

Management of Angio-oedema

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INTRODUCTION

Hereditary angio-oedema was first reported by Quincke in 1882¹. Osler described the major clinical features of hereditary angio-oedema occurring over five generations in an affected family². He observed attacks of abdominal pain, laryngeal and cutaneous oedema in this family and realized that it was all one disorder. Landerman in 1962 found that hereditary angio-oedema resulted from a deficiency in complement inhibition³. A year later, Donaldson and Evans discovered low level of C1 esterase inhibitor to be the causative factor⁴. The acquired form of the disease was recognised in 1972⁵. Since then, much has been known about the genetics and molecular basis of hereditary angio-oedema although the pathophysiology of acquired angio-oedema is not so well understood.

The term angio-oedema refers to a group of disorders with multifactorial etiology but a similar clinical expression. It is characterised by the sudden onset of one or more localised swellings measuring up to several centimetres in diameter. The lesions are due to oedema involving the skin, subcutaneous tissue and mucous membrane.

CLASSIFICATION

Angio-oedema may be hereditary or acquired (Table 1). The acquired forms include those caused by physical agents such as cold, exercise and sun exposure. Most of the causes manifest as a combination of urticaria and angio-oedema alternating and coinciding to various degrees. Deficiency of C1 inhibitor, whether hereditary or acquired, presents strictly as angio-oedema without accompanying urticaria unless by coincidence.

MANAGEMENT

Evaluation

A thorough history is of great importance in the evaluation of patients with angio-oedema. Particular emphasis should be made on the age of onset of angio-oedema, recognised precipitating factors, associated features, frequency of attacks and family history.

Physical examination should be performed and some types of associated urticaria may be identified by their characteristic appearance, such as small wheals with a large erythematous flare in cholinergic urticaria,

Table 1: Classification of angio-oedema

Hereditary- there are two phenotypic variants of angio-oedema:

Type I: it is characterized by low antigenic and functional plasma levels of a normal C1 inhibitor protein.

Type II: it is characterized by the presence of normal or elevated antigenic levels of a dysfunctional mutant protein together with reduced levels of the functional protein.

Acquired

Acquired C1 inhibitor deficiency - there are two types:

Type I: this occurs in the majority of the case. An associated lymphoproliferative disorder is seen

Type II: rarer occurrence with no associated lymphoproliferative disorders

Idiopathic

Allergic

Drug-induced

Angio-oedema with lupus erythematosus

Angio-oedema with hypereosinophilia

Angio-oedema associated with physical urticarias

the linear wheals in dermographism and the localization of lesions to exposed areas suggestive of light-induced or cold-induced urticaria and angio-oedema.

Tests for physical urticaria include the application of ice cube to detect cold urticaria, physical exertion to elicit cholinergic urticaria etc. Elicitation of solar urticaria requires instruments available in certain dermatology departments.

A complete blood count with differential analysis are useful initial tests. Eosinophilia may suggest IgE-mediated allergic disorders or drug reactions. Further investigations should be guided by the history, physical findings and clinical suspicion. For instance, skin biopsy may be needed to exclude urticarial vasculitis.

C4 level in plasma is a useful screening test for angio-oedema (Figure 1). If C4 level is normal, one can simply investigate along the line of urticaria rather

than angio-oedema. If C4 level is low, an immunoassay test for C1 inhibitor should be done. If C4 level is low and C1 inhibitor level is normal, one should perform the functional assay for C1 inhibitor level since hereditary angio-oedema type II can give rise to a dysfunctional protein. If the functional assay for C1 inhibitor is normal, the patient does not have hereditary angio-oedema. C1q level should be measured as well; it is low in patients with acquired C1 inhibitor deficiency and normal in hereditary angio-oedema. If acquired C1 inhibitor deficiency is diagnosed, a search for lymphoproliferative disorder, especially B cell lymphoma, should be made.

A low C2 or C4 level along with normal C1 inhibitor levels can result from exposure to radiocontrast media, as well as from immune complex formation syndromes⁶. A skin biopsy will rule out vasculitis in these situations and work-up for autoimmune diseases and infectious conditions should be initiated.

