Summer 2015

Pathophysiology and Treatment of Life-Threatening Angioedema

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Introduction

Angioedema is a potentially lethal swelling of the interstitial space from extravasation of intravascular plasma (Wood, Choromanski, & Orlewicz, 2013). Angioedema may present in any medical setting with a broad range of severity. Angioedema is commonly seen in emergency departments and intensive care units. According to Barbara, Ronan, Maddox, & Warner (2013), "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" (p. 335). Anesthesia professionals may also respond to airway management emergencies throughout the hospital setting and may treat angioedema secondary to anesthetics. Emergency providers and advanced practitioners should be able to recognize the signs and symptoms, differentiate between histaminergic and non-histaminergic, and provide emergent treatment of angioedema in all care settings.

Classification

Primary angioedema may be classified as mast cell mediated (histaminergic) or bradykinin mediated (non-histaminergic) (Bartal, Zeldetz, Stavi, & Barski, 2015). Angioedema can be caused by reactions to many different substances including drugs, food, and insect bites/stings (Barbara et al., 2012). The most common drugs associated with angioedema are angiotensin converting enzyme (ACE) inhibitors, ARBs, antibiotics, muscle relaxants, opioids, NSAIDS, and radiocontrast agents (Barbara et al., 2012). Sonny, Avitsian, Hussain, & Elsharkawy (2015) note a 1.3% to 5.1% incidence of angioedema following infusion of recombinant tissue plasminogen activator (rtPA). Hereditary angioedema episodes can be triggered by stress trauma, estrogen, or surgery, especially dental surgery (Senaratne, Cottrell, & Prentice, 2012). Secondary angioedema may present as a symptom of anaphylaxis, "a sever life threatening generalized or systemic hypersensitivity reaction" (Dhami et al. 2013, p.169).

Characteristics of Edema

- Non-pitting
- Non-gravity dependent
- Often asymmetric
- Transient
- Self-Limiting

Location

- Face
- Eyelids
- Tongue
- Oral cavity
- Neck
- Throat
- Glottic structures
- Extremities
- Trunk
- Genitals
- Bowel

Signs and Symptoms

- Dyspnea
- Dysphagia
- Odynophagia
- Stridor
- Hoarseness
- Drooling
- Tachypnea
- Hypovolemic shock
- Hypotension
- Tachycardia
- Urticaria (histaminergic only)
- Abdominal pain (Bowel edema may present like an acute abdomen; avoid surgery.)
- Vomiting (Hereditary Angioedema; HAE)
- Weakness (HAE)

Nursing Implications

- Assess the extent of tissue involvement
- Apply treatment algorithms
- Ongoing assessment of airway, vital signs, symptom progression, and response to treatment
- Continuous cardiac monitor
- Continuous pulse-ox
- Fluid resuscitation
- Medical & family history

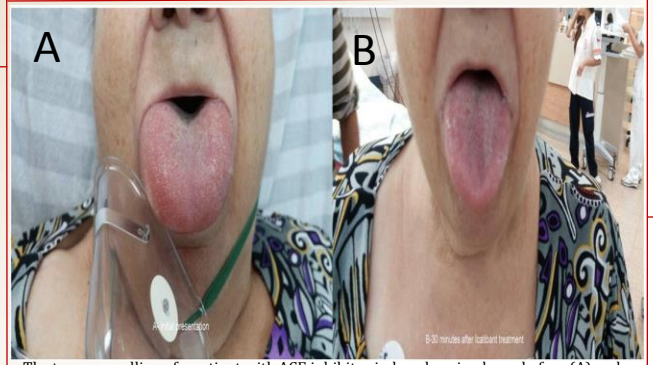
Treatment

It is important to differentiate between histaminergic angioedema, non-histaminergic angioedema (bradykinin), and anaphylactic reactions. For all etiologies, treatment can begin with anti-histamines and corticosteroids, and include epinephrine in the presence of stridor, new hoarseness of voice, or life threatening reaction (Moellman, Bernstein, & Lindsell, 2014). Although Moellman et al. (2014) note that "the only potential acute treatment currently readily available for the treatment of ACE-induced or other bradykinin-mediated angioedema in the ED is fresh-frozen plasma (FFP)" (p. 473), approved plasma C1-INH protein concentrates, kallikrein inhibitors (Ecallantide), and bradykinin 2-receptor blockers (Icatibant) may be available at some facilities when patients are suspected to have hereditary angioedema and can be considered for other non-histaminergic (bradykinin induced) angioedema (Moellman et al. 2014).

Pathophysiology
Histamine vs. Bradykinin

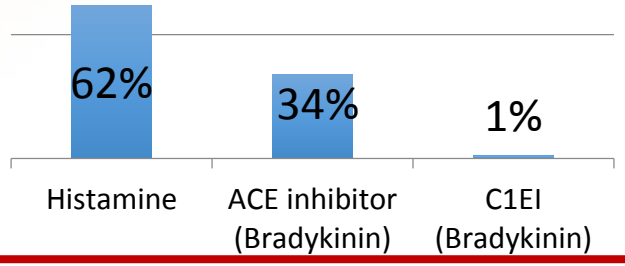
Histaminergic angioedema is an IgE mediated, type 1 hypersensitivity reaction that results in the degranulation of histamine from granulocytes, primarily mast cells. Histamine release causes localized vasodilation and increased vascular permeability resulting in the extravasation of intravascular plasma into the interstitial space causing swelling of the subcutaneous and submucosal tissues (Wood et al., 2013). Because the majority of angioedema cases are histaminergic reactions, first line medications for treatment of all types of angioedema include anti-histamines (H1 and H2 receptor blockers), corticosteroids to blunt the immune response, and epinephrine to inhibit mast cell degranulation (Moellman, Bernstein, & Lindsell, 2014).

