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Review Article

Perioperative angioedema: background, diagnosis, and management☆

David W. Barbara MD (Instructor in Anesthesiology)[a,*], Kevin P. Ronan MD (Assistant Professor of Anesthesiology)[a], Daniel E. Maddox MD (Assistant Professor of Medicine)[b], Mark A. Warner MD (Professor of Anesthesiology)[a]

[a]*Department of Anesthesiology, Mayo Clinic College of Medicine, Rochester, MN 55905, USA*
[b]*Department of Allergic Diseases, Mayo Clinic College of Medicine, Rochester, MN 55905, USA*

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Abstract Angioedema is a potentially life-threatening condition that may present at any point in the perioperative care of patients. It requires prompt recognition and diagnosis; the primary concern during acute attacks is airway management. The pathophysiology, various causes of angioedema, and treatment strategies according to underlying etiology are presented.

1. Introduction

Angioedema involves the extravasation of local plasma to the interstitium resulting in non-pitting, nondependent, and often asymmetric edema [1]. It typically develops quickly over minutes, rarely occurs over hours, and usually resolves in less than 48 hours. Areas of involvement primarily include the skin and mucosa of the face, throat, larynx, genitalia, extremities, and bowel. It is thought that subcutaneous or submucosal capillaries and post-capillary venules develop increased permeability as a result of vasoactive mediators such as histamine, bradykinin, complement, prostaglandin D2, and proteases [2].

Angioedema is of particular importance to anesthesiologists, as it may present at any point in the perioperative period and it may rapidly become life-threatening if it involves airway compromise. Previous reviews of angioedema related to the perioperative period have generally focused on only one specific etiology of this disorder [3,4]; this review discusses the breadth of multiple causes and enzymatic pathways involved in perioperative angioedema.

The two primary etiologies of angioedema are mast cell-mediated or kinin-related; however, there are less frequent, often unknown etiologies. Clinicians should be vigilant to recognize signs and symptoms of angioedema to hasten

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* Correspondence: David W. Barbara, MD, Mayo Clinic, 200 First St., SW, Rochester, MN. Tel.: +1 507 255 6219.
E-mail address: barbara.david@mayo.edu (D.W. Barbara).

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appropriate evaluation and diagnosis. Acute treatment strategies vary according to underlying etiology but center around airway protection. In addition, prophylactic measures may be taken to prevent life-threatening angioedema in patients with a known history of this problem.

2. Etiologies of angioedema

Angioedema results from various triggers involving various enzymatic pathways [Table 1 and Fig. 1].

2.1. Mast cell-mediated etiologies

Acute allergic angioedema is a form of mast cell-mediated angioedema characterized by exposure to an allergen to which the patient has been previously sensitized. It is associated with urticaria in the vast majority of cases [2]. Immunoglobulin E (IgE) receptor activation leads to mast cell degranulation, resulting in release or formation of substances such as histamine, leukotrienes, prostaglandins, and tryptase and the synthesis of other vasoactive substances. Causative substances include drugs, latex, foods, and stinging insects. In retrospective reviews of intraoperative IgE-mediated anaphylaxis, the most commonly identified causative agents have been antibiotics (12% - 50%), neuromuscular blocking drugs (11% - 93%), opioids (2% - 6%), and latex (4% - 20%) [5–8]. However, in 53% of cases of anaphylaxis from a single large institution, no causative agent was found on postoperative allergy skin testing [6]. Skin testing of these drugs has not been standardized or validated, with the sole exception of penicillin, and the absence of drug identification with skin testing should not be extrapolated to signify a drug not being the provoking agent. Most patients experience onset of symptoms within minutes of exposure to the antigen, and these symptoms typically resolve within 24 to 72 hours [1,2]. In addition, up to 30% of patients with chronic urticaria may have autoantibodies to IgE receptors and may present similarly to those patients with acute allergic angioedema [9,10]. Although edema associated with allergic angioedema may occur in any distribution, the extremities and face are commonly involved. Symptoms such as respiratory stridor, change in voice, or gastrointestinal (GI) involvement (eg, abdominal pain secondary to mucosal edema) also may be present but are difficult to identify in the anesthetized patient. Life-threatening cases of anaphylaxis are often marked by involvement of the larynx, throat, and tongue and associated dyspnea [2].

In addition to acute allergic IgE-mediated angioedema, mast cells may be directly stimulated by substances, resulting in degranulation [11]. Examples of drugs capable of causing direct mast cell mediator release include opioids (especially morphine and meperidine), muscle relaxants (often succinylcholine, atracurium, and mivacurium), and radiocontrast agents [11,12].

Nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin in particular, may cause acute angioedema [13]. NSAID-associated angioedema is not a true allergic reaction. Although there is controversy over the involved mechanism, one hypothesis holds that NSAID-induced inhibition of cyclooxygenase-1 (COX-1) within mast cells and other leukocytes results in a decrease in prostaglandin synthesis and an increase in activity of the lipoxygenase pathway [2]. This action causes a subsequent increase in pro-inflammatory cysteinyl leukotrienes and other hydroxy fatty acids that are highly vasoactive. COX-2 inhibitors are considered safe, as only NSAIDs, including COX-1 inhibitors, affect the aforementioned pathway, potentially resulting in angioedema [14]. These patients present with signs and symptoms similar to acute allergic angioedema, including urticaria [2,14].

Table 1 Causes of angioedema

Mast cell-mediated	Kinin-related	Other
Acute allergic (IgE-mediated) etiology	ACE-I	Idiopathic
Direct mast cell stimulation	ARB	Infections
NSAIDs	HAE	Urticarial vasculitis
	AAE	Hypereosinophilia

ACE-I = angiotensin-converting enzyme inhibitors, ARB = angiotensin receptor blocker, NSAIDs = nonsteroidal anti-inflammatory drugs, HAE = hereditary angioedema, AAE = acquired angioedema.

2.2. Kinin-related etiologies

Many kinin-related events are related to the use of drugs that work via the angiotensin system [eg, angiotensin-converting enzyme inhibitors (ACE-Is)] [4]. Bradykinin, a potent vasodilator, is produced from cleavage of high-molecular weight kininogen by the enzyme kallikrein [15]. Angiotensin-converting enzyme (ACE), also referred to as kininase-II, functions by converting angiotensin I to angiotensin II and inactivating bradykinin [4]. Angiotensin II results in potent vasoconstriction, stimulation of autonomic ganglia, sodium resorption from the proximal tubule, increased secretion of vasopressin and aldosterone, and inhibition of renin secretion. The function of ACE-Is is to decrease angiotensin II concentrations and also results in increased bradykinin levels. They are commonly used for the treatment of heart failure, hypertension, and other conditions. ACE-I-induced angioedema may result from an accumulation of bradykinin, leading to vasodilatation. This edema forms due to stimulation of vascular bradykinin B2 receptors; however, other vascular mediators also may be involved [2,4]. Angioedema is encountered in up to 1% of patients taking an ACE-I and is more common in African Americans than Caucasians. ACE-Is have been the cause of