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Clinical Immunology Review Series: An approach to the patient with angio-oedema

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Summary

Angio-oedema is a common reason for attendance at the accident and emergency department and for referral to immunology/allergy clinics. Causative factors should always be sought, but a large proportion of patients have the idiopathic form of the disease. A minority of patients represent a diagnostic and treatment challenge. Failure to identify the more unusual causes of angio-oedema may result in life-threatening situations. Common and rare causes of angio-oedema will be discussed in this article, as well as the diagnostic and treatment pathways for the management of these patients. A comprehensive history and close monitoring of response to treatment are the most cost-effective diagnostic and treatment tools.

Keywords: angio-oedema, angiotensin converting enzyme inhibitors, C1 inhibitor

Introduction: definition

The term angio-oedema refers to localized, transient swelling of the deeper layers of the skin or mucous membranes of the upper respiratory or gastrointestinal tract. The swelling can affect any part of the body, but has a predilection for the areas of more loosely attached skin. Angio-oedema is non-pitting, erythematous or skin-coloured with ill-defined margins. A burning sensation or pain may be present but pruritus is absent. This is in contrast to urticaria (with or without angio-oedema), which is characterized by itching and wheals. This paper addresses the clinical approach to patients with isolated angio-oedema; urticaria is reviewed elsewhere in this series [1]. Oedema associated with other clinical conditions, such as venous obstruction or nephrotic syndrome, will not be discussed further here, but the clinician should be aware of the other causes that can present occasionally as 'angio-oedema'.

Pathophysiology/classification (see also Box 1)

Histamine-mediated angio-oedema

Excess histamine causes increased local blood flow, endothelial permeability and swelling resulting in angio-oedema, urticaria and, in severe cases, anaphylaxis. In immunoglobulin E (IgE)-mediated reactions, allergen binding results in cross-linking of IgE bound on mast cells which causes mast cell degranulation and release of histamine and other mediators, notably tryptase [2]. Mast cells may also degranulate in direct response to a number of agents, notably anaesthetics, contrast medium and opiates, resulting in a non-IgE-mediated anaphylactoid reaction, which may be clinically indistinguishable from true anaphylaxis [3]. Autoantibody against the mast cell IgE receptor or mast cell-bound IgE (or basophils) is another common cause of histamine release [1].

Bradykinin-mediated angio-oedemas

Bradykinin (BK) plays a physiological role in the control of vascular tone. Kallikrein catalyses production of BK from high molecular weight kinins. Kallikrein itself is activated by a variety of mediators, including factor XII of the contact system. (Fig. 1). BK binds to receptors on the vascular endothelium. BK-1 receptors are inducible by tissue injury and BK-2 receptors are expressed constitutively. BK-2 receptor binding results in substance P release from nerve fibres leading to increased vascular permeability, and leakage of plasma into the interstitial space [4–6].

Box 1. Diagnostic Classification of angioedema.

- Allergic
- Drug-related (ACEI, NSAIDs, salicylates)
- C1 inhibitor deficiency (HAE, AAE)
- Idiopathic
- Miscellaneous causes

Other mechanisms

Excess leukotrienes resulting from inhibition of prostaglandin (especially PGE_2) production by salicylates or non-steroidal anti-inflammatory drugs may result in angio-oedema, in association with urticaria [7]. Rare causes include vasoactive complement components, for example in hypocomplementaemic urticarial vasculitis [1].

Hereditary angio-oedema types 1 and 2

Hereditary angio-oedema (HAE) occurs as a result of C1 inhibitor deficiency (C1 INH). Those affected are heterozygous for C1 inhibitor mutations, which result in either a truncated or abnormally folded protein with low levels of circulating C1-inh (HAE1) or normal or raised levels of a non-functional C1-inh (HAE2). Two unusual families have been described with autosomal recessive HAE, resulting from homozygous point mutations near the active site and in the promoter region respectively [8].