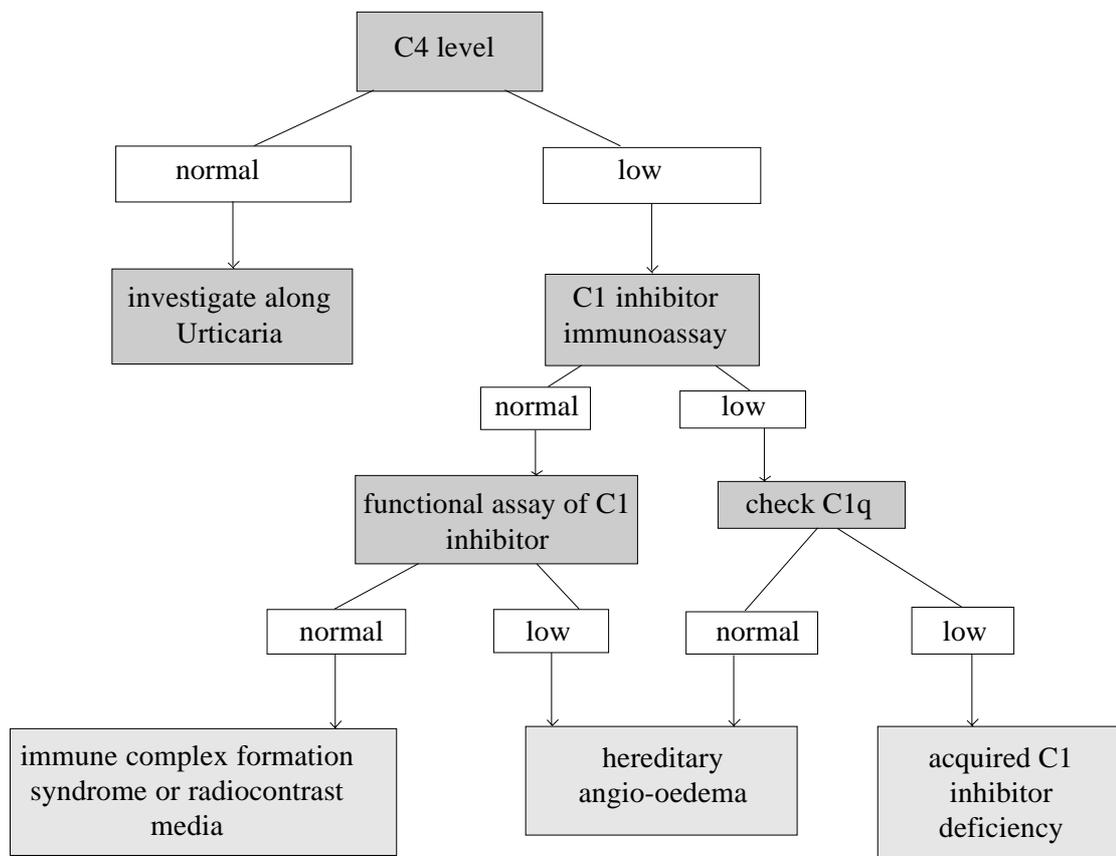


Figure 1: Immunological evaluation for patient with angio-oedema

Treatment

Hereditary angio-oedema

Acute attacks are both unpleasant and life threatening; attempts should thus be made to prevent them. Violent physical exertion should be avoided and trauma should be minimized. Dental and surgical procedure should only be undertaken with adequate prophylaxis.

Angiotensin converting enzyme inhibitors should be avoided. Estrogen may lead to low levels of plasma C1 inhibitor and patients with hereditary angio-oedema are advised not to take pills containing estrogen. For contraceptive measure, these patients may consider to use norgestrienone.

It is helpful to give a card to the patients. The diagnosis, current medications, and elementary precautions should be clearly listed. Family members should be traced and given proper assessment.

The specific treatment can be divided into 3 distinctive phases: long-term prophylaxis, short-term prophylaxis and treatment of acute attacks.

