Angio-oedema: an overview of differential diagnosis and clinical management

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Key points
Angio-oedema is a rare, but potentially life-threatening condition. Anaphylaxis, hereditary angio-oedema (HAE), and acquired angio-oedema (AAE) are the most likely conditions to cause airway oedema and are therefore the most relevant for the anaesthetist.

Prompt recognition and treatment of the underlying clinical condition can prevent significant morbidity and mortality.

Once the diagnosis is made, preventative measures should be put in place to avoid future episodes of angio-oedema.

Advances have been made in recent years in the development of new treatments for HAE and acquired angio-oedema (AAE).

Causes of angio-oedema
Angio-oedema is caused by an increase in vascular permeability with extravasation of fluid into submucosal or subcutaneous tissues. The exact mechanism that leads to the increase in vascular permeability depends on the underlying clinical condition. It can result from mast cell degranulation (in allergic reactions), accumulation of bradykinin [in angiotensin-converting enzyme (ACE)-inhibitor treatment], or occur from lack of C1 esterase (in hereditary or acquired angio-oedema), that also leads to an increase in bradykinin. In cases where, despite thorough investigation, no underlying cause can be identified, the angio-oedema is deemed idiopathic.

The most common trigger for angio-oedema is an allergic reaction. The second most common presentation is idiopathic angio-oedema, followed by ACE-inhibitor-induced angio-oedema. Hereditary and acquired angio-oedema (AAE) are very rare conditions.

Allergic angio-oedema
Allergic angio-oedema can be due to IgE-mediated anaphylaxis or non-IgE-mediated anaphylaxis (previously known as anaphylactoid reactions). The final common pathway for these reactions is mast cell degranulation, release of inflammatory mediators, such as histamine, and complement activation. Clinically they present in the same way. Severe allergic reactions can display a number of signs and symptoms, such as cutaneous flushing and urticaria (70%), bronchospasm (40%) and cardiovascular signs ranging from hypotension to cardiac arrest (75%). Symptoms can vary from merely cutaneous signs to the full-blown picture of anaphylactic shock and tend to manifest within a few minutes of antigen exposure. During anaesthesia, recognition of an allergic reaction can be delayed, as key features such as bronchospasm and hypotension can result from many other causes. Angio-oedema only occurs in 12% of anaphylactic reactions. Onset can be fulminant, with rapid development of airway compromise.

Diagnosis
Diagnosis relies upon interpretation of the clinical picture, in the context of exposure to a potential allergen. During anaesthesia, neuromuscular blocking agents, antibiotics, and nonsteroidal analgesics are the most common culprits. Clues might lie in the medical history, such as previous sensitivity to drugs, food products, insect bites, latex, etc. However, as in the case of non-IgE-mediated reactions, previous exposure to an allergenic agent is not always necessary.

Treatment
Co-operation within a skilled team is essential, to simultaneously diagnose and treat, following...
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the ABC approach. The suspected antigen should be removed immediately. Ventilation with 100% oxygen should be maintained and tracheal intubation considered early. Smaller endotracheal (ET) tube sizes may be necessary to succeed in an oedematous airway. If hypotension is present, elevation of the legs, commencement of basic life support, if indicated, and administration of i.v. crystalloid at rapid infusion rates are the first steps in treatment. Early administration of epinephrine (0.5 ml increments of 1:1000 i.m. or 0.5 ml boluses of 1:10 000 i.v.) is essential. Secondary treatments include steroids (hydrocortisone, 100–300 mg i.v.) and antihistamines (chlorphenamine, 10–20 mg i.v.).