C1 inhibitor exerts local anti-inflammatory effects via inhibition of factors XIIa, XIa and kallikrein in the contact system, controlling production of BK from high molecular weight kininogen. Reduced level or function of C1 INH results in overactivation of the contact system and excess local BK leading to swelling [9–13]. Patients with HAE have high plasma BK which increases at the time of an attack, with extremely high local levels at sites of swelling [10,11]. Uncontrolled consumption results in a secondary deficiency of the early classical pathway components. This may explain the increased incidence of SLE in HAE, but is probably not the direct cause of the swelling [14,15].

The HAE1 and HAE2 are indistinguishable clinically. Patients experience intermittent swellings, most commonly affecting skin, mucosae, intestinal tract or abdominal viscera (Fig. 2). Attacks are typically of slow onset, reaching maximum intensity after several hours. Following this there is a plateau phase of 1–5 days, with resolution over several hours [16,17]. Twenty-five per cent of patients report a prodromal reticulate rash, or non-specific symptoms.

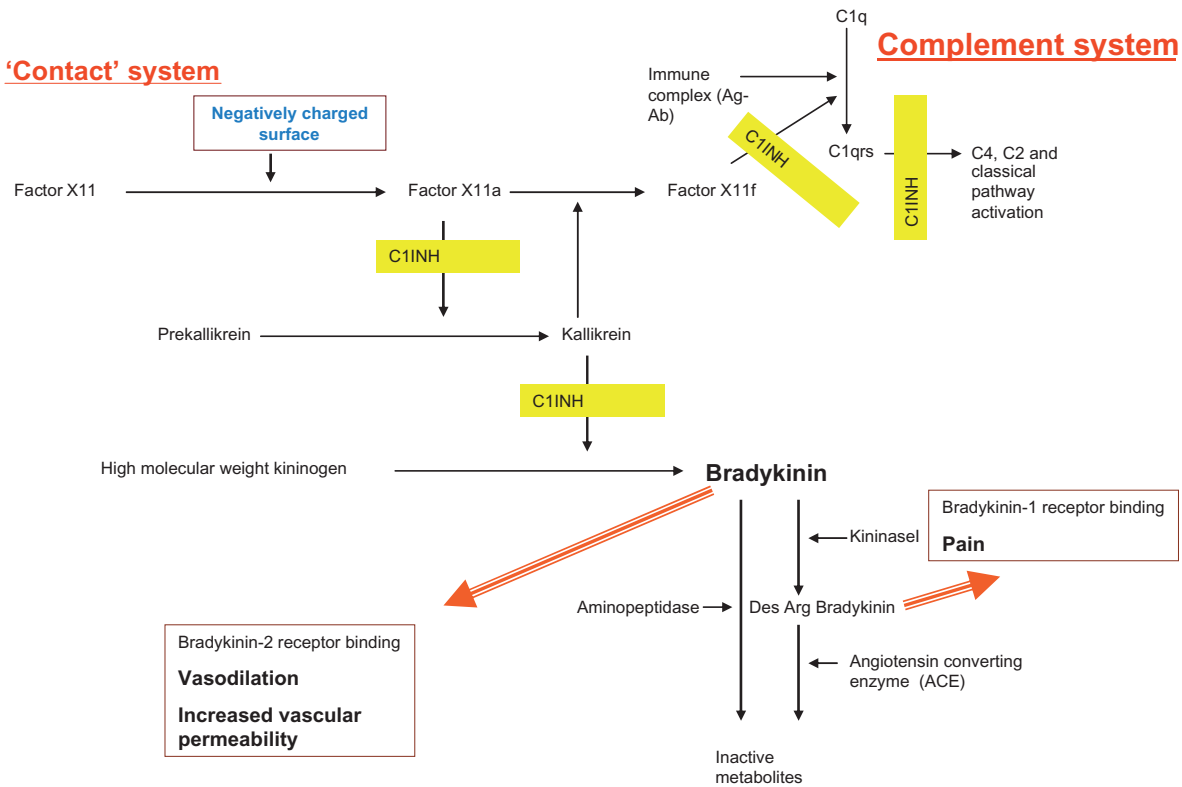

Fig. 1. Following contact activation of Factor XII by exposure to a negatively charged surface, kallikrein catalyses the production of bradykinin from high molecular weight kininogen. Contact system activation also enhances