

PRACTICE

RATIONAL TESTING

Investigating recurrent angio-oedema

Where do you start with investigating causes of angio-oedema? This article will guide you through key information and tests

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

A 57 year old man visited his local emergency department with his fourth episode of non-itchy swelling affecting the tongue and mouth in the past four months. Previous episodes had resolved over one to two days without treatment. On this occasion the patient woke from sleep and had difficulty swallowing and speaking. He took an antihistamine, but it had no clear effect. Clinical examination confirmed non-erythematous swelling, mainly affecting the tongue and lips (fig 1). The airway was adequate on first assessment, with an oxygen saturation of 97% on room air, blood pressure 150/90 mm Hg, respiratory rate of 20 breaths/min, pulse 90 beats/min. No urticaria or other rash were present.

What is the next investigation?

This patient is most likely to have angio-oedema (box 1 describes this and the related conditions urticaria and anaphylaxis). Additional clinical information is essential to guide relevant investigation in angio-oedema. This patient had no history of urticaria. Swelling began hours after last eating, and he had taken no over the counter medications such as non-steroidal anti-inflammatory drugs, which may precipitate angio-oedema. He had been diagnosed with hypertension two years ago and been prescribed enalapril 10 mg daily, increased to 20 mg daily five months ago, with sitagliptin 100 mg daily also started five months ago. He had no family history of angio-oedema. Box 2 outlines key items in the history and examination to direct investigation and management.

In patients taking ACE inhibitors

Recurrent angio-oedema of the tongue and oropharynx, without urticaria, suggests that his angiotensin converting enzyme (ACE) inhibitor (enalapril) may be the underlying cause. Recurrent angio-oedema is experienced by 0.1-0.7% of those taking ACE inhibitors.² No specific diagnostic tests can determine whether a patient's angio-oedema results from use of an ACE inhibitor.

Typically angio-oedema affects the tongue and oropharynx, but intestinal involvement may result in recurrent abdominal pain and other gut symptoms. Angiotensin converting enzyme also functions as a kininase, which degrades bradykinin, so bradykinin accumulates in the presence of an ACE inhibitor, interacts with bradykinin B2 receptors, and results in vasodilation and increased vascular permeability (fig 2).^{3,4} Clinical trials are under way to examine the role of icatibant, a bradykinin B2 receptor antagonist, in acute management of this condition.

Although symptoms often develop within weeks of starting an ACE inhibitor, they may not develop for months or even years. A dose change (usually an increase) or addition of another medication may precede onset. Angio-oedema usually stops after drug withdrawal, but sometimes persists for months or even years. Clinical response to antihistamines, steroids, and adrenaline is relatively poor, and deaths have been reported. All ACE inhibitors are subsequently contraindicated as this is a class effect.^{3,4} A meta-analysis identified that the risk of any subsequent angio-oedema with angiotensin receptor blockers was 2.5% (1.5% for confirmed cases).⁵ No test is available to determine who is at risk of angio-oedema induced by ACE inhibitors.

Exclusion of hereditary and acquired C1 inhibitor deficiency

C1 inhibitor deficiency should be excluded in all patients with recurrent angio-oedema without associated urticaria, including those taking an ACE inhibitor, as this drug may precipitate

Learning points

- In acute angio-oedema a detailed history may show that a food, drug, or sting triggers acute angio-oedema
- Stop angiotensin converting enzyme (ACE) inhibitors in any patient who develops angio-oedema
- In recurrent angio-oedema without urticaria, consider conditions including angio-oedema induced by ACE inhibitors and C1 inhibitor deficiency. Screen for C1 inhibitor deficiency in these patients (including those taking ACE inhibitors) by measuring C4 levels, and if levels are low refer for confirmation of diagnosis
- Chronic spontaneous urticaria associated with angio-oedema is unlikely to be IgE mediated, and investigation for the presence of specific IgE is rarely indicated

Box 1 Descriptions of angio-oedema, urticaria, anaphylaxis*Angio-oedema*

- Dilatation and increased permeability of the capillaries in the deep dermis or subcutaneous or submucosal tissues leading to localised swelling often affecting the upper respiratory and gastrointestinal tracts. Increased vascular permeability may be:
 - Mast cell mediated (for example, as in IgE mediated acute angio-oedema or anaphylaxis). Mast cell mediators (such as histamine) are usually associated with urticaria and itch
 - Bradykinin mediated (for example, as in angio-oedema induced by angiotensin converting enzyme inhibitors). Bradykinin and complement derived mediators are not associated with urticaria or itch
 - Of unknown origin.

