Angioedema – assessment and treatment

BACKGROUND Angioedema has numerous hereditary, acquired and iatrogenic causes. A number of studies show that angioedema is inadequately assessed and treated during its acute phase as well as in the follow-up period. We present an algorithm for the assessment and treatment of patients with angioedema.

KNOWLEDGE BASE The article is based on a literature search in PubMed, a review of bibliographies and the authors' clinical experience and research.

RESULTS The majority of angioedema patients have accompanying urticaria. Pathophysiologically, angioedemas are divided into histaminergic and non-histaminergic forms. In a large group of patients no positive trigger is identified. On assessment in hospital the most frequently identified cause is drug intake, normally angiotensin-converting-enzyme inhibitors and NSAIDs , while allergic/pseudoallergic and idiopathic reactions are more commonly seen in general practice. There are a number of rare causes of angioedema, all of which are important to keep in mind. The acute and prophylactic treatment will depend on the subtype of angioedema and is best provided through cross-disciplinary collaboration.

INTERPRETATION Angioedema is a potentially life-threatening condition and should be assessed and treated systematically. It is important to remember that angioedema is either histaminergic or non-histaminergic, as the treatment of the two types is different.

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MAIN MESSAGE

Angioedema is a localised, self-limiting swelling of the skin and/or submucosa with or without accompanying urticaria.

Monosymptomatic angioedema may be drug-induced, associated with hereditary angioedema types I-III or acquired C1 inhibitor deficiency, or it may be idiopathic.

The treatment of histaminergic angioedema will depend on its cause; during the acute phase the treatment will involve antihistamine, corticosteroid and, in severe cases, adrenaline.

Non-histaminergic subtypes of hereditary angioedema, acquired C1 inhibitor deficiency and ACE inhibitor-induced angioedema may be treated with C1 inhibitor concentrate or icatibant.

Angioedema is a sudden localised and often asymmetric swelling of skin and mucous membranes caused by temporarily increased endothelial permeability with plasma extravasation in the deep dermis and subcutis/submucosa (Figure 1). Angioedema varies in severity and is always self-limiting after a number of hours or up to a few days. Loose facial and genital skin is often involved, but the extremities, airways and abdomen may also be affected. The majority of patients with angioedema have accompanying urticaria (1–4).

There are numerous reasons for developing angioedema: some causes are hereditary, others are acquired or iatrogenic. In a large group of patients no positive trigger factor is identified, and approximately 1 in 3 patients assessed in hospital eventually receive the diagnosis of idiopathic angioedema (5, 6). When the assessment is made in hospital, the most frequently identified cause is the intake of drugs, most often angiotensin-converting-enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs (NSAID) and beta-lactam antibiotics (5, 7). Histaminergic angioedema (normally accompanied by urticaria) and idiopathic cases are most commonly seen in general practice.

This article reviews the various forms of angioedema with and without accompanying urticaria as they present to a wide variety of specialist disciplines and can give rise to diagnostic and therapeutic problems. Hereditary angioedema types I-III and acquired C1-inhibitor (C1INH) deficiency will not be reviewed in detail; reference is instead made to existing literature (8–10).

Knowledge base

Studies on the assessment and treatment of angioedema were found by conducting a literature search in PubMed, using the search words «angioedema», «anaphylaxis», «urticaria», «hereditary angioedema», «idiopathic angioedema», «allergic angioedema» and combinations of these search words. Only articles in English, Danish and Norwegian published since the year 2000 were included in the initial search. A search for exclusively «angioedema» produced 5 375 hits, thus proving the need for a more restrictive search strategy. The search produced 438 hits. In order to find the original articles, the bibliographies of selected reviews were then examined. The search was terminated on 1 August 2012.

Epidemiology

Epidemiological data is scarce in the literature, where the lifetime prevalence for angioedema and/or urticaria is given as up to 25 % (11). A population survey from Denmark gives a lifetime prevalence for angioedema of 7.4 % (self-reported data), of which the condition becomes chronic in approx. 50 % of cases. Just over a third of the angioedema patients reported accompanying urticaria (12). ACE inhibitor-induced angioedema is found in 0.1 % – 2.2 % of patients treated, the incidence being higher in the black population than in the Caucasian population (13–17).