complement activation. Bradykinin binding to B2-receptors on the vascular endothelium causes local oedema. Bradykinin is metabolized by a variety of enzymes, including angiotensin converting enzyme (ACE). C1 inhibitor (C1INH) regulates the contact and classical complement pathways by inhibition at a variety of points, shown in yellow.

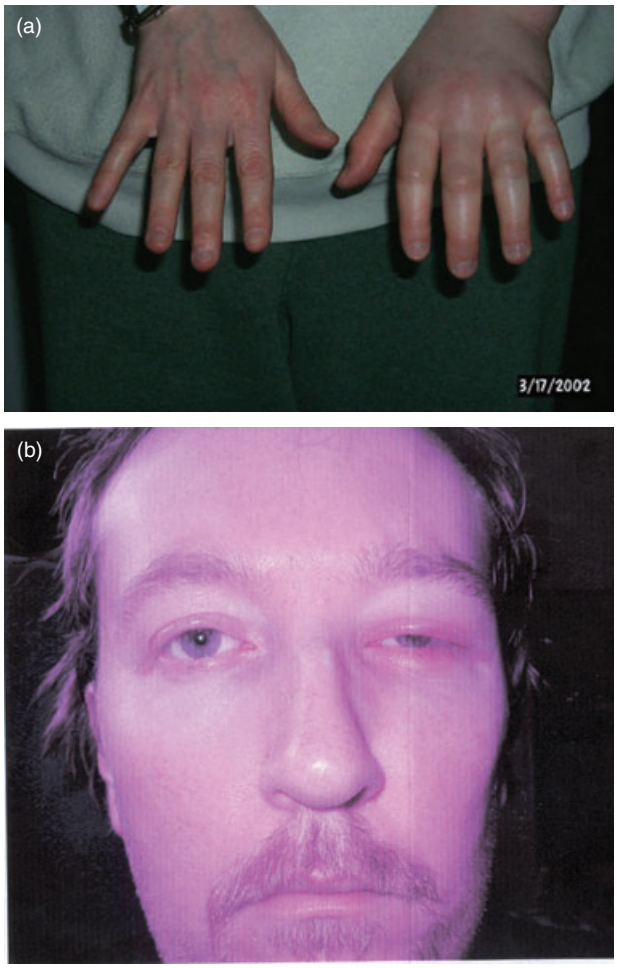

Fig. 2. (a) Swollen left hand in patient with hereditary angio-oedema (HAE). (b) Mild oedema of left eye in patient with HAE. Symptoms resolved after 500 units of C1 inhibitor given by slow intravenous injection. Delay in treatment typically results in more severe swelling requiring 1000 units of C1 inhibitor for relief.

Cutaneous swellings are diffuse, non-pruritic and usually not painful. In contrast, swellings of intra-abdominal organs are extremely painful, and associated with vomiting or diarrhoea. Hypotension, signs of bowel obstruction and ascites may be present, leading to misdiagnosis and sometimes unnecessary surgery [17–19]. Intra-oral swellings may extend to involve the larynx and cause asphyxiation, accounting for the reported mortality of up to 30%, mainly in undiagnosed patients [20–22]. Attacks are precipitated by minor trauma, particularly dental work [20], infection [23,24] or emotional stress. Angiotensin converting enzyme (ACE) inhibitors and oestrogens exacerbate HAE and are contraindicated [25].

