



HAEUK

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Understanding Hereditary Angioedema and Acquired C1-Inhibitor Deficiency

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What is HAE?

Hereditary Angioedema (HAE) is an inherited condition. If a parent has HAE, there is a 50% chance they will pass it on to their children. Family members who have been tested and who do not have HAE will not pass the disease on to their children.

HAE can also occur with no family history as a spontaneous gene mutation.

HAE affects between 1/10,000 to 1/50,000 of the population. Because it is so rare most doctors would not see a case in their entire career, and misdiagnosis is common. Patients can suffer for many years before they receive the correct diagnosis.

HAE patients have a defect in the gene that controls a blood protein called C1 Inhibitor (C1 INH). C1 INH is part of a complex cascade of reactions that control the release of fluids from capillaries into the surrounding tissues, thereby causing oedema (swelling).

People with HAE experience swelling of the tissues (angioedema) which last from 3 to 5 days and can be huge. These swellings can occur on any part of the body; hands and feet, arms and legs, trunk, intestines, genital organs, face, tongue, neck and airway.

HAE attacks can start at any time from early childhood, in adolescence or later in life.

The frequency of attacks can vary from once or twice a year to every few days in the most severely affected patients.

Intestinal swelling causes sickness and diarrhoea and very severe pain.

Swelling of the face and tongue can lead to swelling of the airway which is life threatening.



Example of hand swelling:

Left, normal (no swelling)
Right, untreated oedema attack



Example of facial swelling:

Left, normal (no swelling)
Right, untreated oedema attack



Example of gastrointestinal swelling:

Left, normal (no swelling)
Right, untreated oedema attack



Example of an untreated throat swelling (with high risk of spreading to block the airway)



Some patients can identify warning symptoms (prodromal symptoms) in the 24 hours before an attack. These symptoms can include extreme tiredness, a rash or tingling over the affected site.

Example of a HAE rash



Types of HAE

Type I and Type II HAE are due to a known genetic mutation and there is a 50% chance that children will inherit the condition from an affected parent.

Unaffected parents cannot pass on HAE.

Type I

There are low levels of C1 INH (in most cases).

Type II

The blood levels are normal but the C1 INH has impaired function.

Type III

This is a very rare recently documented form: It mainly affects females and is exacerbated by high oestrogen levels e.g. oral contraceptives and pregnancy. HAE Type III is not due to C1 INH deficiency; it is linked to elevated levels of bradykinin. The exact reasons it occurs are still being studied.

Acquired C1 Inhibitor deficiency – AAE

Acquired C1 Inhibitor deficiency is not inherited but is caused when the body produces an antibody to its own C1 inhibitor or uses too much C1 inhibitor.

AAE is often associated with an underlying condition of white blood cells, which is usually mild, but tests should be done to exclude more serious conditions such as lymphoma.

Diagnosis and investigation

Diagnosis

Pointers to a diagnosis of hereditary angioedema (HAE) are:

- Family history – other family members have had similar symptoms.
- Recurrent episodes of swelling (without hives) lasting more than 24 hours and unresponsive to antihistamines.
- Recurrent, unexplained abdominal pain.
- Symptoms starting in childhood and worsening in adolescence.

Investigations

For diagnosis of HAE types I and II:

- Serum C4 levels – usually low in untreated HAE.
- If C4 is low, measure C1 INH level and function.
- If C4 is normal but HAE is suspected, measure C1 INH levels and function, and if normal, repeat C4 levels during an attack and assess C1 INH level and function if abnormal.
- Genetic testing may be done in some cases where there is doubt.

Type III HAE:

- C4 and C1 INH levels are normal.
- Diagnosis is from the clinical picture.
- Kininogenase activity measurement and genetic analysis for F12 gene mutation may be considered.

Testing relatives

If you receive a positive diagnosis for HAE, it is advisable for relatives to be tested, whether or not they exhibit symptoms at the present time.

It is important that HAE patients are treated by a specialist who has experience of treating HAE patients.

Treatment

The level of severity of HAE can vary greatly from patient to patient, and at different stages in life, so it is important that an individual treatment plan is developed for each patient according to their particular situation.

At present there is no 'cure' for HAE, but it is possible to achieve good management of your symptoms so that you can have a good quality of life.

Strategies for managing HAE

- Avoidance of precipitating factors
- Treatment of acute attacks
- Prevention

Precipitating factors

Many attacks have no obvious triggers. However the following things are potential triggers for HAE attacks:

- Infected teeth and other foci of infection
- H. pylori (a bacteria that can be present in the stomach)
- Dental treatments
- Minor trauma
- Intubation for anaesthetics
- Hormone changes
- Puberty
- Contraceptives containing oestrogens
- Pregnancy
- Hormone replacement therapy
- ACE inhibitors (used to treat blood pressure or heart conditions).
- Physical or psychological stress

Treatment of acute attacks

Swelling of the abdomen, face or airway should be treated promptly with an intravenous injection of C1 Inhibitor concentrate or Icatibant.