39–46 % of hospitalised patients with acute angioedema are treated with ACE inhibitors (6,18); the percentage is lower

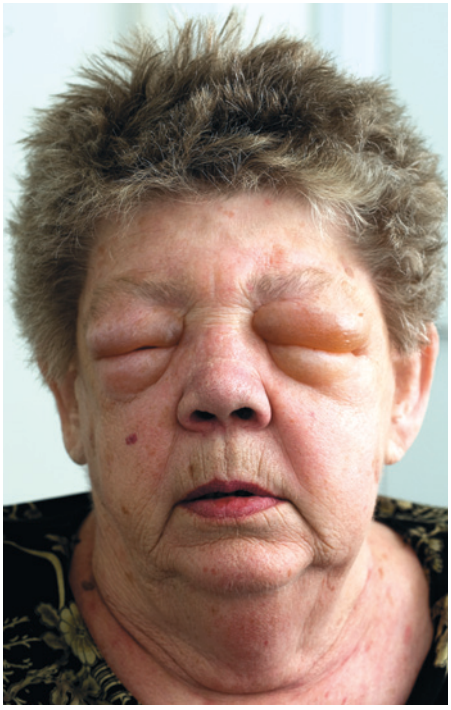

Figure 1 *Bilateral, periorbital angioedema induced by treatment with angiotensin converting enzyme inhibitor. The patient has given her consent to the publication of the picture.*

(11 %) for outpatients referred for assessment of angioedema (5). In general practice, histaminergic (allergic/pseudoallergic) and drug-induced angioedemas are believed to be the most frequent forms (19).

Angioedema and urticaria

Urticaria and angioedema often occur together. It is important for the assessment of angioedema to know whether there is accompanying urticaria as this gives a pointer to the pathophysiology and consequently the treatment strategy (Figure 2). The most important differences between the two conditions are set out in Table 1.

Classification and pathophysiology

Histaminergic angioedema

Histaminergic angioedema occurs when mast cells and basophil granulocytes release histamine and other vasoactive molecules. Patients most often present with accompanying urticaria, and sometimes bronchospasm, and may develop life-threatening anaphylaxis. The condition often occurs spontaneously (without a known cause), is rarely caused by an allergic reaction, in which case it would be IgE-mediated, while morphine, x-ray contrast agents, NSAIDs etc. may cause direct mast cell degranulation and intolerance via other non-allergic mechanisms such as inhibition of cyclooxygenase (also referred to as a pseudoallergic reaction) (3, 4, 7).

Approximately 30 % of patients with chronic spontaneous urticaria have circulating antibodies against IgE or the IgE-receptor, which similarly may trigger angioedema (autoreactivity) (3, 4, 11). The incidence of autoimmune isolated angioedema is not known. Physical stimuli such as pressure, cold, vibrations or ultraviolet light may trigger angioedema (physical angioedema) in some people, presumably via histamine and other mast cell derived mediators. The mechanism is not fully understood (20).

Angioedema caused by infection is primarily associated with infections of the upper airways, but may also occur in connection with parasitic infestations (3, 5, 21). The mechanism by which infections activate mast cells is unclear.

Non-histaminergic angioedema

Non-histaminergic angioedema may be triggered by bradykinin (bradykinergic angioedema) and complement-derived mediators (5, 22, 23). Bradykinin is a vasoactive nonapeptide from the contact activating system which is quickly degraded by various pepti-