The HAE type 3 (HAE3, HAE with normal C1 inhibitor activity)

Two groups have recently described HAE3, an autosomal dominant inherited angio-oedema without abnormalities of complement or C1 inhibitor [26,27]. Clinical features are similar to those of HAE1 and HAE2. Orofacial involvement appears to be more common, abdominal attacks slightly less frequent, and prodromal erythema not reported [28]. HAE 3 is oestrogen-sensitive and is usually symptomatic only in women, often appearing during pregnancy or after oestrogen administration [25,29]. Symptomatic men are uncommon; angio-oedema appears later in life and is less severe [30].

In some kindreds, those affected have point mutations of the coagulation factor XII (FXII) gene [31–34]. FXII transcription is enhanced by oestrogens, explaining the female preponderance [35].

Acquired C1 inhibitor deficiency (acquired angio-oedema)

Acquired C1 inhibitor deficiency starts commonly in middle age, whereas most patients with HAE experience their first attack during childhood or adolescence. This and the lack of a family history should alert the clinician to the possibility of acquired angio-oedema (AAE). Symptoms are otherwise similar to HAE [36]. AAE is associated with lymphoproliferative disease [36,37], autoimmune disease [38–40] or less commonly vasculitis [40] or infection [24]. Lymphoproliferative disease is often indolent and may only become evident some time after the AAE diagnosis [36,37]. C1 inhibitor deficiency occurs as a result of increased consumption by paraprotein, or immune complexes (AAE type I), or direct cleavage by C1 inhibitor autoantibodies (AAE type II) [38].

Idiopathic angio-oedema

In contrast to anaphylaxis, which occurs within minutes of exposure, idiopathic angio-oedema does not have a clear relationship with any allergen and may take hours to reach maximum severity. In 40% of cases, idiopathic angio-oedema is mediated by autoantibodies which bind either to the Fcε1 of the IgE itself, or to the mast cell FcεR1 causing cross-linking and histamine release [41].

Autoimmune angio-oedema is associated strongly with urticaria, and the autoimmune nature can be demonstrated by the autologous serum test. There is an association with organ-specific autoimmune disorders, particularly of the thyroid, reviewed elsewhere in this series [1].

Eight to 11% of patients do not have urticaria and may be clinically, aetiologically and therapeutically distinct [42,43]. A review from a large specialist centre identified 254 cases of idiopathic angio-oedema in a series of 929 consecutive patients with angio-oedema without urticaria, presenting over a 10-year period [44]. The majority (86%) responded to long-term anti-histamines. Non-responders requiring treatment had complete or partial symptom control with tranexamic acid (median therapy duration 46 months). This group had increased frequency of upper airways involvement or recurrent abdominal pain.

The ACE inhibitor-related angio-oedema

Although the mechanism of ACE-inhibitors (ACEI)-related angio-oedema remains to be established; evidence to date suggests that impaired metabolism of BK is the principal mechanism of this type of angio-oedema. ACE has two functions: it inactivates BK and converts angiotensin I to angiotensin II. ACE inhibition causes angio-oedema by increasing local tissue BK. Genetic variation of other enzymes involved in the catabolism of BK or substance P, such as aminopeptidase P and dipeptidyl peptidase IV, respectively, influence susceptibility to ACEI-induced angio-oedema in specific populations [4,45–47].

The ACEI-associated angio-oedema usually affects the lips, face and tongue. The gut wall is rarely involved [48,49] with episodic abdominal pain, which may lead to unnecessary surgical interventions. Fatal cases because of laryngeal angio-oedema have been reported [50–54]. Continued use of ACEIs may lead to more severe attacks over time [55,56].

The incidence of angio-oedema in people treated with ACEIs is 0·1–6% [53,57–59]. African American origin, smoking, female gender and increasing age are associated with increased risk [59–63].

Although the risk of angio-oedema is higher in the first month, most cases occur after several months up to 10 years of initiation of therapy [53,55,56,60,64–68]. Because symptoms are not associated temporally with initiation of treatment or medication time, clinicians often fail to consider this diagnosis.

