The Journal of Emergency Medicine, Vol. 43, No. 2, pp. 391–400, 2012

0736-4679/$ - see front matter

ELSEVIER

doi:10.1016/j.jemermed.2011.06.125

Clinical Reviews

DIAGNOSIS AND MANAGEMENT OF HEREDITARY ANGIOEDEMA: AN EMERGENCY MEDICINE PERSPECTIVE

Joseph J. Moellman, MD* and Jonathan A. Bernstein, MD†

*Department of Emergency Medicine and †Clinical Research, Department of Internal Medicine, Division of Immunology/Allergy Section, University of Cincinnati College of Medicine, Cincinnati, Ohio

Reprint Address: Joseph J. Moellman, MD, Department of Emergency Medicine, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Cincinnati, OH 45267-0563

☐ **Abstract—Background: Hereditary angioedema (HAE) is a rare and often debilitating condition associated with substantial morbidity and mortality in the absence of appropriate intervention. An underlying deficiency in functional C1-inhibitor (C1-INH) protein induces a vulnerability to unchecked activation of the complement, contact, and coagulation/fibrinolytic systems. The clinical consequence is a pattern of recurring attacks of non-pitting, non-pruritic edema, the urgency of which varies by the affected site. Laryngeal edema can escalate rapidly to asphyxiation, and severe cases of abdominal swelling can lead to hypovolemic shock. Objectives: This report reviews the emergency diagnosis and treatment of hereditary angioedema and the impact of recently introduced treatments on treatment in the United States. Discussion: Until recently, emergency physicians in the United States were hindered by the lack of rapidly effective treatment options for HAE attacks. In this article, general clinical and laboratory diagnostic procedures are reviewed against the backdrop of two case studies: one patient presenting with a known history of HAE and one with previously undiagnosed HAE. In many countries outside the United States, plasma-derived C1-INH concentrate has for decades been the first-line treatment for acute attacks. The end of 2009 ushered in a new era in the pharmacologic management of HAE attacks in the United States with the approval of two new treatment options for acute treatment: a plasma-derived C1-INH concentrate and a kallikrein inhibitor. Conclusion: With access to targeted and effective treatments, emergency physicians are now better equipped for successful and rapid intervention in urgent HAE cases.** © 2012 Elsevier Inc.

☐ **Keywords—hereditary angioedema; C1-inhibitor; non-pitting, non-pruritic edema; HAE attack; bradykinin; kallikrein**

INTRODUCTION

Despite its description more than a century ago by William Osler and the discovery of its biochemical abnormality by Donaldson and Evans in 1963, hereditary angioedema (HAE) has been poorly studied and suboptimally managed in the United States (1–3). The estimated prevalence of HAE is between 1:10,000 and 1:50,000 in the general population, suggesting a range of 2000–30,000 affected individuals in the United States (3). The disorder seems to occur in equal proportions among all ethnic groups and races, and correlations between genotype and phenotype have not been identified (4). Epidemiological data on the number of emergency department (ED) treatment visits by patients with HAE have not been published. But 63 patients with HAE who responded to an online survey of their clinical status reported an average of 4.7 ED visits annually. About one-fifth of these patients were treated for anaphylaxis (5). For the emergency physician, acute exacerbations of HAE symptoms (attacks) have presented a particular challenge due to a multitude of factors, including the relative infrequency of presentation, an inadequate understanding of HAE pathophysiology, and, until recently, a lack of effective treatments in the United States (3,4,6,7).

RECEIVED: 2 September 2010; FINAL SUBMISSION RECEIVED: 25 February 2011;
ACCEPTED: 1 June 2011

With recent advances in novel therapies, the emergency physician is now in a position to provide the initial treatment of acute exacerbations of HAE. It is essential that the emergency physician understand both the pathophysiological and clinical aspects of HAE. We report two HAE cases from our ED experience, one patient who presented with a known history of HAE and one with previously undiagnosed HAE.