Bronchodilators (salbutamol, 5 mg nebulized or 3–20 μg min⁻¹ i.v. infusion) can be used to treat persistent bronchospasm. I.V. aminophylline or magnesium sulphate can also be considered. A catecholamine infusion (epinephrine 0.05–0.1 μg kg⁻¹ min⁻¹ or norepinephrine 0.05–0.1 μg kg⁻¹ min⁻¹) may be required, as cardiovascular instability may last several hours. Patients will subsequently require close monitoring in a high dependency area.¹

Investigations

The most important test to help confirm a diagnosis of anaphylaxis is a serum mast cell tryptase. In the case of reactions during general anaesthesia, the ideal sample requirement is an initial sample as soon as feasible after resuscitation has started, a second sample at 1–2 h after the start of symptoms, and a third sample either at 24 h or in convalescence (e.g. in a follow-up allergy clinic). The latter provides a baseline tryptase level. If tryptase levels are raised, the patient should be referred to an allergy clinic for skin prick or specific IgE testing. Issue of a medicalert bracelet (analyser and an EpiPen®) should also be considered. Drug reactions should be reported to the CSM and the AABGI National Anaesthetic Anaphylaxis Database. According to AAGBI guidelines, there should be a dedicated anaesthetist within every department who is the clinical lead for anaesthetic anaphylaxis.

The immunological mechanism

The immunological mechanism underlying type I allergic reactions is the IgE-mediated degranulation of mast cells and basophils after exposure to an antigen, leading to release of histamine, leukotrienes, tryptase, and prostaglandins and activation of the complement cascade. Non-IgE-mediated reactions are caused by direct mast cell degranulation, release of mediators, such as histamine, and complement activation. There is no prior antigen exposure or IgE involvement.

Idiopathic angio-oedema

In a considerable number of patients attending outpatient allergy clinics, acute or recurrent angio-oedema has occurred without any obvious trigger. In these situations, the angio-oedema can occur in isolation and is then known as idiopathic angio-oedema, or together with urticaria, when it is called chronic idiopathic (spontaneous) urticaria.² Recent studies in our own department, at Plymouth Hospitals NHS Trust, have shown a role of stress in these conditions. Such patients are at risk of angio-oedema due to the physical and emotional stress associated with surgery, although attacks occurring in the immediate or later postoperative period are often difficult to distinguish from reactions to drugs given either during general anaesthesia or on the patient’s return to the ward (analgesics, antibiotics). Although laryngeal oedema in this scenario is less common, it may still occur.

Diagnosis

Diagnosis is made by exclusion of any of the other causes of angio-oedema.

Treatment

Treatment consists of antihistamines and, in refractory cases, corticosteroids. Annual medical review is also recommended to exclude any underlying occult disease.

ACE-inhibitor-related angio-oedema

ACE-inhibitors and, less commonly, angiotensin II inhibitors are the most common causative agents resulting in angio-oedema. It is particularly common in African Americans and can occasionally lead to life-threatening airway oedema. ACE-inhibitors should certainly be avoided in patients with a known history of idiopathic or hereditary angio-oedema (HAE).

Most of the ACE-inhibitors on the market have been reported to cause angio-oedema but it is not clear why only some patients on ACE-inhibitor treatment develop this side-effect. Angio-oedema occurs in 0.1–0.5% of the patients treated with ACE-inhibitors. Symptoms are usually sporadic and resolve within 2 months of discontinuing the medication.

Angiotensin converting enzyme normally cleaves angiotensin I and bradykinin into smaller molecules. Bradykinin is inactivated by this process. It is thought that patients who develop angio-oedema on ACE-inhibitor treatment have a congenital or acquired impairment of carboxypeptidase N activity, an enzyme that normally degrades bradykinin. This could lead to bradykinin excess, causing angio-oedema.³

Diagnosis

Diagnosis can be made on the basis of a thorough medical history, the fact that the angio-oedema is particularly affecting the lips and mouth, and a lack of a family history of angio-oedema. C3 and C4 levels are normal.

Treatment

Treatment consists of drug cessation and avoidance of ACE-inhibitors. Subcutaneous and nebulized epinephrine should
be administered in cases of airway compromise, along with emergency airway management as indicated.