Long-term prophylaxis

Attenuated androgens

The best drugs for prophylaxis are the attenuated androgens danazol and stanozolol⁷. These drugs require a few days to act and are limited to prophylactic use only. They correct the lowered C1 inhibitor and C4 levels by inducing hepatic synthesis of C1 inhibitor and they are effective in hereditary angio-oedema type I and II.

A dose and time dependent toxicity of attenuated androgens has been reported. The most common side effects are hepatic dysfunction, hirsutism and menstrual irregularities. Other side effects include hyperlipidaemia, hyperglycemia, thrombocytosis, polycythaemia, impaired renal function. Surveillance measurements of appropriate blood tests need to be followed. Special attention has been given to their possibility to induce liver neoplasia⁸.

It is clear that the use of attenuated androgens should be accompanied with a careful consideration of risks and benefits. Such therapy may not be justified in

patients who have only two or three attacks a year. First to be considered is the actual harm of attacks to the patient's life. Frequent attacks may impair the normal working capacity and in certain situations may be even life-threatening. Prepubertal age, female sex, pregnancy and coexisting liver disease are additional risks for the use of androgens⁹. In children who have not achieved adequate growth, treatment with androgens for extended period will seriously limit their growth. Androgens should not be used in pregnant women because of the side effect of masculinization of female fetus.

The dosage used should be no more than that required to keep the patients free of attacks of angio-oedema. It is not necessary to aim at achieving a normal level of C1 inhibitor or C4. Both danazol and stanozolol are equally effective but stanozolol is less expensive. Patients may be started at higher doses with gradual tapering to the minimum effective dose, which varies greatly from patient to patient. Some authors advocate using alternate day or even greater interval dosing to reduce side effects¹⁰. The majority of patients are maintained on 2mg or less per day of stanozolol or 300mg or less per day of danazol. Two of the recommended regimens are as follows:

1. danazol 200-600mg/day, daily for 1 month, then 5 days on and 5 days off;
2. stanozolol 1-2mg/day, daily for 1 month, then 5 days on and 5 days off.

There may be spontaneous improvement in hereditary angio-oedema and thus the need for prophylactic treatment may diminish with time. The feasibility of discontinuation of androgens should be assessed regularly.

Esterase-inhibiting drugs

These drugs act by preventing the C1-esterase activation by plasmin. A number of inhibitors are available, including tranexamic acid and epsilon aminocaproic acid. Epsilon aminocaproic acid, an analogue of lysine, has been used in divided doses of 8-15g daily for long term suppressive treatment¹¹. Treatment with epsilon aminocaproic acid causes no detectable increase in levels of C1 inhibitor, C2 or C4¹². Dose related toxicity includes muscle weakness with raised serum creatine phosphokinase, vascular

thrombosis and postural hypotension. Tranexamic acid, a derivative of epsilon aminocaproic acid, is given orally at a dose of 1g t.d.s. for prophylaxis. The efficacy of esterase inhibiting drugs is not as good as androgens in terms of prophylaxis in hereditary angio-oedema and the side effect of thromboembolic complication is occasionally encountered. For these reasons, the use of esterase-inhibiting drugs is usually restricted to patients such as children, who have major contraindications to androgen treatment.

C1 inhibitor

In Europe, C1 inhibitor concentrate can be obtained from the Netherlands Red Cross Blood Transfusion Service. It is easily reconstituted in a small volume of sterile saline solution and can be easily administered by a nurse or physician or even self-administered by the patient. The standards of preparation are rigorous, involving vapour heating. There has been no evidence of transmission of viral hepatitis, HIV or other infections. A small number of patients with severe clinical disease of hereditary angio-oedema did not respond to or could not tolerate the prophylaxis of androgens and esterase-inhibiting drugs¹³. They were treated with ongoing infusions of C1 inhibitor at 4- to 5-day intervals for a period of approximately 1 year. These patients responded well with excellent control of disease. There was no evidence of development of antibodies to C1 inhibitor protein.