CASE REPORTS

Case 1 (Known History of HAE)

A 28-year-old man with a known history of HAE was brought to the ED with increasing facial edema and neck swelling. The patient stated that the swelling began approximately 12 h before arrival, after he accidentally fell, striking his nose. His medical history consisted of HAE characterized by recurrent acute abdominal symptoms and subcutaneous symptoms (i.e., edema) that would resolve over a period of several hours. His only medication for HAE was danazol 200 mg twice a day. He had no known allergies to drugs or foods. A review of systems was positive for mild abdominal pain, which felt like his prior HAE abdominal attacks. He had no stridor or difficulty swallowing.

The patient's vital signs upon arrival consisted of a temperature of 36.9 °C (98.4°F), pulse of 73 beats/min, blood pressure 147/87 mm Hg, respiratory rate of 14 breaths/min, and oxygen saturation of 97% on room air. His general appearance was that of a well-appearing man of stated age with obvious facial and upper neck swelling, but without signs of respiratory distress (e.g., intercostal retraction, accessory muscle use, or change in voice). Upon examination, the head and neck had significant well-demarcated edema to the subcutaneous tissues of the right mandibular and paranasal regions without ecchymosis. The oropharynx had no evidence of edema. The lungs were clear to auscultation, and the heart was regular without murmur, rub, or gallop. The abdominal examination consisted of mild mid-abdominal tenderness without any evidence of ecchymosis or signs of trauma. The skin was warm and dry without any evidence of edema. The neurological examination was normal.

The patient was monitored and, despite the infusion of aminocaproic acid (Amicar; Xanodyne Pharmaceuticals, Inc., Newport, KY) and fresh-frozen plasma (FFP), his facial edema had progressed slightly, although he exhibited no signs of respiratory distress. The patient was admitted to the intensive care unit, subsequently nasotracheally intubated for 48 h, and finally successfully extubated when his edema subsided. He was discharged to home the following day without complications.

Case 2 (Previously Undiagnosed HAE)

A 22-year-old woman was brought to the ED complaining of localized regions of swelling to her upper and lower extremities for the previous 4 h. There was no history of trauma, fever, or exposures to new medications, unusual or new food groups, or environmental contaminants such as airborne chemicals. The affected regions were somewhat painful and non-pruritic. She had no significant symptoms of a past medical history of HAE with the exception of recurrent attacks of localized edema to her extremities, which had been treated with corticosteroids and antihistamines by her primary care physician. She listed no regular medications or drug allergies. Her review of systems was remarkable for recurrent abdominal pain that resolved over 24–48 h and for which she had never sought care. Because she was adopted, she had no knowledge of family history of illness.

The patient's vital signs consisted of a temperature of 36.5 °C (97.8°F), pulse of 88 beats/min, blood pressure of 120/76 mm Hg, respiratory rate of 14 breaths/min, and oxygen saturation of 98% on room air. In general, she was a well-appearing, well-nourished female in no serious distress. The physical examination was remarkable for various non-erythematous, well-demarcated, firm regions of edema of approximately 5–10 cm in size at various sites on the upper and lower extremities. The oropharynx was without edema, the lungs were clear, and the abdominal examination was without tenderness or any significant findings.

This patient's ED course consisted of the administration of a corticosteroid and an antihistamine, without improvement. Her condition remained stable without any new regions of edema or airway compromise. After discussion with the patient's primary care physician, a consulting allergist recommended that a C4 level be obtained, after which the patient could be discharged from the ED with follow-up and further evaluation.

The patient subsequently followed-up with the allergy consultant as an outpatient and was found to have a C4 level < 25% and a low C1-INH level. She was diagnosed with HAE (Type I) and placed on androgen therapy for prophylaxis. However, due to the side effects of the androgens and her relatively infrequent number of attacks, the patient declined further prophylactic therapy with androgens.

DISCUSSION

Background

Hereditary angioedema is an autosomal dominant disorder characterized by recurrent episodes of relatively abrupt onset of transient non-pitting and non-pruritic