**C1 esterase inhibitor deficiency**

C1 esterase inhibitor (C1-INH) plays an important role in the complement system. It prevents autoactivation of C1, the first factor of the classical pathway. It also inhibits several proteases involved in the coagulation and fibrinolytic system activation, although this seems to have no clinical effect on haemostasis or clotting. The lack of C1-INH leads to uncontrolled complement activation with the release of vasoactive and chemotactic peptides, causing increased vascular permeability, vasodilatation, and contraction of the vascular smooth muscle. This causes acute, localized, non-pitting, non-pruritic, non-erythematous, and demarcated angio-oedema. Oedema can involve any part of the body, including the gut wall. Swelling typically lasts for 2–5 days before resolving spontaneously. The major mediator is thought to be bradykinin. Agents used for allergy treatment (epinephrine, steroids, antihistamines) will be ineffective.

**Symptoms**

Symptoms are those of swelling in affected areas and potential airway compromise, and symptoms of acute bowel obstruction with anorexia, vomiting, and severe abdominal pain. Areas most commonly affected by swelling include the face (lips, eyelids, tongue), extremities, and genitals. Misdiagnosis is common since the symptoms associated with angio-oedema can mimic other, more common, clinical conditions such as allergy, appendicitis, gallbladder spasm, diverticulitis, or irritable bowel syndrome. This can lead to unnecessary medical procedures and treatments or even psychiatric referral.4 C1 esterase inhibitor deficiency can be hereditary or acquired. Clinically these two entities are indistinguishable.

**Hereditary C1 esterase inhibitor deficiency**

Hereditary C1 esterase inhibitor deficiency, also known as HAE, has an estimated prevalence of 1:50,000 and affects men and women equally. It is either due to impaired production of C1 esterase inhibitor (type 1, 85% of cases) or poor function of the protein (type 2, 15% of cases). More recently, another form of HAE (type 3) has been discovered, where C1-INH levels and function appear normal. It only occurs in women and is thought to be an X-linked condition where a mutation in coagulation factor XII results in increased kinin production.

The mode of inheritance for types I and II is autosomal dominant, although 20–25% of cases are thought to be due to spontaneous mutations. The responsible gene has been mapped to chromosome 11. There are over 100 different mutations with no correlation between the actual defect and the clinical picture. Patients and their families should be offered genetic counselling.

The onset of symptoms of HAE tends to occur in the first or second decade of life, with 75% of the patients experiencing their first attack before the age of 15. The condition lasts lifelong but symptoms tend to decrease with increasing age. The lifetime incidence of laryngeal oedema is said to be 70%. Mortality rates from laryngeal oedema and subsequent asphyxiation are estimated at 15–33%. Airway oedema tends to occur at the level of or above the larynx and is therefore amenable to treatment by emergency tracheostomy, should intubation fail. Ominous signs suggesting airway involvement include dysphagia, voice change, and stridor.

There will generally be a family history of angio-oedema. However, 5% of adults carry the mutation for the C1-INH gene while remaining asymptomatic. Screening for this condition involves measuring complement C3 and C4 levels. Diagnosis is made by demonstrating a normal complement C3 and a low complement C4 together with low antigenic and functional C1-INH (in type I HAE) and normal antigenic and low functional C1-INH (in type II HAE). C4 is the complement protein that is cleaved by activated C1. Levels of functional C1-INH or absolute levels of C4 do not change between attacks, so that the diagnosis can be made at any time.

Attacks can be precipitated by a variety of triggers, such as dental treatment, surgery, trauma, stress (mental or physical), exercise, infection, alcohol consumption, anaesthesia, menstruation, and certain drugs (ACE-inhibitors, estrogens).

**Treatment of acute attacks**

Treatment of acute attacks requires early assessment of the airway, and if any compromise is present, prompt intubation or even emergency tracheostomy may be necessary. Treatment of the underlying cause has traditionally been by infusion of plasma-derived C1-INH concentrate. Symptoms tend to improve rapidly and resolve completely within 24 h. Annual viral screening and vein-to-vein tracking of blood from the donor to the recipient are essential, but the safety of the new preparations is excellent. Recombinant C1-INH was licensed for clinical use this year and avoids all the risks associated with infusion of plasma products. To our knowledge, it is not yet routinely available in the UK.