Short-term prophylaxis

This is mainly used for patients undergoing invasive oral procedure such as dental treatment, endoscopy and endotracheal intubation. Local trauma in patients with hereditary angio-oedema may precipitate an acute attack. For these kinds of prophylaxis, some authors recommend the administration of attenuated androgens (danazol 600mg/day or stanozolol 6mg/day) 6 days before and 3 days after the invasive procedure.

C1 inhibitor may also be used if it is anticipated that laryngeal oedema will develop because of its rapid action. Although C1 inhibitor does not appear to be primarily a prophylactic drug, this use may be indicated when there is no time for androgen prophylaxis and it is important to avoid oedema⁹.

Treatment of acute attacks

Most of the acute attacks of hereditary angio-oedema are not life-threatening but may result in disfigurement and severe abdominal pain. However, if laryngeal oedema occurs, it is a medical emergency and airway management should be a prime concern. Intubation or tracheostomy may be needed for laryngeal oedema with respiratory distress.

Antihistamines, corticosteroids and adrenergic agents are ineffective in acute attacks, and time should not be wasted in administering them⁷. Hospitalization is recommended so that close observation can be offered. Most of the patients can be discharged within 72 hours if no tracheostomy is required.

Freshly reconstituted freeze-dried plasma has been used for attacks. The action is quite rapid and usually two units are needed to raise the C1 inhibitor level in blood to give a satisfactory response. There are, however, two potential disadvantages. Whole plasma, apart from replacing the C1 inhibitor, also adds substrates C1, C2 and C4 to the patients. These may aggravate the angio-oedema. The second disadvantage is the risk of transmitting a viral infection with the whole plasma.

C1 inhibitor is considered to be the treatment of choice for laryngeal oedema in patients with hereditary angio-oedema. However, the preparation is quite expensive. One unit of Immuno corresponds to the amount of C1 inhibitor present in 1 ml of normal human plasma. Administration of 1000/1500 units is the effective dose in reversing laryngeal oedema and abdominal pain. No acute adverse reaction has been reported. Since the use of steam-treated preparation, no hepatitis C infection has occurred.

Esterase-inhibiting drugs can be given either as an adjunct to C1 inhibitor or as a primary treatment. The dosage of tranexamic acid is 1g every 2 hours orally and that of aprotinin is 100,000 units every 4 hours intravenously.

Pain control with narcotics and volume replacement with intravenous fluid also need to be addressed.

Acquired C1 inhibitor deficiency

The treatment of acute attacks of acquired C1 inhibitor deficiency is more or less the same as that of hereditary angio-oedema. The responses in acquired C1 inhibitor deficiency, however, are unpredictable^{14,15}.

Patients with acquired C1 inhibitor deficiency type I usually require higher doses of attenuated androgens to achieve a therapeutic response¹⁴. Epsilon aminocaproic acid therapy for this condition has not been widely used. Long-term C1 inhibitor infusion has been successful but inconvenient¹³. The treatment of the underlying neoplastic conditions will often cure the acquired C1 inhibitor deficiency¹⁶.

In patients with acquired C1 inhibitor deficiency type II, which is characterized by the presence of C1 inhibitor autoantibodies, corticosteroid, immunosuppressives and even plasmapheresis are needed to bring about a remission¹⁷.

Idiopathic angio-oedema

This condition is often associated with chronic idiopathic urticaria. Treatment of urticaria may control the angio-oedema as well. Oral antihistamines are used. In a patient whose angio-oedema is not controlled by oral antihistamines and who has severe attacks of laryngeal oedema, it is important to ensure a patent airway first. Adrenaline should be administered; it may be given as self-injection by the patient. Adrenaline may abort the acute attack. If adrenaline does not work, intravenous antihistamines and hydrocortisone should be given.

Allergic angio-oedema

The most important thing is to identify the cause of the angio-oedema and avoid it in the future. It may be precipitated by foods, drugs, stings, parasites and inhalants. Eradication of parasitic infestation may cure the problem. Symptomatic treatment is otherwise similar to that of idiopathic angio-oedema.

