Angioedema refers to swelling involving the skin, mucosa, and subcutaneous tissues. It may be an isolated symptom or may be a manifestation of an underlying disorder. Etiology of angioedema with urticaria and angioedema without urticaria differs significantly and clinical presentation guides further investigations. In this article, etiology, pathophysiology, clinical features, diagnosis, differential diagnosis, and management of angioedema are described.

Definition of Angioedema

Angioedema is defined as localized, self-limiting, non-pitting swelling involving the skin, mucous membranes, subcutaneous tissues, and/or submucosal tissues.
Etiology of Angioedema

There are many causes of angioedema. It can be an isolated symptom or a sign of a more serious disorder. Etiology of angioedema with urticaria and angioedema without urticaria is different.

Angioedema with urticaria

- **Angioedema with acute urticaria**: angioedema is present in < 50 % cases of acute urticaria; common causes include infections, food allergies, anaphylaxis (allergic and non-allergic), drug allergies, insect stings, etc.
- **Physical urticaria-angioedema**: cold urticaria, vibration-induced urticaria, pressure urticaria, exercise-induced anaphylaxis, cholinergic urticaria, etc.
- **NSAID-induced urticaria-angioedema**: aspirin (most common) and other COX-1 inhibitors
- **Angioedema with chronic spontaneous urticaria (CSU)**: recurrent angioedema of skin or other organs is seen in > 50 % of patients with CSU; exact etiology is unknown.
- **Urticarial vasculitis**: includes isolated urticarial vasculitis, urticaria-angioedema associated with connective tissue diseases (SLE, PAN, Wegener granulomatosis, cryoglobulinemia), hypocomplementemic urticarial vasculitis syndrome
- **Geich syndrome (Episodic angioedema with eosinophilia)**: recurrent episodes of angioedema, urticaria, fever, weight gain, eosinophilia, and elevated serum IgM.

Angioedema without urticaria

- **Hereditary angioedema (HAE) due to C1-INH deficiency**: HAE is caused by a quantitative deficiency (type I) or qualitative deficiency (type II) of C1-INH, which inhibits spontaneous activation of C1 of the complement system and is also important for inhibition of plasma kallikrein and factor XIIa.
- **HAE with normal C1-INH (HAE type III)**
- **Acquired angioedema with C1-INH deficiency**: C1-INH deficiency is acquired due to increased C1-INH catabolism (type I) or autoantibodies against C1-INH (type II).
- **Drug-induced angioedema**: recurrent angioedema involving face, lips, or tongue is seen in 0.1-2.2% of patients taking ACE inhibitors, and rarely those taking ATII receptor blockers.
- **Idiopathic acquired angioedema**: the terms idiopathic (cause not known) and acquired (not present since birth) are self-explanatory.

Pathology and Pathophysiology of Angioedema

Basic pathophysiology of angioedema is **local vasodilation, increased vascular permeability, and increased endothelial permeability** resulting in localized extravasation of fluid into deep dermal layers of skin/mucosa and subcutaneous/submucosal tissues. Urticaria and angioedema share similar pathophysiologic features; urticaria involves superficial layers of skin, while angioedema involves deeper layers of skin and subcutaneous tissues.

Most common mechanisms are mast cell degranulation (IgE mediated or non-IgE
mediated) or activation of kallikrein-kinin cascade. Leukotrienes may play a role in angioedema caused by cyclooxygenase-1 inhibitors.

Histamine plays an important role in most cases of angioedema with urticaria-like acute urticaria-angioedema, chronic spontaneous urticaria, physical urticaria-angioedema, etc. Bradykinin is an important mediator involved in most cases of angioedema without urticaria-like angioedema due to C1-INH deficiency or due to ACE inhibitors. Role of other vasoactive substances like prostaglandins, tryptase, cytokines, chemokines, etc. is possible but not known.

In autoimmune causes, IgG antibodies against IgE or α-subunit of IgE-receptor trigger release of histamine from IgE-linked mast cells or basophils. Immune complexes can also cause degranulation of mast cells or basophils by complement activation followed by the release of anaphylatoxins C3a, C4a, and C5a.

Clinical Features of Angioedema

Angioedema presents with swelling of deeper layers of skin and/or subcutaneous tissues. The swelling is non-pitting and usually lasts for a few hours to 3 days. Most common sites involved are lips and periorbital area, followed by hands, feet, and genitalia. Angioedema involving tongue, pharynx, or larynx can cause airway obstruction and asphyxiation.

Unlike urticaria, intense pruritus is rarely seen at the site of angioedema; sensations like burning, tingling, numbness are more common, which may precede the onset of swelling.

Symptoms of angioedema involving mucous membranes of internal organs depend upon the organ involved, e.g., abdominal pain, vomiting, diarrhea in angioedema of bowel, etc.