Fresh frozen plasma (FFP) has also been used for acute attacks; however, because this also contains factor C4, it can fuel further cleavage of complement factors and occasionally exacerbate symptoms. Solvent/detergent-treated plasma has a better viral safety profile.

Patients already taking prophylactic anabolic attenuated androgens (such as danazol or stanozolol, see long-term prophylaxis) can increase the dose for mild attacks.

Newer treatments include the kallikrein inhibitor ecallantide (licensed in the USA) and the bradykinin receptor antagonist icatibant (licensed in Europe). These have been shown to be equally effective and safe when compared with C1-INH concentrate but carry the advantage of being pre-prepared subcutaneous injections. C1-INH concentrate requires reconstitution with sterile water, which requires time for preparation and attention to dosing and an aseptic technique (Table 1).
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**Table 1** Treatment of acute attacks of HAE

<table>
<thead>
<tr>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>Observation alone if isolated peripheral oedema, that is, no abdominal, facial, or laryngeal involvement</td>
</tr>
<tr>
<td>Consider early intubation if signs of progressive laryngeal oedema</td>
</tr>
<tr>
<td>Plasma-derived C1-INH concentrate (by i.v. infusion, dose recommendations vary and depend on the product used)</td>
</tr>
<tr>
<td>Icatibant (bradykinin receptor blocker), 30 mg subcutaneously (licensed in European Union)</td>
</tr>
<tr>
<td>Ecallantide (kallikrein inhibitor), 30 mg subcutaneously (licensed in the USA, under review in Europe)</td>
</tr>
<tr>
<td>Recombinant C1-INH concentrate</td>
</tr>
<tr>
<td>If above not available consider solvent/detergent-treated plasma or fresh frozen plasma</td>
</tr>
<tr>
<td>Consider doubling dosage of anabolic androgens</td>
</tr>
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**Long-term prophylaxis**

Long-term prophylaxis of attacks is by treatment with attenuated androgens. These increase C1-INH synthesis by the liver. Side-effects may include weight gain, altered libido, hirsutism, liver enzyme abnormalities, hypercholesteraemia, and microscopic haematuria. These agents are contraindicated during pregnancy, while breastfeeding and in children who have not attained full growth potential or sexual maturity. Regular monitoring of liver function tests and liver and splenic ultrasound scans are recommended since appearance of focal lesions and hepatocellular carcinoma have been reported.

Other prophylactic agents are antifibrinolytics (tranexamic acid, E-aminoacaproic acid). It is thought that the inhibition of plasminogen activation subsequently leads to ‘sparing’ of C1-INH. These agents can be used in children or where androgens are contraindicated. Their use is not recommended during pregnancy, due to potential teratogenic effects. Antifibrinolytic agents are generally less effective for prophylaxis than androgens. Side-effects include myalgia, muscle weakness, hypotension, fatigue, and elevation of serum creatine kinase (CK). Liver and renal function, serum CK, and ocular pressures (risk of glaucoma) need to be monitored on treatment (Table 2).

Home infusion programmes are also available, where patients self-administer C1-INH concentrate. This is reserved for cases where other agents are contraindicated or ineffective.