Drug-induced angio-oedema

Angiotensin converting enzyme inhibitor-induced angio-oedema

The angiotensin converting enzyme inhibitor should be withdrawn in any patient who presents with angio-oedema, however mild and however long after the introduction of the angiotensin converting enzyme inhibitor¹⁸. In a very mild attack, withdrawal of the angiotensin converting enzyme inhibitor may be sufficient to control the problem. However, very often, intravenous antihistamines and steroids are needed and sometimes repeatedly. When laryngeal oedema occurs, inhaled, subcutaneous or intravenous adrenaline should be given. The dose of subcutaneous adrenaline is 0.01ml per kg body weight of 1:1000 aqueous adrenaline and it may be repeated every 15 to 20 minutes as needed. Oral or nasal intubation, tracheostomy or retrograde intubation over a guide wire through the cricothyroid membrane may be needed. Close observation in intensive unit is advisable in extremely severe cases. Intravenous saline infusion should be started if hypotension is present.

The course can be unpredictable and the angio-oedema may worsen rapidly. There may be a poor response to the initial treatment, especially if the angio-oedema is well established at presentation.

In general, the angio-oedema resolves after one to two days, and does not recur if the angiotensin converting enzyme inhibitor is withdrawn^{19,20}. It is not advisable to replace the original angiotensin converting enzyme inhibitor with another, as further episodes are likely to occur^{19,20}. A Medic Alert bracelet is useful and clear instruction about the avoidance of angiotensin converting enzyme inhibitors should be given to the patient and other doctors involved in the care of the patient. When the situation is stable, the patient may be discharged with a short course of oral antihistamines and a tapering course of oral corticosteroids²¹.

Nonsteroidal anti-inflammatory drug-induced angio-oedema

Angio-oedema caused by aspirin is occasionally seen. The proposed mechanisms include cyclooxygenase inhibition leading to amplified mast cell

degranulation and enhanced biosynthesis of lipoxygenase products. It is essential for the patient to avoid the offending drug and also the whole group of nonsteroidal anti-inflammatory drugs in the future.

Angio-oedema with lupus erythematosus

The management is basically directed to treat the underlying cause. The treatment of the angio-oedema per se may involve the use of antihistamines, systemic steroid and adrenaline.

Angio-oedema with hypereosinophilia

Patients with angio-oedema and urticaria associated with markedly elevated peripheral blood eosinophil counts have been reported. Skin biopsies showed infiltration of dermis with eosinophils. Deposition of proinflammatory major basic protein in the dermis appeared to be responsible for the angio-oedema in these cases. The body weight of the patient may increase during attacks, which are associated with fever. The condition responds to systemic prednisolone.

Angio-oedema associated with physical urticarias

Severe angio-oedema can often be prevented by avoidance of the cause. For example, patients with cold urticaria should not swim in cold water. Tolerance treatment has been reported to be successful in some forms of physical urticaria, including solar urticaria²² and cold urticaria²³. This treatment involves repeated exposure of skin to the specific provoking factor until a state of tolerance has developed⁷. The frequency of exposure is then gradually reduced to the point at which reactivity to the physical stimulus begins to occur. Systemic antihistamine may be effective in reducing the itching associated with angio-oedema caused by physical stimuli.

CONCLUSION

Angio-oedema is characterized by localized swelling of sudden onset, affecting the skin and mucosa. It can be classified into hereditary and acquired forms. Different mechanisms are involved in different types of angio-oedema. Some are IgE-mediated or complement-dependent immunologic disorders while

others are non-immunologic disorders in which there is a direct effect on the mast cell or on arachidonic acid metabolism. Some conditions are idiopathic as well. Evaluation of patients should focus on a detail history, supported by selected laboratory investigations. Management of angio-oedema is dependent of accurate diagnosis of the type of angio-oedema. Although the general measures to handle the acute attack of angio-oedema are similar in different types of angio-oedema, specific treatments are available in different situations.

Learning points:

1. *Angio-oedema is not a definitive diagnosis. Proper management depends on its underlying cause.*
2. *ACE-inhibitor should NOT be given to patients with history of angio-oedema.*

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