Rare causes of angio-oedema

Gleich's syndrome. Gleich's syndrome is characterized by recurrent episodes of angio-oedema and/or urticaria, fever, weight gain, eosinophilia and elevated serum IgM level [69,70]. The episodes occur every few weeks to months and can last a few months. Patients are asymptomatic between attacks. Blood eosinophilia correlates with disease activity. The disease is thought to be caused by increased levels of cytokines such as interleukin (IL)-5 and IL-6 that induce inflammation and activate eosinophils. Treatment is with low-dose corticosteroids, with interferon (IFN)-α or IL-5 antagonists in refractory cases. The prognosis is good compared with other hypereosinophilic syndromes, as there is no systemic organ involvement.

A different entity of non-episodic angio-oedema and peripheral blood eosinophilia has been described in young Japanese females [71,72]. The attack usually occurs once, can last several months and resolves spontaneously. The underlying pathogenic mechanism is similar to Gleich's syndrome.

NERDS syndrome. The association of synovial nodules, eosinophilia, rheumatism, dermatitis and swelling (NERDS) syndrome has been described recently. Serum IgE levels are high. On histology the disease is characterized by necrotizing granulomas, non-specific vasculitis, eosinophilic infiltration and eosinophil major basic protein deposition. The course is usually benign [73].

Box 2. Important clinical features in evaluation of angioedema.

- Speed of onset
- Association with urticaria/without urticaria
- Site of angioedema facial/peripheral/abdominal pain
- Precipitating factors
- Natural history of attack
- Age of first onset
- Response to treatment (antihistamines/steroids/epinephrine)
- Drug history – ACE inhibitors (AR2 antags/Salicylates & NSAIs)
- Family history
- Associated features suggesting rare angioedemas-connective tissue disease or lymphoproliferative disease symptoms

Clarkson syndrome. Clarkson syndrome, or idiopathic capillary leak syndrome, can cause acute or chronic generalized oedema [74–76] because of rapid plasma extravasation. In 80% of cases it is associated with an IgG monoclonal paraprotein, and the attacks can be life-threatening because of renal failure, pulmonary oedema and shock. Treatment includes plasma expanders and corticosteroids.

Angio-oedema has also been described with therapeutic use of cytokines such as recombinant IL-2 and IFN-α [77,78].

Differential diagnosis/evaluation

Confirmation of clinical features and time–course are essential to the correct diagnosis, and therefore the importance of a careful history cannot be overemphasized (Box 2). Speed of onset of symptoms is very rapid in systemic anaphylaxis, occurring in most cases within minutes of exposure to an allergen. In other types of angio-oedema, sometimes labelled erroneously as anaphylaxis, symptoms take several hours to reach maximum intensity. Similarly, anaphylaxis often resolves within minutes of definitive treatment, whereas other types of angio-oedema improve over hours or days. Factors precipitating anaphylaxis are usually obvious, in contrast to other forms of angio-oedema (Table 1).

An important discriminating feature is the presence or absence of urticaria. Urticaria occurs with allergic and most idiopathic angio-oedemas [79], but not with ACE inhibitor-induced or HAE.

A history of peripheral swelling and recurrent abdominal pain should alert the clinician to the possibility of HAE or acquired C1 inhibitor deficiency. A relationship with oestrogens, either exogenous or endogenous, is typical of HAE [18,25]. Family history, and in most cases, onset in the first

Table 1. Clinical features and management of angio-oedema.

Type of angio-oedema	Anaphylaxis	Idiopathic (histamine responsive)	Idiopathic (histamine unresponsive)	HAE1 and HAE2	HAE3	AAE	ACE-inhibitor-related
Typical rate of onset	Minutes	Hours	Hours				
Precipitating factors	Usually obvious: food, drugs, insect stings	No clear relationship	Unknown	Trauma, infection, emotional stress, oestrogens, ACE inhibitors			ACE inhibitors
				Lymphoma, infection, autoimmunity			
Emergency treatment	Epinephrine, (antihistamines, corticosteroids, fluids)	Anti-histamines, corticosteroids, (epinephrine)	Observation and airway protection measures (plasma?)	C1 inhibitor concentrate			Observation and airway protection measures

ACE, angiotensin converting enzyme; HAE, hereditary angio-oedema.

