Angioedema

Angioedema is a condition in which small blood vessels leak fluid into the tissues, causing swelling. There is no known cure, however it may be possible to prevent swelling with medications. Wheal like swellings on the surface of the skin are called hives (urticaria). Angioedema involves swelling deeper in the tissues. Allergy is very rarely the cause of isolated angioedema (swelling without any other symptoms).

How common is angioedema?

Up to 20% of people will develop hives (urticaria) at some time in their life, and around one in three of these will have angioedema as well. Having angioedema on its own (without hives) is much less common.

There are three major patterns of angioedema:

- Angioedema plus hives (urticaria): the hives itch and the angioedema is itchy, hot or painful.
- Angioedema alone: itchy, hot and red swellings, often large and uncomfortable.
- Angioedema alone: skin-coloured swellings, not itchy or burning, often unresponsive to antihistamines.

Angioedema eventually disappears in most people. It may reappear following infection, when under stress or for no particular reason that can be identified. Occasionally it is a recurrent problem that reappears throughout life. Angioedema is seldom caused by a serious underlying disease, nor does it make you sick or cause damage to organs such as kidneys, liver or lungs.

Where does angioedema occur?

The most common areas of the body involved are the face, lips, tongue, throat and genital areas. Swelling in one area usually lasts between one to three days. Occasionally, swelling of internal organs like the oesophagus, (food pipe or gullet that leads to the stomach), stomach, or bowel can trigger chest or stomach pains.

Whilst angioedema may be itchy, tingling, or burning, often there are no symptoms other than the discomfort of the swelling. Sometimes the swelling can be painful, particularly when it occurs over joints. These swellings can be large and may last for days. If swelling is constant rather than coming and going, other possible causes of swelling should be considered.

Is angioedema dangerous?

Angioedema does not damage internal organs like kidneys, liver or lungs. The only danger is if the throat or the tongue swell severely, as this can cause difficulty breathing. Severe throat swelling requires early use of medication such as adrenaline for anaphylaxis or icatibant for hereditary angioedema (HAE), and transfer to hospital by ambulance.

Swelling on the outside of the neck is uncomfortable but does not affect breathing. Swelling that interferes with breathing is uncommon, even in people with recurrent angioedema.

People with recurrent angioedema should be referred by their doctor to a clinical immunology/allergy specialist to investigate for an underlying cause and optimise treatment.

When to suspect an allergic cause

Allergic causes for isolated angioedema are rare but should be suspected with short-lived episodes of swelling that occur under similar situations, such as after taking certain foods or medications. Allergy to foods or drugs usually causes hives (urticaria), or itching as well as angioedema at the same time.

Food allergy reactions are sometimes severe, dramatic and often associated with symptoms like trouble breathing, a drop in blood pressure, stomach upset and itchy hives (urticaria), as well as angioedema. Symptoms usually occur within one to two hours of eating the offending food and disappear within 12 to 24 hours. Allergy tests can be useful for this type of reaction, but it is important to note that food allergy is a very rare cause for isolated angioedema.
The role of food intolerance (which is different to allergy) remains controversial. Dietary changes such as avoiding naturally occurring food chemicals and food additives may sometimes be tried under the supervision of suitably experienced medical practitioners and accredited dietitians.

Main causes of angioedema

ACE (angiotensin converting enzyme) inhibitor medications

Around 1 in 200 people who take these heart and blood pressure medications develop swellings. Most swellings appear within the first few months of treatment. However, sometimes the onset can be delayed for months to years, or only appear when the dose is increased. Why some people get swellings and others don't is unclear, but simply switching to another brand or type of ACE inhibitor doesn't seem to help.

The swellings from these medications are not itchy or painful, usually occur around the face, tongue and throat and are not accompanied by hives (urticaria). These are not allergic reactions and therefore can't be proven by any skin or blood allergy tests. If the symptoms disappear when the drug is stopped the diagnosis is usually considered confirmed. Resolution of swellings can take a number of weeks after stopping the medication.

Hereditary angioedema (HAE)

This is a rare condition occurring in approximately 1 in 50,000 people, who have low levels (deficiency) or reduced effectiveness of C1-inhibitor enzyme. The face, tongue, throat and gut can be involved, and upper airway attacks can be life threatening. The swellings are not itchy or painful and skin colour is often normal. Internal swelling is relatively common, resulting in presentation to hospital with severe stomach or chest pains without external swelling at the same time. It is important to note that HAE is not associated with hives (urticaria), but sometimes a red circular rash can occur. Episodes can be triggered by emotional stress, alcohol, hormonal changes or trauma (such as dental surgery). HAE can be detected from blood testing.

Whilst HAE often runs in families, genetic changes associated with HAE may appear in a new generation that were not present in the parents. HAE usually presents in adolescence rather than in infancy, but presentation can also be delayed.

Acquired C1-inhibitor deficiency

In even rarer cases, low levels of C1-inhibitor occur in association with some cases of lymphoma, malignancies and in autoimmune diseases such as Systemic Lupus Erythematosus (SLE). The swellings are similar to those described above.

