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Clinical Reviews

ANGIOEDEMA: ETIOLOGY, PATHOPHYSIOLOGY, CURRENT AND EMERGING THERAPIES

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☐ **Abstract—Background: Angioedema (AE) is characterized by nonpitting edema of the dermis and subcutaneous layers. The most common sites of involvement are the tongue, lips, face, and throat; however, swelling can also occur in the extremities, genitalia, and viscera. Life-threatening airway swelling can also occur. AE may be allergic or nonallergic. The overall lifetime incidence of AE is reported to be as high as 15%. Objective: This article summarizes the etiology, pathophysiology, and current treatment of several forms of nonallergic AE (including hereditary, acquired, and idiopathic AE) and focuses on angiotensin-converting enzyme inhibitor–induced angioedema (ACEi-AE), which is responsible for 30%−40% of all AE seen in United States emergency departments. Discussion: Although the triggers, which are primary biologic mechanisms, and treatments for ACEi-AE may differ from those of the hereditary and acquired forms of AE, the clinical effects of ACEi-AE are mediated through a shared pathway, the kallikrein-kinin system. Thus, although current therapeutic options for ACEi-AE are limited, recent advances in the treatment of hereditary AE (HAE) appear promising for improving the outcomes of patients with ACEi-AE. Conclusions: New HAE medications that correct imbalances in the kallikrein-kinin system may prove safe and efficacious in the treatment of ACEi-AE. © 2013 Elsevier Inc.**

☐ **Keywords—angioedema; kallikrein-kinin system; ecallantide; icatibant; angiotensin-converting enzyme inhibitor–induced angioedema**

INTRODUCTION

Angioedema (AE) is characterized by nonpitting edema of the dermis and subcutaneous layers. The most common sites of involvement are the tongue, lips, face, and throat; however, swelling can also occur in the extremities, genitalia, and viscera (1). Symptoms can include the sensation of a "lump in the throat," dyspnea, difficulty swallowing, and abdominal pain (2). Other signs include difficulty speaking, drooling, stridor, and diarrhea (2,3). Airway swelling, rare but potentially life threatening, is the primary indication for emergency therapy and hospitalization (4). The overall lifetime incidence of AE has been reported as 10%−15%, with angiotensin-converting enzyme inhibitor–induced angioedema (ACEi-AE) being responsible for 30%−40% of all AE seen in United States (US) emergency departments (5−10).

DISCUSSION

AE is a clinical diagnosis based on the characteristic signs and symptoms described previously. Distinguishing the etiology of AE in the emergency department can often be accomplished with a thorough medical history and physical examination. The medical history should include a familial or personal history of similar episodes, current medications, exposure to known allergens or

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physical stimuli, and timing of the episode (11). The location of the swelling and the presence or absence of urticaria helps to distinguish between allergic and nonallergic AE. Urticaria is common in allergic and rare in nonallergic forms of AE; swelling of the hands and feet is more common in hereditary angioedema (HAE), and facial swelling is more common in ACEi-AE (11–13).

CLASSIFICATION AND PATHOPHYSIOLOGY OF AE

AE is categorized as either allergic (mast cell or immunoglobulin E [IgE]–mediated) or nonallergic (not mediated by IgE, usually bradykinin mediated) (12). Allergic AE is usually associated with urticaria and is treated as an allergic reaction, including the use of epinephrine for severe reactions (anaphylaxis). Nonallergic AE is further subcategorized into the following types: HAE, acquired AE, renin-angiotensin-aldosterone system blocker–induced AE, pseudoallergic AE, and idiopathic AE (12). Acquired AE, pseudoallergic AE, and idiopathic AE will be discussed briefly before we focus on HAE and renin-angiotensin-aldosterone system blocker angioedema (RAE), in particular, ACEi-AE.

Acquired AE is uncommon. The mechanism appears to be idiotypic autoantibodies directed against C1q, which results in a nongenetic reduction in the C1-inhibitor (C1-INH), previously called C1 esterase inhibitor. Acquired AE is often associated with lymphoproliferative disorders (12).

Pseudoallergic AE mimics an acute allergic reaction but is not mediated by IgE. The most common medications implicated in pseudoallergic AE are nonsteroidal anti-inflammatory drugs, contrast agents, and opioids. The pathophysiology of pseudoallergic AE is based on the underlying drug effect. For example, i.v. contrast media and opiates are thought to directly cause mast cell degranulation, whereas nonselective nonsteroidal anti-inflammatory drugs appear to cause pseudoallergic AE through an increase in cysteinyl leukotrienes secondary to their cyclooxygenase-1 inhibition (12,14). Selective cyclooxygenase-2 inhibitors appear to be better tolerated (15).

Idiopathic AE is a common cause of chronic AE or urticaria and, by definition, has no defined underlying pathophysiology. Idiopathic AE is often associated with chronic urticaria and appears to be triggered by a number of factors, including emotional or physical stress (e.g., heat, cold, vibration, or exercise), as well as nonspecific infection (11,16).

HAE consists of three subtypes (17). Type I is characterized by low levels of C1-INH and accounts for 80%–85% of cases (17). Normal levels and decreased function of C1-INH are seen in type II HAE, which accounts for most of the remaining 15%–20% of cases (17,18). A third type of HAE (type III) with normal levels and normal function of C1-INH has been described, primarily in women (19). Type III HAE is thought to be estrogen induced (20). Much of the reported experience cited, even with the most recent therapeutic agents, is from studies in HAE.

RAE is caused by certain antihypertensive drugs, most notably ACEi agents (12). ACEi therapies induce renal vasodilation, increased vascular permeability, and plasma extravasation by mechanisms that will be discussed in more detail subsequently (21). For reasons that remain unclear, some individuals who take ACEi drugs develop a sensitivity that leads to a specific kind of RAE called ACEi-AE. The incidence of severe ACEi-AE requiring hospitalization or admission to an intensive care unit or that results in death is reported to be 0.136 per 1000 new users of ACEi drugs (22).

INCIDENCE AND RISK FACTORS

The overall incidence of ACEi-AE has been reported to be between 1 per 1000 and 2 per 1000 person-years (1,23,24). However, many studies citing the overall incidence of ACEi-AE are retrospective and may have underestimated the true incidence. Kostis et al. looked at AE induced by an ACEi as an end point in a randomized, double-blind study comparing enalapril with omapatrilat and found an incidence of 6.8 per 1000 subjects given enalapril during a 24-week period (13). Several studies have shown a significantly increased risk of ACEi-AE in certain populations, including women and African Americans (13,22,25).

Miller et al. conducted the largest observational study to date of medication-related AE in which 595,081 veterans receiving health care through the Veterans Affairs Health System were followed (22). These researchers found that the incidence of ACEi-AE was higher in older subjects, those with chronic heart failure or coronary artery disease, and confirmed the higher risk in African-American and female subjects. Somewhat surprisingly, the risk of ACEi-AE was lower in patients with diabetes mellitus. The study by Kostis et al., mentioned previously, found that seasonal allergies and a history of drug-related rash were independent risk factors for ACEi-AE (Table 1) (13,22). Almost all studies show that ACEi-AE most often occurs early in therapy, with more than half of all cases occurring in the first 90 days (13,22). However, the risk remains elevated even among patients using an ACEi for more than a year (22). Several studies based on visits to an emergency department and subsequent hospitalization found that 30%–40% of all cases of AE seen and treated in an