Box 3. Rare causes of angioedema.

- Autoimmune thyroid disease
- Connective tissue disease (SLE, urticaria/vasculitis)
- Gleich's syndrome
- Clarkson syndrome
- NERDS

or second decade, make HAE more likely. However, 25% of patients with HAE have no family history of angio-oedema [80]. Salicylate, non-steroidal anti-inflammatory and opioid usage may occasionally precipitate angio-oedema in association with urticaria [42].

Features of associated disease (for example lupus) may indicate one of the less common angio-oedemas [81]. Box 3 lists the diseases that are occasionally associated with angio-oedema. Other cutaneous reactions can mimic angio-oedema, especially when symptoms are atypical. The majority of these are rare, but can occasionally be confused with angio-oedema (Box 4).

Clues to diagnosis may come from response to treatment, while bearing in mind that epinephrine in particular has a major placebo effect. Non-response to epinephrine, antihistamines or corticosteroids is typical of ACE-associated angio-oedema or HAE. An algorithm for the diagnostic approach of a patient with recurrent angio-oedema is proposed in Fig. 3.

Investigations/laboratory tests

If anaphylaxis is suspected, serial measurements of serum mast cell tryptase should be obtained. Tryptase has a half-life of 4 h; raised levels taken 1 and 4 h after the reaction, with return to baseline after 24 h, would support a diagnosis of anaphylaxis. Skin prick testing or specific IgE antibodies, where indicated, should be deferred to convalescence.

Patients with suspected C1 inhibitor deficiency should have C3/C4 complement and C1 inhibitor level and function measured. Normal C3, low C4 and low C1 inhibitor

Box 4. Angioedema mimics.

- Facial cellulitis
- Superior vena cava syndrome
- Thyroid eye disease
- Blepharochalasis
- Systemic amyloidosis
- Dependent oedema
- Hypoproteinemia-related oedema
- Crohn's disease
- Eosinophilic fasciitis
- Acute idiopathic scrotal oedema
- Burns
- Infections (viral, parasitic)