Infection

A viral infection is usually the most common cause of hives (urticaria) and angioedema in children, especially if they last for more than 24 hours.

Food or drug allergy

Swellings due to allergic reactions to foods or drugs are sometimes severe and dramatic, but usually resolve within 24 hours.

Other causes

Thyroid gland disease and some types of inflammatory arthritis are more common in people with hives (urticaria) and angioedema. In some people whose swellings persist for years without an obvious cause, an autoimmune process may be responsible. This means that part of the body's immune system may be attacking the skin. In most cases a single cause is not found. Allergic disease is almost never the cause of swellings that last for days or recur for weeks at a time.

Swellings that can look like angioedema

- **Contact allergy** from animals or plants is usually localised to the site of direct contact. It is often itchy, short-lived, does not cause internal swelling and causes blistering rashes that weep and peel after a few days.
- **Animal allergy** can cause itchy hives (urticaria) and angioedema, but occurs mostly with severe hay fever (allergic rhinitis) and/or asthma.
- **Insect stings** from bees, wasps and some ants can cause severe local and temporary swellings.
- **Palindromic rheumatoid arthritis** is a rare form of arthritis that causes swellings that last a few days at a time, mainly over joints and affecting the limbs. Swellings are usually painful and hot, rather than itchy. Some people with this condition will eventually go on to develop rheumatoid arthritis.
- **Less common mimics of angioedema** include the following causes of swelling that tend to persist:
  - Dermatomyositis (muscle weakness, facial redness and swelling).
  - Blockage of the superior vena cava (a major vein in the chest which can result in fixed fluid accumulation in the neck and face and arms).
  - Underactive thyroid gland (which can cause puffiness of the face and lips known as myxoedema).
  - Facial rosacea (causing non-specific puffiness of the face, redness, flushing and pimples).
  - Orofacial granulomatosis (fixed facial and lip swelling sometimes associated with inflammation of the bowel).
  - Subcutaneous emphysema (leakage of air into the soft tissues, often occurring after trauma or surgery).
  - Cluster headache (severe one-sided headache associated with puffiness around the eye on the same side).

How long does angioedema last?

This depends on the cause. If a treatable cause is found or if the cause is an ACE-inhibitor which is stopped, then the episodes of swelling should cease. If no cause is found, the swellings may stop after a few weeks or months or may continue for years, and it is not possible to predict when it will go away.

Aspirin, other pain medications and angioedema

If you are allergic to aspirin or similar pain medications, taking them may trigger swelling. One in three people with angioedema will quickly have their swellings made worse if they take these medications, even if they are not allergic to them. It is therefore better to take paracetamol for pain management. If you are already on aspirin or similar pain medications regularly and without symptoms, then there is no need to stop taking them.

Why do tests?

The main reason for testing is to exclude underlying diseases, which may appear as angioedema first, and other conditions later. These conditions might need separate treatment or investigation. That is why a physical examination and blood tests are carried out in people who have significant or recurrent angioedema.

Management of angioedema

- **Undergo tests to confirm or exclude an underlying cause.** This is important, but in most cases test results are normal.
- **Symptoms may disappear over time.** Some people only have a single episode, whereas others suffer from recurrent bouts, which eventually stop for no apparent reason.
- **Avoid aggravating factors.** Non-specific measures such as avoiding excessive heat, spicy foods or alcohol are often useful. Since Aspirin can make swellings worse, it should be avoided unless already being taken without a problem. ACE (angiotensin converting enzyme) inhibitors are usually avoided in people with a history of angioedema. Another group of heart and blood pressure medications called Angiotensin 2 receptor blockers are generally considered safe.
- **Antihistamines are the mainstays of treatment.** The release of histamine within the skin seems to be the trigger for swelling in most people. Antihistamines block this effect. Since they take one to two

hours to reduce symptoms, it is often better to take them regularly, rather than as needed. The aim is to stop the episodes of swelling, or to make them less frequent or less severe. In people with severe angioedema, it is often better to take them every day, stopping every month or two to see if they are needed, and restarting them if they are. Different people respond best to different antihistamines. Non-drowsy antihistamines are available over the counter without prescription. Unfortunately, these are less effective for angioedema than for hives (urticaria), and are often totally ineffective for the non-itchy angioedema, in which histamine appears to play no significant role.

- **Other medications.** Because the likelihood of side effects is greater, other drugs are usually reserved for when antihistamines fail to prevent angioedema, and are generally given under specialist supervision. These types of medications are more likely to be needed in people with frequent non-itchy swellings and in those with C1-inhibitor deficiency (whether inherited or acquired). In recent years several new medications have become available for patients with HAE. These include C1- inhibitor concentrate and an inhibitor of a bradykinin receptor (Icatibant).

Drugs during pregnancy and breast feeding

Treatment of angioedema, like other allergic conditions, is complicated in pregnancy and breast feeding. Few studies examining the use of medications in pregnancy and breastfeeding exist. Local guidelines suggest that most non-drowsy antihistamines are relatively safe. Older sedating antihistamines are likely to be safe for occasional or short term use. There is no evidence that taking antihistamines will diminish milk supply, however, medical advice should be sought.