Peripheral swellings of the limbs or genital organs that affect quality of life by preventing normal activities or the ability to continue employment or education, should also be treated with C1 Inhibitor or Icatibant.

Acute attack medications

C1 Inhibitor Concentrate – trade name: *Berinert*

Berinert is a concentrate of C1 Inhibitor. Berinert is a blood product which raises the level of C1 Inhibitor in the blood and halts the progress of an acute attack of oedema.

Berinert is given by slow intravenous injection, either in hospital by a medical professional, or at home if the patient has been trained in home therapy.

Berinert is licensed in the UK for use in adults and children.

C1 Inhibitor Concentrate – trade name: *Cinryze*

Cinryze is another plasma derived C1 Inhibitor product that is licensed for use in the UK.

Recombinant C1 Inhibitor (conestat alpha) – Trade name: *Ruconest*

Ruconest is a recombinant C1 Inhibitor which is derived from the milk of female rabbits that have been genetically altered to produce the human C1 Inhibitor protein.

Ruconest is given by slow intravenous injection. It is not suitable for patients who have a rabbit allergy.

Icatibant – Trade name: Firazyr

Icatibant is produced as a synthetic protein (a non blood product), and it is effective in halting an attack of oedema.

Icatibant is given by subcutaneous injection (an injection into the tissues just below the skin).

Icatibant comes in a pre-filled 3ml syringe ready for injection. More than one syringe may be required to fully resolve attacks.

Icatibant is licensed for adults for administration by a medical professional or at home if the patient has been trained in home therapy.

HAE patients should carry a letter from their Specialist stating the nature of their disease, the recommended treatment and a telephone number where the Specialist can be contacted.

All HAE patients should be offered home possession of a therapeutic dose of C1 inhibitor concentrate or Icatibant to take to hospital in the case of a severe abdominal or laryngeal attack.

Short term prevention of acute attacks

It is important to discuss management of possible precipitating factors with your specialist.

Danazol or Stanazolol or C1 inhibitor concentrate may be used to prevent an attack.

If a person with HAE or AAE requires surgical procedures (including dental treatment) actions should be taken to prevent a possible attack.

The person should receive an infusion of concentrate prior to surgery. There will be a slight increase in the risk of swelling in the 3 days following surgery. This should be treated with C1 inhibitor or Icatibant in the usual way.

Long term preventative treatment

The frequency and severity of attacks of angioedema can be reduced by attenuated androgens such as Danazol and Stanazolol, or by Tranexamic Acid. Your doctor will discuss these treatment options fully with you.

Preventative Medications - drugs used to reduce the incidence and severity of an attack

Danazol

Danazol may be used to reduce the level of HAE attacks. However, Danazol is an attenuated androgen which may cause unacceptable side effects, particularly in females. It is important to keep the doses of the medication as low as possible, and side effects should be reported as they are usually reversible if danazol is stopped promptly.

Stanazolol

Stanazolol is also an attenuated androgen that is used to reduce the level of HAE attacks. Stanazolol may be helpful even if Danazol has not been effective, or if Danazol has not been well tolerated.

Attenuated androgens, if used wisely, can be well tolerated even in women, and can improve quality of life for HAE patients.

Attenuated androgens should not be used in pregnancy or for children.

Tranexamic Acid

Tranexamic Acid can be used in children and adults in an effort to reduce the number of attacks of angioedema.

Even if prophylactic medications are used, patients may still get a severe breakthrough attack, so it is important to always have an emergency treatment plan in place.

Maintenance therapy using C1 inhibitor concentrate

Occasionally regular injections of C1 Inhibitor may be needed as a preventative measure.

The use of regular injections of C1 inhibitor may be recommended in:

- Cases of frequent severe attacks of angioedema where attenuated androgens are insufficient or unacceptable
- In frequent severe attacks in pregnancy
- In severe HAE in children

Home Therapy for HAE patients

Suitable patients who get frequent severe attacks of HAE will be offered training to give their acute attack medications at home.

See our website www.haeuk.org for a summary of the NHS England Policy for treatment of acute attacks of Hereditary Angioedema. This provision for home therapy applies to both adults and children.

Management of special situations

HAE patients will need to discuss management of the following situations with their HAE specialist:

- Dental treatments
- Surgical operations
- Infections
- Travelling safely (always take your treatment with you in your hand luggage and ensure you have enough supplies when abroad)
- Pregnancy
- Birth control
- Hormone replacement therapy/menopause

Management of HAE in childhood and adolescence

In a family where one parent has HAE it is important to test the children for HAE, as there is a 50% chance that the children will inherit the condition.

HAE can also occur as a spontaneous mutation in children who have no family history of HAE.