Allergic angioedema always appears within one to two hours of exposure to the allergen. Cold urticaria occurs after contact with a cold object. Cholinergic urticaria is associated with exercise, perspiration, or hot showers. Vibratory angioedema is seen after use of a pneumatic hammer or massage devices.

In urticarial vasculitis, urticaria typically lasts longer (24-48 hours) and are more common
than angioedema.

**ACE-inhibitor induced angioedema is not dose-related:** ~ 50% of the patients taking ACE inhibitors develop angioedema within the first week of treatment, while others may develop symptoms after several months or years. Commonly involved sites are the head, neck, face, mouth, tongue, pharynx, larynx, subglottic region, and intestines.

HAE due to C1-INH deficiency are autosomal dominant disorders, presenting most commonly in the first or second decade of life; **characterized by recurrent episodes of angioedema of skin (extremities, face, genitals, buttocks) lasting for 3-4 days.** Gastrointestinal symptoms like abdominal cramps, vomiting, diarrhea, intestinal obstruction, etc. and circulatory symptoms like hypotension are also present due to activation of the complement system and/or kallikrein-kinin system.

Mucosal involvement (tongue, pharynx, larynx) can cause respiratory obstruction, asphyxia, and death. Possible triggers of attacks of angioedema are trauma, physical or psychological stress, physical exercise, infections, menstruation, ovulation, alcohol consumption, certain drugs (ACE inhibitors, angiotensin receptor blockers, estrogen), etc.

HAE may be associated with **autoimmune diseases** like SLE, autoimmune thyroiditis, Sjogren syndrome, **glomerulonephritis**, etc.

HAE with normal C1-INH (HAE type III) is an **autosomal disorder with incomplete penetrance, predominantly seen in women.** Symptoms are similar to those of HAE with C1-INH deficiency. Some patients have mutations involving factor XII. Pregnancy, oral contraceptives, and hormone replacement therapy are known precipitating factors.

Symptoms of HAE due to acquired C1-INH deficiency are similar to those of HAE type I and II. **B-cell lymphoma is the most common malignancy associated with acquired C1-INH deficiency;** other associated disorders include monoclonal gammopathy of unknown significance (MGUS), SLE, carcinoma, etc.

Idiopathic angioedema is common in clinical practice. The exact cause is not known and there is no family history. Unlike HAE, laryngeal and bowel edema are not seen.

**Diagnosis of Angioedema**

A detailed history is very important to identify the triggers like allergens, drugs, physical factors, etc. **Allergy skin tests or in vitro tests can be performed to identify foods or certain drugs** (like penicillins) causing allergic (IgE-mediated) angioedema. To identify food allergies, double-blind placebo-controlled food challenges (DBPCFC) or a trial of elimination diet can be suggested by trained allergists.
Workup for *H. pylori*, hepatitis B, and hepatitis C and stool analysis for ova and parasites is performed to diagnose associated infections.

Ice cube challenge and assays for cold agglutinins and cryoglobulins are performed for diagnosis of cold urticaria. Specific tests are performed to diagnose physical urticaria-angioedema like an application of pressure or vibration for pressure or vibratory angioedema respectively, exercise challenge in a warm environment for cholinergic urticaria, etc.

Antithyroid antibodies, anti-IgE antibodies, and anti-FceRII (low-affinity IgE receptor) antibodies are present in different groups of chronic urticaria associated with autoimmunity. Tests for antinuclear antibody, rheumatoid factor, and cryoglobulin levels are also performed.

For diagnosis of urticarial vasculitis, evaluation of connective tissue disorders and skin biopsy may be helpful. In hypocomplementemic urticarial vasculitis syndrome, serum C4 and C3 are low and circulating IgG antibody to C1q is present.

CH50 and serum C4 levels are used as screening tests in patients with angioedema without urticaria. If either of them is low, tests for C1-INH function and serum C1q level are considered.

Angioedema due to C1-INH deficiency is characterized by decreased C1-INH function and reduced serum C4 levels. Differentiation of their types is made as follows:

<table>
<thead>
<tr>
<th>Type of angioedema without urticaria</th>
<th>C1 INH protein</th>
<th>C1q</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAE type I</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td>HAE type II</td>
<td>N or ↑</td>
<td>N</td>
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<tr>
<td>Acquired angioedema with C1-INH deficiency (type I)</td>
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</tr>
<tr>
<td>Acquired angioedema with C1-INH deficiency (type II)</td>
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HAE with normal C1-INH (HAE type III) is characterized by normal C1-INH levels and activity and normal C4 levels.