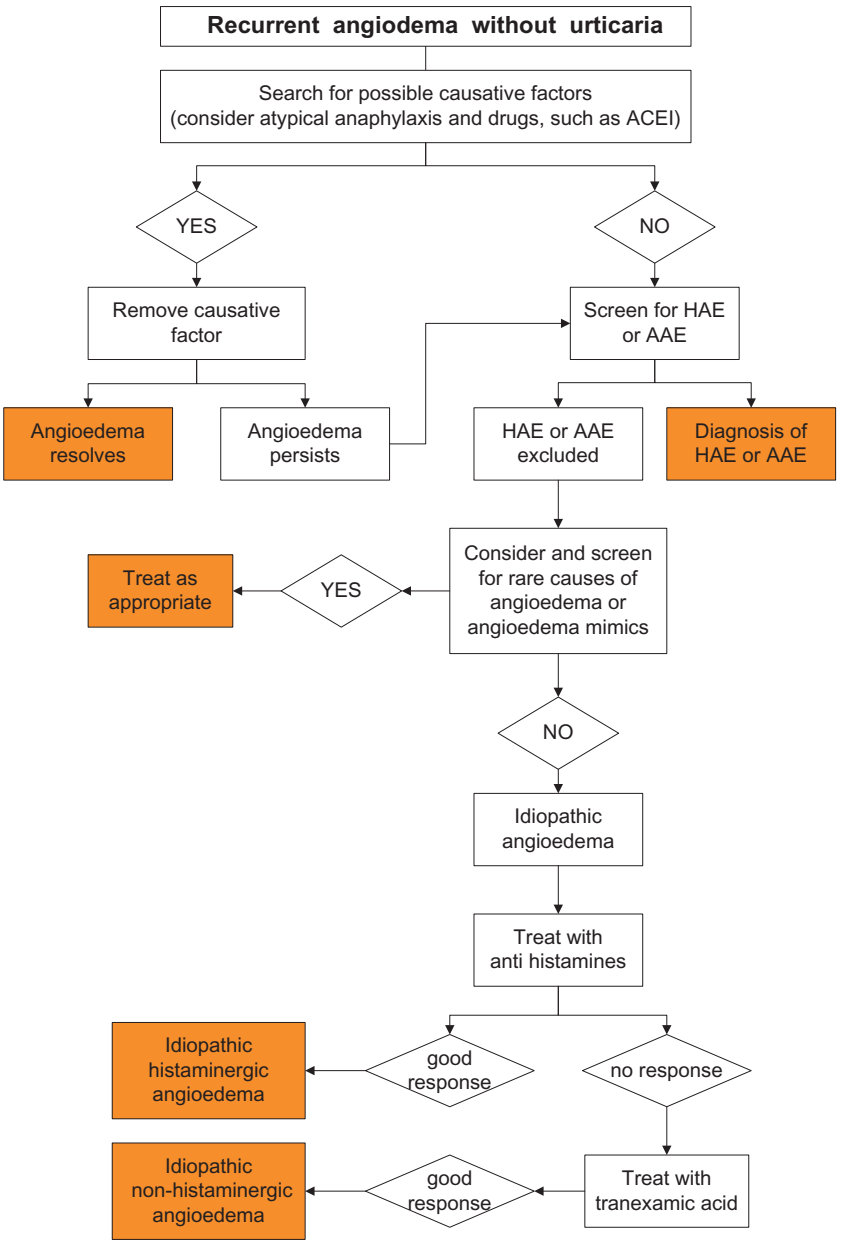

Fig. 3. Diagnostic algorithm for the patient with recurrent angioedema.

function with low C1 inhibitor level (HAE1) or normal/high C1 inhibitor level (HAE2) are diagnostic. C1q is low in acquired C1 inhibitor deficiency but normal in HAE. Of the available methods for C1 INH function, the chromogenic and enzyme-linked immunosorbent assay methods have different performance characteristics. The former may have better sensitivity whereas the latter has higher specificity, at least in some laboratories. Laboratories should generate local reference ranges, as manufacturers' reference ranges may not be optimal [82,83]. Although screening with C4 complement levels has been recommended for the diagnosis of HAE, C4 may occasionally be normal in asymptomatic individuals and therefore testing for C1 INH level and function should be performed when there is a strong clinical suspicion of HAE [83–85]. Prolonged delay in processing or refrigeration leads to sample deterioration and should be avoided [86,87]. C1 inhibitor genotyping is useful in cases of diagnostic uncertainty, although mutations can be identified only in approximately 85% of cases [88]. HAE3 genotyping is not universally available, nor are mutations identifiable in many patients, therefore diagnosis relies largely on clinical features, family history and lack of complement abnormalities.

In cases of acquired C1 INH deficiency, lymphoproliferative disease screening should include: full blood count and film, erythrocyte sedimentation rate or plasma viscosity, liver function tests, Ig and protein electrophoresis. Where suspicion is high, urinary electrophoresis for Bence Jones protein,

peripheral blood lymphocyte immunophenotyping, bone marrow examination and computed tomography imaging of the thorax/abdomen/pelvis may be required. Rheumatoid factor, anti-nuclear antibodies, C3/C4 complement levels and C1q antibodies should be performed if connective tissue disease or urticarial vasculitis is suspected. The role of testing for anti-C1 inhibitor antibodies in the diagnosis of AAE is controversial.

