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.

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.

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 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 (autoimmunity) (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-
Swelling of skin and/or submucosal tissue from a few millimetres to several centimetres. Skin (localised or generalised) normally not normally, sometimes light pain. Most often acellular edema with ACE inhibitors (26, 27). Angioedema, particularly in patients treated antidiabetic DPP-IV inhibitors can induce cause angioedema (24). Similarly, the new renin inhibitor aliskiren, may also cause increased formation of bradykinin (8, 10). Approximately one in four patients with 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 contraceptive 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 allergy departments for assessment 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 gammapathy, and sometimes myelomatisis. 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 and facial oedema or peri-orbital 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 be considered:

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristic features of angioedema and urticaria</th>
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<tbody>
<tr>
<td><strong>Angioedema</strong></td>
<td><strong>Urticaria</strong></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Swelling of skin and/or submucosal tissue</td>
</tr>
<tr>
<td></td>
<td>Normally the face and genitalia, but extremities, airways and abdomen may also be involved.</td>
</tr>
<tr>
<td><strong>Colour</strong></td>
<td>Skin-coloured or pale red</td>
</tr>
<tr>
<td><strong>Itchy</strong></td>
<td>Not normally, sometimes light pain</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Typically 24–48 hours</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td>Varying</td>
</tr>
<tr>
<td><strong>Symmetry</strong></td>
<td>Asymmetric</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>Most often acellular edema</td>
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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 anaesthesia 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 antagonists (cicatibant (Firazyr) (9, 10, 32, 40, 41). For 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)."
The majority of patients have histaminergic edema. Since 2002 she has participated in an international collaborative project on hereditary angioedema. The author has completed the ICMJE form and declares no conflicts of interest.

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References