Idiopathic acquired angioedema is a diagnosis of exclusion; C1-INH is qualitatively and quantitatively normal and laboratory evaluation of allergy and complement system is also normal.
Differential diagnosis

1. Edema associated with hormonal changes in females
2. Peripheral edema due to cardiac, hepatic, renal or venous etiology (such edema is of pitting type)
3. Facial edema caused by superior vena cava syndrome
4. Facial edema caused by granulomatous cheilitis (Crohn disease, Melkersson-Rosenthal syndrome, etc.)
5. Cellulitis

Management and Therapy of Angioedema

Management of angioedema depends upon etiology and severity of symptoms. Allergen avoidance is important in allergic etiology and patients should be educated about the avoidance of triggers.

Acute allergic angioedema is treated with oral antihistamines; hydroxyzine or diphenhydramine is used if nonsedating antihistamines are not effective. Oral corticosteroids can shorten the duration of symptoms. Intramuscular epinephrine is used when angioedema involves tongue, pharynx or larynx or angioedema is a symptom of anaphylaxis. Intubation or tracheostomy may be required for maintenance of airway.

Nonsedating oral antihistamines are the drug of choice for treatment of chronic urticaria-angioedema; up to four-fold increased doses can be used before using sedating antihistamines. H$_2$-antagonists and leukotriene antagonists are used as additional treatments. Severe diseases may require cyclosporine or prednisolone.

Treatment of urticarial vasculitis includes management of underlying connective tissue disorder, antihistamines (may not be effective), and low dose corticosteroids. Some patients may respond to dapsone, colchicine, or hydroxychloroquine. Hydroxychloroquine is very effective in hypocomplementemic urticarial vasculitis syndrome.

Avoidance of aspirin and other COX-1 inhibitors is important for patients with NSAID-induced angioedema. Acetaminophen and COX-2 inhibitors can be used in these patients.

Emergency management of ACE inhibitor-induced angioedema is the same as that of acute allergic angioedema, but antihistamines and corticosteroids may be less effective. All ACE inhibitors must be avoided in future, although generally, these patients can tolerate ATII receptor blockers.

Intravenous fresh frozen plasma or C1-INH concentrate is the mainstay of emergency management of acute angioedema in HAE type I and II. Subcutaneous epinephrine may be helpful, but antihistamines and corticosteroids are ineffective. Intubation or tracheostomy must be performed when indicated. Ecallantide (kallikrein inhibitor) and icatibant (bradykinin B$_2$-receptor antagonist) are newer drugs for the treatment of acute episodes.

Androgens (danazol and stanazolol) reduce recurrent episodes of angioedema in HAE type I and II by increasing circulating levels of C1-INH. They should be used in the lowest effective doses due to possible side effects like hepatotoxicity, hepatic tumors, masculinization in females, etc. C1-INH concentrate or fresh frozen plasma can be administered prophylactically before dental or surgical procedures to prevent an episode of angioedema in patients with HAE type I and II.
Antihistamines, corticosteroids and C1-INH inhibitor concentrates are ineffective in HAE type III. Icatibant, fibrinolytic (ε-aminocaproic acid and tranexamic acid), and danazol may be effective in some patients.

In the management of acquired C1-INH deficiency, treatment of the underlying condition is most important. Similar to the management of HAE type I and II, androgens can be used as prophylactic treatment and C1-INH concentrate or fresh frozen plasma can be used in the treatment of acute episodes.

Due to autoimmune destruction of C1-INH, treatment of type II acquired C1-INH deficiency is difficult and may require plasmapheresis or cytotoxic agents. Tranexamic acid is also effective.

A group of idiopathic acquired angioedema (“histaminergic group”) responds well to antihistamines, while antihistamines are not effective in other patients. Oral corticosteroids can be helpful in prophylaxis.

Prognosis of Angioedema

Prognosis depends upon the cause of angioedema. Idiopathic angioedema and physical angioedema tend to undergo a variable course over the duration of a few months to a few years. Hereditary angioedema is a lifelong disorder.

Review Questions on Angioedema

The correct answers can be found below the references.

1. Which of the following is the most common group of drugs associated with angioedema without urticaria?
   A. COX-1 inhibitors
   B. Opiates
   C. Penicillins
   D. ACE inhibitors
   E. ATII receptor blockers

2. An 18-year-old male adolescent presents with recurrent episodes of angioedema without urticaria. His laboratory evaluation shows decreased serum C4, elevated serum C1-INH, and normal serum C1q. What is the most probable diagnosis?
   A. HAE type I
   B. HAE type II
   C. HAE type III
   D. Acquired C1-INH deficiency type I
   E. Acquired C1-INH deficiency type II

3. Which of the following is the drug of choice in the management of acute angioedema associated with anaphylaxis?
   A. Intravenous pheniramine maleate
   B. Intravenous hydrocortisone
   C. Intramuscular epinephrine
   D. Oral prednisolone
   E. Oral hydroxyzine
References


Correct answers: 1D, 2B, 3C

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