Non-histaminergic angioedema is bradykinin mediated and can be due to hereditary deficiency or dysfunction of C1-inhibitor, or drugs including ACE inhibitors. Bradykinin is an inflammatory mediator that causes vasodilation, increased vascular permeability, nonvascular smooth muscle contraction, and oedema formation (Spyridonidou et al., 2010). It should be noted that anti-histamines and corticosteroids are ineffective in the treatment of non-histaminergic angioedema, and epinephrine is only minimally effective (Moellman, et al. 2014).



The tongue swelling of a patient with ACE inhibitor induced angioedema, before (A) and 30 minutes after (B) treatment with 30mg SubQ icatibant, Source: Bartal, Zeldetz, Stavi, & Barski, p. 479e2 (2015).

Estimated Classification in Primary Angioedema Cases Presenting to the Hospital



Significance of Pathophysiology

Hereditary angioedema (HAE) is caused by an autosomal dominant defect in the C1-INH gene that results in low levels of C1 esterase inhibitor (C1-INH) or ineffective C1-INH protein (Senaratne et al. 2012). C1-INH is a protein responsible for the inhibition of the complement inflammatory pathway and inhibition of B2 receptors in the kinin pathway (Senaratne et al. 2012). Without inhibition of the kinin pathway, bradykinin levels rise resulting in episodic angioedema. Rarely C1-INH may become deficient due to the development of autoantibodies or a lymphoproliferative disorder (Moellman et al., 2014).

Diagnosis of HAE is difficult in the acute setting, but HAE can be suspected if the patient's family history indicates autosomal dominant penetrance. Moellman et al. (2014) recommends checking serum C4 and tryptase levels during acute episodes of suspected HAE to aid in diagnosis, but these values are rarely useful in the acute setting and provide the most utility to immunologists in follow-up appointments. Serum C1 inhibitor level and C1 inhibitor activity level may be used in sub-acute setting (Senaratne et al. 2012). Plasma C1-INH concentrates, B2 receptor antagonists (icatibant), and kallikrein receptor blockers (ecallantide) can be used to treat bradykinin-mediated angioedema in the acute setting (Moellman et al., 2014) or prophylactically in the preoperative and perioperative setting (Senaratne et al., 2012).

ACE inhibitor therapy can cause angioedema at any time, but most reactions occur within the first few weeks after initiation or dose changes (Chan & Soliman, 2015). Angiotensin converting enzyme (ACE, identical to Kinase II) is responsible for the breakdown of bradykinin at the B2 receptor on the cell membrane (Bartal et al. 2015). When ACE (Kinase II) is inhibited, bradykinin levels can progressively increase and cause angioedema. Discontinue the ACE inhibitor. Fresh frozen plasma administration has been successfully used to treat ACE inhibitor related angioedema presumably because plasma contains small amounts of Kinase II (ACE), which can breakdown excess bradykinin (Senaratne et al. 2012). More research needs to be completed on the potential benefit of administering plasma C1-INH concentrate, B2 receptor antagonist, or kallikrein receptor blockers in patients with ACE inhibitor induced angioedema (off-label use) (Moellman et al., 2014) . However, small studies are emerging with promising results. Bartal, Zeldetz, Stavi, & Barski (2015) presented a case study that showed rapid resolution of ACE inhibitor induced, refractory, life-threatening laryngeal edema after a single subcutaneous icatibant (B2 antagonist) injection. Other case studies show similar results (Bartal et al. 2015).

Airway Risk Assessment Tools

In 2001, Chiu, Newkirk, Davidson, Burningham, Krowiak, & Deeb (2001) classified patients with angioedema into 3 risk categories for intubation based on the specific locations of facial, oral, and oropharyngeal swelling. Type 1 included facial and oral edema that excluded the floor of the mouth (0% intubated); type 2 included oropharynx and/or floor of the mouth edema (21.4% intubated, 7.1% surgical airway), and type 3 included oropharyngeal edema including the supraglottic and glottic structures (33.3% intubated) (Chiu et al, 2001). This categorization system for patients with angioedema remains useful for airway risk assessment when airways are not acutely compromised and fiberoptic bronchoscopy is immediately available (Wood et al., 2013).

In 1999, Ishoo, Shah, Grillone, Stram, and Fuleihan proposed a staging criteria for angioedema: stage 1 facial rash, facial edema, and lip edema, stage 2 soft palate edema, stage 3 lingual edema, and stage 4 laryngeal edema. Stages 1 and 2 could be treated outpatient or as inpatient observational, while 7% of stage 3 and 24% of stage 4 required artificial airways (Ishoo et al. 1999). Ishoo et al. (1999) found that voice changes, hoarseness, dyspnea, and stridor were the strongest predictors of the need for an artificial airway. Moellman et al. (2014) note that while the Ishoo criteria have been used for years to help decide whether to admit or discharge a patient, "these criteria have not yet been validated" (p. 473). While more information may be needed, the Ishoo criteria and study remain useful.

Conclusion

Healthcare providers need to be able to promptly recognize the clinical manifestations of angioedema because airway involvement and hypovolemic shock can be life-threatening. Airway management is of primary importance. Most angioedema reactions are histaminergic. Bradykinin-mediated angioedema is becoming more common with increased use of ACE inhibitors. Hereditary angioedema should be recognized with a detailed family history, and prophylactic treatment prior to surgical procedures is recommended (Moellman et al. 2014). Patients presenting with angioedema rely on healthcare providers to possess the clinical skill and medical expertise to prevent adverse outcomes.

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