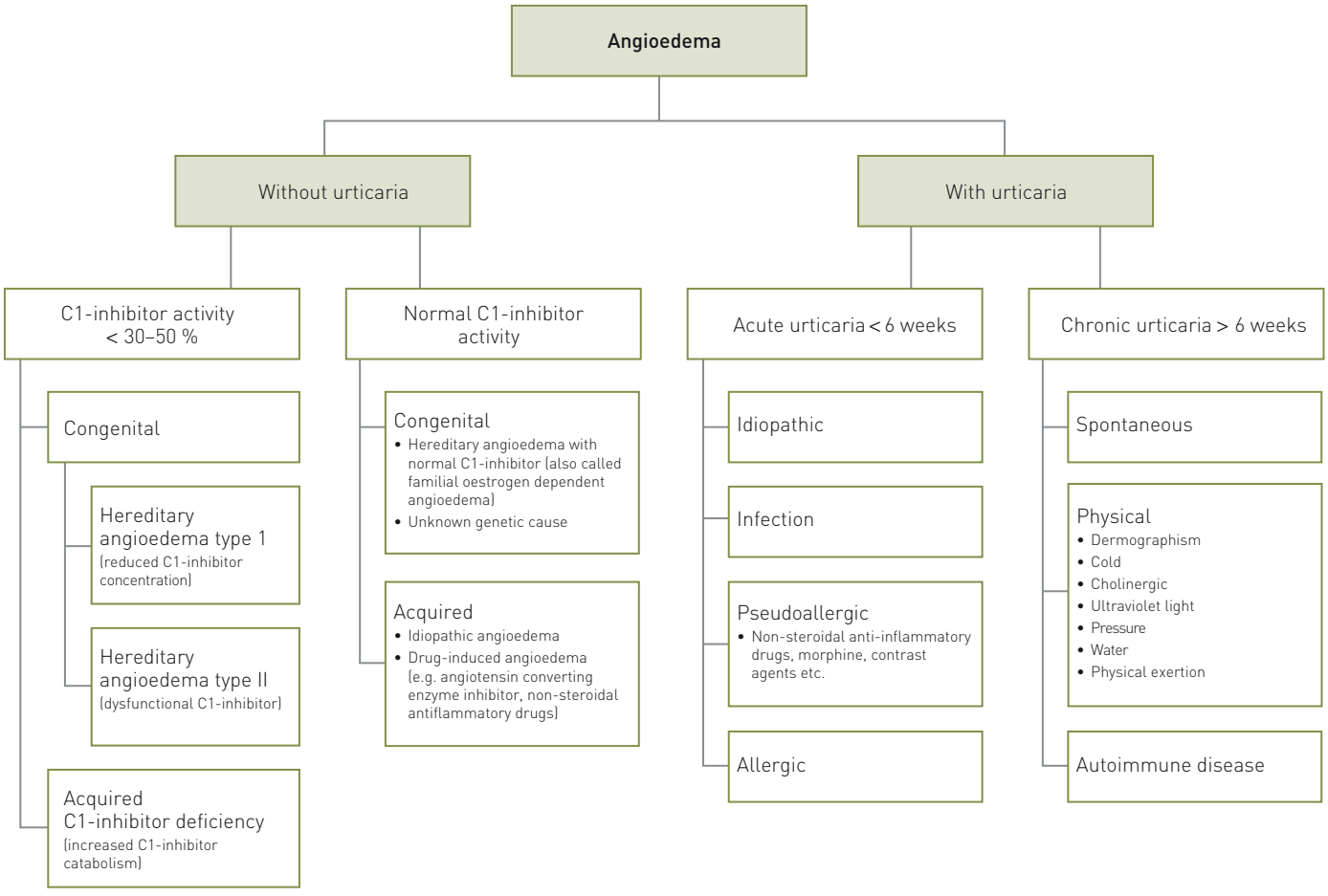

Figure 2 *Classification of angioedema and its most common causes*

dases such as angiotensin-converting enzymes (ACE) and carboxypeptidase N. Other enzymes that contribute to the degradation of bradykinin include neutral endopeptidase, aminopeptidase P and dipeptidyl peptidase IV (DPP-IV) (23).

ACE inhibitor treatment reduces the conversion of angiotensin I to angiotensin II and inhibits the degradation of bradykinin. An accumulation of bradykinin is therefore considered to be the most significant cause of angioedema induced by ACE inhibitor drugs (24). The activity of bradykinin catabolising enzymes may affect the patients' individual risk of angioedema. It has already been shown that there is lower plasma activity of aminopeptidase P in patients with ACE inhibitor-induced angioedema than in hypertonic patients without angioedema who have been treated with ACE inhibitors (25).

Other drugs that interfere with the renin-angiotensin-aldosterone system (RAAS), such as angiotensin II receptor-blockers and the direct renin inhibitor aliskiren, may also cause angioedema (24). Similarly, the new antidiabetic DPP-IV inhibitors can induce angioedema, particularly in patients treated with ACE inhibitors (26, 27).