Angioedema symptoms may start at a very early age, or they may not show until adolescence or even later in life. Symptoms tend to get more severe with the hormonal changes of adolescence.

Treatment for children follows the same structure as for adults, that is:

- Avoidance of precipitating factors
- Treatment of acute attacks.
- Short and long term preventative treatment.

Tranexamic acid may be prescribed, but danazol and stanazolol are not suitable for children.

A child's HAE management plan will include advice regarding school and trips away from home. Adolescents will receive particular support regarding transition to adult HAE services and independent living.

Children with HAE should be under the care of a Paediatric HAE specialist, or in a family clinic served by both adult and paediatric specialists.

HAE - A patient's story

My name is Rachel and I was born in 1978. At the time, my family were unaware that HAE existed in our family.



It was when I was about two years old that my parents began to notice I was vomiting on a regular basis, but the doctors were not convinced there was anything wrong with me. Throughout my early school years I was regularly poorly and suffered abdominal cramps, at least once or twice a fortnight, and on the odd occasion I had swelling in my hands or feet.

Over the years I was tested for various food allergies and spent months on special food diets, but none of these seemed to make a difference. My problems were classed by doctors as migraine tummy, for which I received no treatment and struggled through them.

Although this interrupted my every day life, thankfully I generally managed to miss no more than one day of school at a time due to an attack, so I didn't fall behind with schoolwork too much. It was difficult though, as friends and teachers didn't understand, and I had no reason to explain why I had cramps and felt sick, tired, faint and unable to concentrate at times.

In 1993, aged 15, I attended yet another appointment with a new specialist at a nearby hospital, who decided to test for a rare and unlikely condition called Hereditary Angioedema. He said it was extremely unlikely this was what I had, but he was otherwise at a loss as to what was wrong with me. The tests came back positive, and finally I had a diagnosis.

Because of this diagnosis, we now managed to trace it back through the family and realised this was the cause of my fathers and grandmothers abdominal attacks, although rare, and my late great grandmothers facial swellings, the cause of which had always been a mystery.

After my diagnosis I was sent to see a fantastic consultant and was finally

put on medication that stabilised my attacks. This medication was Danazol, and for the next 17 years, combined with Tranexamic Acid, I remained fairly healthy with three or four breakthrough attacks each year. This came at a great time, helping me through my GCSE exams and college years, and enabling me to secure a full time job.

Because of the use of Danazol, it was important I had regular blood tests to monitor my C1 levels as well as ultrasound scans on my liver area. Over time I developed a small adenoma on my liver which caused me a little discomfort and was monitored closely with MRI scans. Due to personal reasons and because of the adenoma, in 2010, in consultation with my doctor, I decided to take a break from the Danazol completely. Within a few weeks the tenderness in my liver area subsided and a scan a few months later showed the adenoma had shrunk in size.

Since stopping the danazol I have been having regular infusions of C1 Inhibitor when necessary, but this meant regular trips to the hospital for it to be administered. This wasn't always practical, I felt I couldn't be too far from the hospital and it often meant waiting before having the treatment. My consultant helped me apply to my local Primary Care Trust (PCT) for special approval to allow home therapy, but sadly this was refused. After 18 months and two appeals, the PCT finally agreed and I was trained to self infuse at home.

In 2013 NHS England produced a national policy for treatment of acute attacks of HAE. This means that our acute attack treatments are now centrally commissioned and funded, and home therapy is no longer dependent on PCT approval for funding.

Having home therapy has made such a huge difference to my life. I can now feel confident to travel anywhere away from home, safe in the knowledge that I have my medication with me and can administer it myself as soon as I need to.

Patient support

HAE patients often find great support from meeting other HAE patients and by the services of their own patient support association.

HAE UK is the UK support group for HAE patients. Please visit our website: www.haeuk.org for more practical advice and information.

The mission of HAE UK is to help our members access HAE management that will allow them to gain good control over their symptoms, so that they can maintain independence and a good quality of life.

Our HAE UK website and support hub provides:

- Information about hereditary angioedema
- Information about the treatments that are available
- Practical information about issues such as travel, employment legislation, benefits, dental treatment, management of special situations and schools advice.

We have a private Facebook group as well as a Twitter feed.

You can contact us for support by e-mailing: support@haeuk.org or by writing to us: HAE UK, PO Box 448, Bridgwater, Somerset, TA6 9GB.

HAE UK works under the umbrella of HAE International: www.haei.org

Medical information published by HAE UK is approved by our Medical Advisory Panel. However, it is intended for general guidance only and should not be used in place of the personal consultation needed with your physician.

Reference documents:

NHS England Policy; Service Specifications for the treatment of acute attacks of Hereditary Angioedema

Revised Consensus Document for the Management of Hereditary Angioedema 2015

Dr Hilary Longhurst et al