Treatment

The HAE1 and HAE2

Treatment of HAE may be divided into emergency treatment of attacks, long-term prophylaxis and short-term prophylaxis to cover high-risk events such as dental work. Recently published consensus documents give guidance on optimum care [89–91].

Emergency treatment of HAE1 and HAE2

Acute swellings require treatment if involving the airway, other intra-oral sites or the face or if causing significant abdominal pain. Plasma-derived C1 inhibitor concentrates have been shown to be effective in double-blind trials for attacks at all sites [92,93]. Relief is typically evident after 30–120 min, with full resolution over about 24 h. Treatment given early in the attack gives optimum benefit [92–96]. Plasma is effective where C1 inhibitor is not available, but not recommended for planned emergency use [97,98]. High-dose fibrinolysis inhibitors, such as tranexamic acid or epsilon aminocaproic acid (EACA), have been advocated [99] but are ineffective in established attacks. Icatibant, a BK-2 receptor inhibitor, has recently been licensed for the treatment of acute HAE attacks and provides a subcutaneous alternative to C1 inhibitor [101]. Future treatment options include a recombinant C1 inhibitor (Rhucin) [100,102] and a kallikrein inhibitor, ecallantide [103,104], all of which have shown efficacy in open-label and double-blind phase II/III studies [105–107].

Prophylaxis

For patients who experience frequent or life-threatening attacks, oral prophylaxis is recommended. Methyltestosterone or the 17 α-alkylated attenuated androgens, such as danazol [108], stanozolol [109], oxandrolone [110] and tibolone [111], reduce frequency of attacks for most patients. They probably work by increasing production of C1 INH by hepatocytes. Side effects are common and are related to the androgenic effects [98,112,113] or to the 17 α-alkylation [114].

Fibrinolysis inhibitors such as EACA and tranexamic acid are partially effective in some patients [99,115], possibly acting via reduced peripheral consumption of C1-inh.

For the minority of patients for whom oral therapies are unsuitable, C1-inh prophylaxis is indicated. This may be infused 'on demand' at the first sign of a moderate or severe attack, or prophylactically, usually every 2–7 days. Home therapy programmes have proved successful for severely affected patients or where access to emergency care is difficult [116,117].

The HAE3

There is no evidence to guide management of HAE3. Anti-histamines appear ineffective, but many patients benefit from anti-fibrinolytics or androgens. Acute attacks may respond to plasma or icatibant (unlicensed indication) (H. Longhurst, personal communication).

The AAE

Management of AAE is similar to that of other C1 inhibitor deficiencies. In contrast to HAE, anti-fibrinolytics are more likely to be effective than androgens [36]. C1-inh is used for acute attacks, although occasionally high doses are required [118]. In this situation, kallikrein or BK receptor antagonists would be a logical option. Treatment of any underlying condition may also be effective in prevention of attacks, and in some cases may normalize complement levels [36,119].

Idiopathic angio-oedema

Recent guidelines describe management of idiopathic angio-oedema with urticaria [120,121], reviewed elsewhere in this series [1]. For patients without urticaria, anti-histamines remain the first-line treatment. If these are ineffective, anti-fibrinolytics often provide relief [44]. For acute attacks, anti-histamines, corticosteroids and sometimes epinephrine are usually used. For some patients, notably those whose angio-oedema is BK-mediated, these will be ineffective [122]. Therefore patients should be observed, with measures to protect the airway if necessary, until the attack is clearly resolving. Plasma may be effective [67,123]and BK receptor or kallikrein inhibition is of interest for the future.

The ACE-inhibitor induced angio-oedema

Discontinuation of the drug results in resolution of symptoms in the majority of cases [67,124]. Although angiotensin receptor antagonists have also been reported to cause angio-oedema [125], switching to this type of drugs is usually successful [124]. C1 inhibitor concentrate and plasma have both been used successfully to treat attacks of ACE-inhibitor associated laryngeal angio-oedema [126]. Therapies currently under trial for HAE such as icatibant and ecallantide may be future options [67,106].

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