Patients with hereditary angioedema are deficient in C1INH (hereditary angioedema type I) or there are deficiencies in the functional activity of C1INH (hereditary angioedema type II), which ultimately increases the amount of bradykinin (8, 10). Approximately 1 in 4 patients with hereditary angioedema type III, also referred to as familial oestrogen-dependent angioedema, or hereditary angioedema with normal C1INH, have mutations in coagulation factor XII which cause increased formation of bradykinin (10, 28). There are also descriptions of sporadic angioedema in women on oral contraceptives or oestrogen substitution, or in connection with pregnancy (29, 30). It appears that oestrogen can induce coagulation factor XII and kallikrein, as well as reduce C1INH, which raises the bradykinin level (31).

Autoimmune thyroid disease may present with angioedema (3–5, 22). Other autoimmune reasons for developing angioedema have also received attention, but the mechanisms and relationships involved have yet to be explained.

Idiopathic angioedema

This is the most common diagnosis among patients referred to specialist dermatology or allergology departments for assesment of angioedema (4, 5). The definition is a minimum of three angioedema episodes within a period of 6–12 months without a cause being identified despite thorough medical examination and regular re-evaluations.

Assessment (Box 1) and treatment is challenging for the doctor as well as the patient and the process is often conducted in partnership with the patient's GP. The health-related quality of life is reduced in many patients with angioedema due to anxiety and frustration associated with unpredictable and hard-to-explain attacks (4).

Rare forms of angioedema

Acquired C1INH deficiency occurs secondary to malignant or autoimmune disease. The case history is similar to hereditary angioedema and is characterised by increased catabolism of C1INH (32).

Gleich's syndrome is recognised by angioedema, raised s-IgM, fever, weight increase, eosinophilia and, in some cases, urticaria. The cause is believed to be increased levels of pro-inflammatory interleukines IL-5 and IL-6. The treatment consists of corticosteroids and interferon-α or interleukin-5 antagonists (33, 34).

Food-dependent exercise-induced anaphylaxis may present as angioedema following physical activity combined with intake of certain foods such as wheat (35).

Systemic capillary leak syndrome (Clarkson's disease) involves sudden inexplicable attacks of massive angioedema with a serious prognosis. Biochemical signs include haemoconcentration, hypoalbuminaemia and monoclonal gammopathy, and sometimes myelomatosis. Treatment with terbutaline, theophylline and corticosteroid is used in combination with plasma expanders (36).

Differential diagnoses

Patients with diseases similar to angioedema (pseudoangioedema) are not infrequently referred for assessment of angioedema. These diseases include acute contact eczema, cellulitis, Morbihan's disease, connective tissue disease with facial oedema or periorbital oedema (systemic lupus erythematosus, scleroderma, dermatomyositis, Sjögren's syndrome), drug reaction with eosinophilia and systemic symptoms (DRESS), hypocomplementary urticarial vasculitis, orofacial granulomatosis, myxoedema, superior vena cava syndrome and dermatitis artefacta (3–5, 7).

Assessment

Patients with diagnostically unresolved recurrent angioedema should be assessed systematically. To secure a correct diagnosis, the most important assessment factor is a precise and comprehensive anamnesis, especially with reference to location, severity, duration and trigger factors. Additionally, any accompanying symptoms should be clarified, as well as the patient's family history of atopy and angioedema. A travel anamnesis should also be requested, and questions should be asked about the effect of any treatment initiated (2–4, 37).

