invasive methods (11). Up to 10% of the patients with acute HAE, required tracheotomy or intubation before the diagnosis was established, according to a series (12).

All angioedema is not histamine-mediated and will not respond to antihistamines or steroids. Hence, Emergency physicians and Otolaryngology teams should have excellent airway management skills with adequate backup facilities as mortality rates associated with undiagnosed HAE are high. Patient education regarding trigger avoidance is essential as is making available prophylactic medication to these patients.

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