Urticaria

- A vascular reaction of the upper dermis marked by itching and the transient appearance of raised patches that are redder or paler than the surrounding skin

Anaphylaxis

- "Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death."¹ Urticaria and/or angio-oedema are accompanied by respiratory compromise, reduced blood pressure, or associated end organ dysfunction.¹

Box 2 Key points in history taking and examination

- Onset timing and frequency may provide clues as to the cause
- Presence of urticaria with angio-oedema suggests the reaction is likely to be mast cell mediated. Antihistamines and adrenaline are typically effective in these, but less so in bradykinin mediated reactions
- Common precipitating factors—for example, medications, concurrent infection, heat or cold, emotional stress, local trauma or pressure, alcohol—may identify important triggers
- Family history of angio-oedema suggests C1 inhibitor deficiency
- Unexplained episodes of abdominal pain are common in C1 inhibitor deficiency
- Take a full medication history—including non-steroidal anti-inflammatory drugs, angiotensin converting enzyme (ACE) inhibitors, bupropion
- Examine areas affected, especially the oropharynx and airway (common in angio-oedema induced by ACE inhibitors)
- Measure vital signs

angio-oedema in patients with C1 inhibitor deficiency. C1 inhibitor has several anti-inflammatory functions in the contact and complement systems (fig 2), and a deficiency in these may result in insufficient local anti-inflammatory control at times of physiological or psychological stress (with generation of excess bradykinin) and associated vascular permeability.

Hereditary C1 inhibitor deficiency or hereditary angio-oedema, an autosomal dominant condition, typically present by young adulthood, though diagnosis is often delayed. Facial, limb, and abdominal angio-oedema are common; death from laryngeal attacks and unnecessary abdominal surgery are well recognised. Acquired C1 inhibitor deficiency is less common and is usually associated with lymphoproliferative or autoimmune diseases in older adults.

Screening tests for hereditary and acquired C1 inhibitor deficiency

Although uncontrolled activation of the classic complement pathway is the basis of the diagnostic tests, it is not responsible for the major symptoms.^{6,7} Measurement of the level of complement component C4 is an excellent screening test, with a negative predictive value of 100% in some studies. It is widely available and cost effective as the initial investigation in these

patients. A normal C4 level is only rarely seen in C1 inhibitor deficiency. The level of complement component C3 is expected to be normal and measurement is not indicated.

Refer all patients with angio-oedema and a low C4 level for specialist investigations. Confirmation of diagnosis will include measurement of the level and/or function of C1 inhibitor by an accredited laboratory.⁸ In type 1 hereditary angio-oedema (85% of cases) C1 inhibitor levels are low, whereas in type 2 the levels are normal or even increased but the C1 inhibitor is dysfunctional and a functional assay is needed. In acquired C1 inhibitor deficiency, the levels and function of C4 and C1 inhibitors are low, as is the C1q level (which is normal in hereditary angio-oedema).