If no obvious cause is identified, paraclinical assessment of the patient should commence (Box 1). In connection with any supplemental assessment, e.g. by a specialist doctor or in hospital, the following tests may

Table 1 Characteristic features of angioedema and urticaria

	Angioedema	Urticaria
Location	Swelling of skin and/or submucosal tissue Normally the face and genitalia, but extremities, airways and abdomen may also be involved.	Skin (localised or generalised)
Colour	Skin-coloured or pale red	Normally red, sometimes clearing centrally
Itchy	Not normally, sometimes light pain	Normally
Duration	Typically 24–48 hours	Temporary skin changes that disappear or move within 24 hours, but may also be of a chronic nature. In case of delayed pressure urticaria, the various elements may present up to several hours after the physical stimulus
Size	Varying	From a few millimetres to several centimetres
Symmetry	Asymmetric	Varying
Pathology	Most often acellular edema	Mast cells, basophils, neutrophils, eosinophils, monocytes and T lymphocytes in varying numbers

be relevant: skin prick test, identification of specific IgE antibodies, histamine release test and possibly a skin biopsy. Potential links between drug intake and angioedema should be considered by consulting reference literature, e.g. www.felleskatalogen.no, product summaries, PubMed or specific reference books such as Litt's Drug Eruption Reference Manual (38).

If there is reason to suspect involvement of food or medication, a provocation test should be conducted while providing anaphylaxis preparedness. It is, however, important to distinguish between allergic reactions and non-histaminergic angioedema caused by e.g. ACE inhibitors, DPP-IV inhibitors or oestrogen as these are class-related and consequently should not be provocation tested. If diagnostic clarification is still not achieved, despite the targeted efforts of a specialist department, the condition will have to be ascribed to the large group of idiopathic angioedema, after which the treatment should be symptomatic.

Treatment

The treatment of angioedema will depend on its subtype. In acute severe instances treatment is provided by A&E, Intensive Care or Ear, Nose & Throat departments. In acute instances of angioedema of the airways, keeping the airways clear is paramount. If the airways are threatened, intubation should be carried out as soon as possible, as emergency tracheostomy may otherwise be required. The favoured option will often be awake nasal intubation guided by a flexible nasendoscope. Due to the risk of aspiration, an oral airway should never be used to maintain clear airways on patients who are awake.

Despite limited evidence, medical treatment of acute histaminergic angioedema consists of antihistamine i.v./i.m. (adults e.g. Tavegyl 1–2 mg), intravenous corticosteroid (adults e.g. Solu-Medrol 80–120 mg) and, for laryngeal edema, inhalation of nebulised adrenaline at 5–10 litres oxygen/min (adrenaline 1 mg in 5 ml NaCl) and possibly intramuscular adrenaline (always in cases of anaphylactic shock) (39). Bradykinergic angioedema in the acute phase may be treated with C1INH concentrate (Berinert, Cinryze, Ruconest) or bradykinin receptor-2 antagonist icatibant (Firazyr) (9, 10, 32, 40, 41). For this group of patients adrenaline is not effective, or only marginally/briefly effective and may trigger unnecessary and sometimes severe side effects involving tachycardia, hypertension, arrhythmia and a risk of cerebral and cardiac insult (felleskatalogen.no).

Angioedema caused by infection are addressed by treating the underlying infection.

In their chronic phases histaminergic angioedema can be treated with non-sedating antihistamines, the doses of which may be increased when disease control is suboptimal, or combined with a leukotriene receptor antagonist (montelukast, limited evidence) or H_2 antagonist (limited evidence). Immune modulation or immunosuppressant therapies are used in certain treatment-resistant cases, e.g. cyclosporine, azathioprine or methotrexate (2–4, 11). Similarly, anti-inflammatory drugs and antibiotics such as sulphasalazine, dapsone and hydroxychloroquine are used with varying degrees of effect and evidence (4, 11). Systemic corticosteroids are often effective, but due to their long-term side effects should be used only briefly in case of flare-ups or when acute treatment is required (3–5, 11). Plasmapheresis and intravenous immunoglobulin are used in rare cases (3–5). In clinical trials and off-label at the clinic omalizumab is used for the treatment of both chronic urticaria and histaminergic angioedema with good effect. As yet, the drug is approved only for the treatment of asthma (42).

Angioedema triggered by specific drugs, foods or physical stimuli is treated by trying to eliminate the trigger factor. Patients with ACE inhibitor-induced angioedema may go on to angiotensin II-receptor blockers (24). Long-term treatment with tranexamic acid or weak androgens (e.g. danazol) may be used for chronic bradykinergic angioedema and idiopathic angioedema (3, 10, 43, 44).