**Table 2** Long-term prophylaxis in HAE

| Consider long-term prophylaxis if more than one severe event of angio-oedema a month and if treatment of acute attacks is not sufficiently effective or not available |
| Anabolic androgens are usually considered first-line agents. Danazol up to 200 mg orally per day or stanozol up to 2 mg orally per day. Use lowest effective dose. Monitor for long-term effects |
| Antifibrinolytic agents are less effective than anabolic androgens but can be used if the latter is contraindicated. Tranexamic acid, 20–50 mg kg⁻¹ day⁻¹, divided between 2 and 3 doses. Maximum dose 3–6 g day⁻¹. Use lowest effective maintenance dose. Monitor for long-term effects |
| Plasma-derived C1-INH concentrate twice weekly. Dose depends on the product used. Home self-infusion programmes are established |

**Short-term prophylaxis**

Short-term prophylaxis will mainly be necessary when planning elective dental or other surgical procedures. The treatment regimen depends on the site of surgery and the impact of the planned procedure. Prophylactic C1-INH concentrate must be given immediately before surgery and additional C1-INH concentrate should be readily available (Table 3).

In addition to pre-treatment with C1-INH concentrate, anaesthetic management will require a few additional precautionary measures. Emergency airway equipment must be on standby. After successful routine intubation, the intraoperative measurement of cuff leak pressures can be a useful indicator of potential airway oedema. Leak pressures of <30 cm of water should be aimed for at the end of surgery, before extubation. The insertion of a Cook Airway Exchange Catheter through the ET tube has also been suggested. This will remain in situ after extubation and would facilitate re-intubation if necessary.

The use of a laryngeal mask in the context of HAE is not recommended. The latter has the potential to cause airway trauma and trigger an acute attack while it would not prevent airway obstruction in the event of acute oedema. There are no known constraints regarding the use of drugs for general anaesthesia, including volatile agents. The successful use of regional techniques and mask inhalation anaesthesia without intubation has been reported.

**Management of patients who present for emergency surgery**

Management of patients who present for emergency surgery will require preoperative infusion of C1-INH concentrate, with further doses available for postoperative infusion as required. At Plymouth Hospitals NHS Trust, emergency supplies of the concentrate are kept in the Emergency Department and pharmacy.

**Acquired C1 esterase inhibitor deficiency**

AAE is either caused by the consumption of C1 inhibitor (usually due to B-cell lymphoproliferative disease) or by autoantibodies to the protein (associated with lymphoproliferative disease or connective tissue disease). The condition is very rare, with an estimated prevalence of 1:100 000 to 1:500 000. However, the actual...
number of cases may be much higher than that because the condition frequently goes unrecognized.

AAE generally presents later in life (i.e. after the fourth decade), and symptoms cannot be distinguished from those of HAE. Laryngeal involvement is possible. Affected patients will have no family history of angio-oedema and it may be the presenting feature of the underlying haematological malignancy. If no neoplasm is found, then regular review is indicated since there may be a long interval between the onset of angio-oedema and the appearance of malignancy. Screening for this condition involves measuring complement C3 and C4 levels. Diagnosis is made by demonstrating a normal complement C3 and a low complement C4 together with low antigenic and functional C1-INH in most cases, and a decrease in C1q. C1q is one of three molecules that make up the C1 complex and levels are found to be normal in HAE.9

Management
Management of AAE depends on the severity of symptoms and may range from observation in a high dependency environment to emergency airway management. Treatment follows the same plan as for HAE, with C1-INH concentrate. However, patients with the acquired form of angio-oedema may show a diminished response. The kallikrein inhibitor ecallantide and the bradykinin receptor blocker icatibant have been used successfully in non-responders to the factor concentrate.

C1-INH concentrate can also be used prophylactically for routine or emergency surgery. Treatment of the underlying haematological disorder can lead to an improvement in symptoms of angio-oedema in AAE. Other prophylactic agents used include attenuated androgens and antifibrinolytics, with the latter achieving somewhat better results.10

Summary
A variety of clinical conditions can lead to angio-oedema. This can cause life-threatening airway compromise. Prompt recognition and treatment are important. The most important conditions for the anaesthetist to distinguish between are allergic angio-oedema, HAE, and AAE, since these are most likely to cause oedema involving the airway. Prompt administration of the correct treatment can make a huge difference in the clinical outcome.

Declaration of interest
None declared.

References

Please see multiple choice questions 21–24.