MINI REVIEW

Angioedema : Current Concepts

G. Hassan, G. Q. Khan, Waseem Qureshi, M. Ibrahim

Introduction

Angioedema is characterized by localized edema formation involving deeper layers of the skin, the subcutaneous tissue, and mucosal and submucosal layers of the respiratory and gastrointestinal tracts due to increased vascular permeability. Unlike urticaria where skin eruptions are distinctly pruritic and can involve any area of body from scalp to the soles of feet, in angioedema the most common sites of involvement are the periorbital tissue and lips (1-3).

Classification and Clinical Manifestations

Episodes of angioedema of less than 6 weeks' duration are called acute, whereas attacks persisting beyond this period are considered chronic. Angioedema may either be acquired due to variety of causes or may be hereditary in nature (Table 1).

Classification of Angioedema
1. Acquired angioedema
a) Acute
- Allergic, IgE mediated (drugs, foods, insect bites, pollens and fungi etc).
- Contrast dyes/drugs.
- Serum sickness.
- Necrotizing vasculitis.
b) Chronic
- Idiopathic.
- Acquired C1 inhibitor deficiency.
- Angioedema – eosinophilia syndrome.
- Vibratory angioedema.
2. Hereditary angioedema
Type 1 – C1 inhibitor absent.
Type 2 – C1 inhibitor dysfunctional.

Angioedema occurring during the seasonal respiratory allergy as a result of exposure to animals or moulds is attributed to inhalation or physical contact with agents like pollens, animal dander and mold spores. Similarly, it may occur secondary to the ingestion of fresh fruits, fish, milk products, chocolates, legumes and drugs. Among the various drugs the most prominent agents include angiotensin converting enzyme (ACE) inhibitors (4). Vibratory angioedema may occur years after occupational exposure or can be idiopathic in nature and may be accompanied by cold urticaria (3).

Angiotensin converting enzyme inhibitors cause angioedema by prolonging bradykinin survival and potentiating its effects and, has been found to occur in 0.1 to 0.2% of patients taking such drugs. More serious forms of angioedema follow the intake of long acting agents like lisinopril and enalapril compared to the short acting ones like captopril. Even the administration of angiotensin receptor antagonists like losartan may not be safe in persons developing angioedema due to ACE inhibitors, they are also known to cause angioedema (4,5).

Hereditary angioedema is a rare autosomal dominant disorder due to deficient or dysfunctional C1 esterase inhibitor (C1INH), manifesting as recurrent episodes of edema involving face, tongue, larynx, gastrointestinal tract or extremities. Type 1, affecting 85% of the patients is characterized by deficient C1 inhibitor whereas type 2 occurs only in 15% of the individuals, having dysfunctional C1 inhibitor. Laboratory diagnosis depends on demonstrating this deficiency or dysfunction of C1 inhibitor (2,3). An acquired deficiency of the C1 inhibitor usually seen in lymphoproliferative disorders like

From The Postgraduate Department of General Medicine Government Medical College, Srinagar (J&K) .
Correspondence to: Dr. Ghulam Hassan, Registrar, Postgraduate Department of General Medicine Government Medical College, Srinagar (J&K).

chronic myeloid leukemia and lymphomas has the same clinical manifestations but differs in the lack of familial element. Another acquired form of C1 inhibitor deficiency due to appearance of IgG anti C1INH is associated with systemic lupus erythematosus. Angioedema eosinophilia syndrome manifests in two forms. An episodic type is characterized by recurrent episodes of angioedema, urticaria, eosinophilia, elevated serum IgM, fever, increased body weight and benign course, and a non episodic type involving the extremities, mainly affecting young females without an increase in the serum levels of IgM (2,3). Angioedema presents clinically with edema of the involved areas. Although self-limited in duration, angioedema of upper respiratory tract can be life threatening due to laryngeal obstruction, while gastrointestinal involvement may present with abdominal colic with or without nausea and vomiting. No residual discoloration skin is usually seen in patients with angioedema (1,3). Angioedema and urticaria may occur together, however, in 10% cases angioedema occurs alone.

Pathophysiology

The mast cell is believed to be the major effector cell in angioedema. These cells are located in the dermis and are distributed about the blood vessels, lymphocytes, nerves and appendages. Activation of cutaneous mast cells by a variety of mediators leads to increased permeability of capillaries and venules. These mediators include histamine, prostaglandin D_2, leucotriene C4, eosinophil and neutrophil chemotactic factors; various enzymes like tryptase, chymase, carboxypeptidase A, cathepsin G, cytokines like interleukin 4,5,6 and 8; tumor necrosis factor á and proteoglycans such as heparin and chondroitin sulfate. Angioedema is characterized by edema of dermis and subcutaneous tissue. Collagen bundles in the affected areas are widely separated, the venules are sometimes dilated and the perivenular infiltrate consists of lymphocytes, eosinophilis and neutrophils in varying number and combinations (1,3).

Diagnosis

The diagnosis is usually made on the basis of clinical picture, although the recognition of the agents or stimuli causing angioedema is also mandatory. In addition analysis for immunoglobulin levels and various mediators of mast cell degranulation, as mentioned above, is to be carried out (1-3).

Treatment

Identification of the etiological factor(s) and their elimination provide the most satisfactory therapeutic program, especially useful in IgE mediated reactions to allergens or physical stimuli. For most cases of urticaria and angioedema, H1 antihistamines such as chlorpheniramine or diphenhydramine and non-sedating antihistamines such as loratadineand cetirizine are quite effective. Doxepin, a dibenzoxepin tricyclic compound with both H1 and H2 receptor antagonist activity, is another alternative. Terbutaline, an á – adrenerjic agonist or a Cys L T_1 R antogonist may be added to the treatment regimen. Topical glucocorticoids are of no value, however, systemic glucocorticoids are useful in the management of idiopathic angioedema with or without urticaria. For the hereditary variety, attenuated androgens correct the biochemical defect by inducing hepatic synthesis and increase in the serum levels of C1 esterase inhibitor. Danazol and stanozolol provide the main prophylactic treatment. Since the use of such agents in children and pregnant women is not yet accepted, the antifibrinolytic agent ? - aminocaproic acid may be used to control spontaneous attacks or for preoperative prophylaxis (2-4). Infusion of C1 inhibitor protein appears useful in prophylaxis and to ameliorate an attack (3).

References

1. Van Dallen RG, Maddox DE, Dutta EJ. Masqurades of angioedema and urticaria. Ann Allergy Asthma Immunol 2002; 88: 10-15.
2. Somani VK. Urticaria and Angioedema. In: Shaikh WA ed. Allergy and Asthma : A Tropical View. IJCP Publictions. Delhi 2001. pp. 231-48.
3. Austen KF. Allergies, Anaphylaxis and Systemic Mastocytosis. In : Kasper E, Braunwald E, Fauci AS et al (eds). Harrison's Principles of Internal Medicine. 16th ed. Vol. II, McGraw Hill, New York 2005. pp. 1947-56.
4. Israili ZH and Hall WD. Cough and angioneurotic edema associated with angiotensin converting enzyme inhibitor therapy : A review of literature and pathophysiology. Ann Intern Med 1992; 117: 234-42.
5. Cha YJ and Pearson VE. Angioedema due to losartan. Ann Pahrmacother 1999; 33(9): 936-38.