Follow-up and treatment of patients with chronic angioedema are often conducted by the GP, an allergologist, pulmonary specialist or dermatologist. Patients whose angioedema has a systemic cause are followed up and treated by medical specialists, e.g. within the fields of rheumatology, endocrinology (thyroid disease), pulmonary medicine or paediatrics. Educating the patient forms a significant part of the treatment (4).

Discussion

The prevalence of angioedema and the incidence of accompanying urticaria are uncertain, as many of the existing surveys suffer from selection bias. The original study by Champion et al. from 1969 has been much quoted in the literature. It describes a group of patients who had been referred to a specialist hospital department for assessment of urticaria and/or angioedema (1). There is also a study of angioedema patients attending an A&E department (6), and a new Danish population survey for which patients with angioedema were selected by questionnaire (12). The figures provided by the latter study must be presumed to be close to the true prevalence, but they are based entirely on self-reporting, which gives the study a certain weakness. Also, there may be selection bias associated with questionnaire surveys as people with symptoms may be more likely to respond, thus giving rise to a false high incidence. In a German population survey, Zuberbier et al. (45) found monosymptomatic angioedema in 6.1 %; a third of these cases presented with accompanying urticaria. This matches the findings made by Madsen et al. (12).

BOX 1

Paraclinical tests for assessing recurrent angioedema. Assessment to be adjusted to the individual patient

Acute angioedema without a known trigger factor:

- Haematology, liver count, kidney count, CRP, SR, TSH, s-tryptase, IgE

If the cause remains unclear when the swelling has subsided, the assessment programme will depend on symptomatology and may include:

- Chest x-ray
- Thyroid antibodies, HR test in case of chronic urticaria
- Assessment for hereditary angioedema or acquired C1 inhibitor deficiency (C1 inhibitor concentration and function, C4, C1q)
- Skin biopsy in rare cases
- Skin prick test, allergen-specific IgE, possibly provocation test at a facility equipped for treatment of anaphylaxis.ANA, ANCA, SSA, SSB, complement-screening, M-component
- Urine dipstick ABS or urine microscopy

In Scandinavia there are no national guidelines for the assessment and treatment of patients with recurrent angioedema. A number of studies have shown that a long period may pass between the first angioedema episode and the correct diagnosis, particularly with respect to hereditary angioedema (5, 13, 46). Similarly, cases of ACE inhibitor-induced angioedema are easily overlooked, as they may develop several years after the drug treatment was initiated and present inconsistently, despite continued treatment (5, 7, 13, 14, 24). The literature provides numerous case histories in which patients with recurrent angioedema have failed to have the trigger drug discontinued or have not been correctly assessed, thus resulting in emergency tracheostomy, hypoxic brain injuries and death. Most often, bradykinergic angioedema is incorrectly interpreted as histaminergic; accordingly, appropriate assessment and treatment are not provided (5, 46). At the same time, the incidense is rising, because increasing numbers of people are being treated with predisposing drugs such as ACE inhibitors and DPP-IV inhibitors (18, 24, 26, 27).

This emphasises the need for more information and the importance of distinguishing between histaminergic and non-histaminergic angioedema, as only the former will respond to classic acute A&E treatment with adrenaline, antihistamine and corticosteroid. Non-histaminergic angioedemas make up a heterogenous group; its sub-group of potentially lethal bradykinin-induced angioedema

may be treated effectively with specific medication. Similarly, the different types of angioedema respond to different prophylactic treatments, which further emphasises the importance of correct diagnostics. The primary assessment may be conducted by the GP or the treating hospital department. Patients whose diagnosis remains unresolved may be given a referral to a dermatologist/allergologist for assessment.

Conclusion

Patients with recurrent angioedema present to a number of different specialist disciplines and may be difficult to assess and treat. The majority of patients have histaminergic angioedema (normally accompanied by urticaria), while a smaller but significant group has non-histaminergic (most often bradykinin associated) angioedema. We present an assessment and treatment algorithm for use during the initial assessment of patients presenting with acute angioedema and for their continued assessment as outpatients.

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The author has completed the ICMJE form and declares the following conflicts of interest: She has been involved in clinical research or educational events involving CSL Behring, Jerini/Shire, Sobi and ViroPharma.

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