Investigating angio-oedema with urticaria

Consensus guidelines recommend that if episodes are acute (that is, occasional and lasting no more than six weeks) and the clinical history does not identify a likely cause, no investigation is needed.⁹

When chronic "idiopathic" or "spontaneous" urticaria and/or angio-oedema are present for more than six weeks, they are rarely IgE mediated, and skin tests or specific IgE measurement

are unhelpful. Full blood count and measurement of C reactive protein or erythrocyte sedimentation rate are recommended for evidence of an underlying inflammatory or parasitic disorder.⁹ Investigation for underlying chronic infection may be relevant. Measurement of thyroid stimulating hormone is usually recommended as thyroid autoantibodies are increased in frequency. IgG autoantibodies that cross link the FcεR1 receptor on mast cells have been identified in 30-50% of cases, but the value of measurement of these is controversial.⁹

Suspected allergic angio-oedema

Suspect an allergic cause if angio-oedema accompanies anaphylaxis or acute urticaria; symptoms almost always occur within two hours (often within minutes) of exposure to the trigger (food, drug, or insect sting). Refer for further assessment and identification of the allergen through skin testing or measurement of specific serum IgE (responsible for mediator release from mast cells and basophils). The absence of food specific IgE has a high negative predictive value (>95%), but the positive predictive value of food specific IgE for clinical disease is only about 50%.¹⁰

Aspirin and all cyclo-oxygenase-1 inhibitors may induce acute urticaria or angio-oedema, or both, with altered metabolism of arachidonic acid. This is not IgE mediated and skin tests are not useful.

Referral

For patients with recurrent angio-oedema, referral to clinical immunology, allergy, dermatology, or paediatric specialist services is appropriate. Caution is needed when what seems to be angio-oedema persists as this may indicate misdiagnosis of other conditions (such as obstruction of the superior vena cava, orofacial granulomatosis, retrobulbar lymphoma, and acromegaly).

Outcome

This patient was treated with adrenaline (0.5 mg intramuscularly) because of concern about his airway, although it was recognised that his response to adrenaline may be poor in angio-oedema induced by an ACE inhibitor. His

angio-oedema resolved slowly over 48 hours and he did not need intubation or tracheostomy. His ACE inhibitor was stopped immediately and replaced with an angiotensin receptor blocker, after discussion with him about the much lower risk of angio-oedema with this agent. Levels of C4 and C1 inhibitors were within normal limits. He had no further angio-oedema episodes during six months of follow-up.

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Figures



Fig 1 Angio-oedema affecting both lips (real case to illustrate scenario)

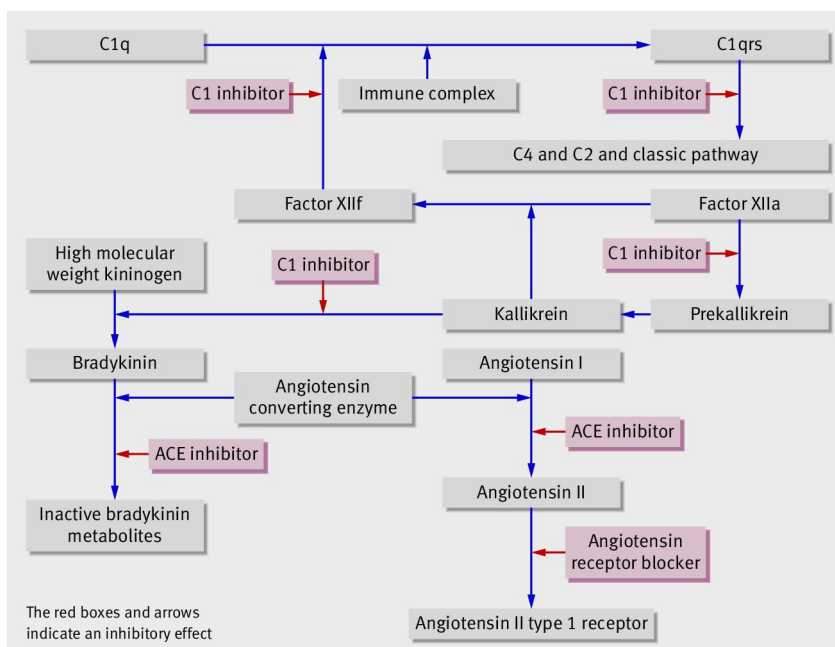


Fig 2 Angiotensin converting enzyme (ACE) inhibitors block degradation of bradykinin. C1 inhibitor inhibits production of bradykinin and activation of early complement pathway components