

UNDERSTANDING HEREDITARY ANGIOEDEMA AND ACQUIRED C1-INHIBITOR DEFICIENCY



INTRODUCTION

Hereditary Angioedema- HAE (also known as C1 inhibitor deficiency) and Acquired C1 inhibitor deficiency are conditions where a deficiency of a substance called C1 inhibitor in the blood can lead to gross swelling of the tissues. These swellings can affect any part of the body. Swelling of the bowel can cause severe abdominal pain; a swelling in the throat can interfere with breathing, and can therefore have fatal consequences. C1 inhibitor deficiency may occur in the following types:

Type 1 Hereditary Angioedema (up to 85% of patients) is caused by a deficiency of C1 inhibitor in the blood.

Type 2 Hereditary Angioedema (15% of patients) In this type the concentration of C1 inhibitor in the blood is normal or high but it is dysfunctional and so swelling of the tissues occurs.

Acquired C1-Inhibitor deficiency Acquired C1-Inhibitor deficiency is not inherited but is caused when the body produces an antibody to its own C1-inhibitor, which prevents C1-inhibitor from performing its normal function (hence the alternative name for this condition: autoimmune C1-inhibitor deficiency).

DIAGNOSIS

HAE may be suspected if you have a history of recurrent swellings affecting any part of the body including limbs, abdomen, face and airway.

Other members of your family may experience the same symptoms. The swellings usually last two to five days.

Diagnosis may be confirmed by having a blood test for C4 levels and functional C1 inhibitor levels.

It is important that HAE patients are referred to a consultant with experience of treating HAE patients. This will usually be an Immunologist or a Dermatologist with a special interest in HAE.

TREATMENT

The level of severity of HAE can vary greatly so it is important that an individualised treatment plan is developed for each patient according to their particular situation.

Three main strategies are adopted in the treatment of HAE:

- Avoidance
- 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

Contraception

Pregnancy

Hormone replacement therapy

ACE inhibitors (used to treat blood pressure or heart conditions)

Physical or psychological stress

Treatment of Acute Attacks

Attacks of swelling affecting the arms and legs do not usually require treatment.

Swelling of the abdomen or airway should be treated **promptly** with intravenous injections of the missing protein, C1 inhibitor concentrate

If an attack of angioedema affects the throat, lips or mouth, the person should go to hospital **immediately**. It is unwise to assume that all attacks of abdominal pain in patients with C1 inhibitor deficiency are necessarily due to angioedema. However, if the symptoms do not respond to therapy they should go to hospital immediately.

In order to save time and help the casualty officer, a person with C1 inhibitor deficiency should carry a letter from their Immunologist stating the nature of their disease, the recommended treatment and the telephone number where the Immunologist can be contacted.

All C1 INH deficiency patients should be offered home possession of a therapeutic dose of C1 inhibitor concentrate 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, Stanazolol, Tranexamic Acid or C1-inhibitor concentrate may be used to prevent an attack.

If a person with HAE or acquired angioedema requires surgical procedures (including dental manipulations) action should be taken to prevent a possible attack. The person should receive an infusion of concentrate or an acceptable equivalent prior to the surgery. In addition the patient's airway should be monitored carefully for 24 hours after surgery.

Long Term Prevention of Attacks

The frequency and severity of long-term attacks of angioedema can be reduced by androgenic steroids such as Danazol or Stanazolol, and by Tranexamic acid. These drugs can produce side effects and it is important that dosage is kept at the lowest effective level. Your doctor will discuss your treatment fully with you.

Patients whose needs and situation meet the necessary criteria may be offered training for self-infusion of C1 inhibitor concentrate.

You might like to discuss this with your HAE Specialist.

Maintenance Therapy Using C1 Inhibitor Concentrate

Very occasionally regular injections of C1 inhibitor may be needed as a preventative measure.

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

Cases of frequent, severe attacks of angioedema

where danazol is insufficient or unacceptable.

In frequent severe attacks in pregnancy.

In severe HAE in children.

Over a period of extensive use, there has never been a case of viral transmission with the C1 inhibitor concentrate that is used. However it is important that HAE patients understand the theoretical risk of viral transmission with all plasma products.

HAE Management in Pregnancy

Danazol and Stanazolol should not be taken during pregnancy. C1 inhibitor concentrate should be used to treat acute attacks of the abdomen or airway. In severe cases it may be appropriate to give regular C1 inhibitor as maintenance therapy. Tranexamic acid may be used to reduce frequency of attacks in some patients.

HAE Management in Children

Stanazolol and Danazol are not recommended for use in children. Treatment will depend on the age of the child and the severity and frequency of symptoms. A treatment program should be agreed with your HAE Specialist.

Potential New Therapies

Three new therapies, DX-88, Icatibant and Recombinant C1 inhibitor are undergoing clinical trials at present. These therapies hold promise for the treatment of acute attacks of HAE in the future.

The Importance of Support

Hereditary angioedema is a rare condition and in the past many people struggled for years to achieve an accurate diagnosis and to access appropriate treatment. Patients have often never met another family with HAE and they can feel very isolated and vulnerable. Because of this the value of a support group like the PIA for people with Hereditary angioedema and acquired c1 inhibitor deficiency is enormous. The PIA aims to keep people informed, to enable contact with others and to give advice on specific non-medical issues when appropriate. In particular we recommend that each person is looked after by a physician experienced in the management of these rare conditions.

GENERAL INFORMATION FOR HAE PATIENTS WHEN TRAVELLING IN THE UK AND ABROAD

It is important for HAE patients to plan appropriate medical cover when travelling abroad.

The PIA offers the following suggestions that you should discuss with your consultant.

- **Plan your trip well in advance in order to set up the best HAE management regime.**
- Wear a Medic Alert bracelet.
- Carry a consultant's letter giving instructions about emergency treatment and a 24-hour emergency advice phone number. If English is not widely spoken in the holiday destination the patient should make arrangements for the Consultant's letter to be translated into the appropriate language.
- The PIA can supply a yellow card with emergency instructions in six languages..
- Obtain E111 form from your local post office if travelling in Europe.
- Arrange travel insurance that will cover HAE patients. Phone the PIA for current details of companies who can supply appropriate insurance.
- **Discuss the situation well in advance with your consultant so that he can advise you about medications and what you should do in the case of an acute attack of HAE affecting the abdomen or throat.** You will need to discuss any particular issues such as pregnancy and dentistry.
- Your Consultant may advise an increased dose of Danazol or Stanazolol for your holiday period.
- All HAE patients should have an emergency dose of C1INH to keep with them when travelling away from their home base.
- If C1 inhibitor is readily available in your holiday destination, it is reasonable to ask for a replacement dose if the original dose is used. This could be refunded by the insurance company if necessary.
- If C1 inhibitor is not readily available in your holiday destination you will need to discuss

with your consultant how much C1 inhibitor is necessary to cover eventualities, and whether other strategies (such as increase in danazol or stanazolol) would be a good idea.

- Carry product literature to explain your medication to any treating physician
- You will need a doctor's letter in order to take your C1INH through the airport controls. You will need to declare your medication as you pass through the baggage checks. You should keep your medication, in a cool bag, with you in your hand luggage. In your holiday accommodation you should arrange for your C1INH to be kept in a fridge.
- Before you book your holiday it is advisable to check out the present availability of hospitals with a working knowledge of HAE management in your chosen destination.
- The PIA is gradually accumulating information regarding European hospitals. (Mainland Spain is a particularly good location for HAE patients!) You may contact the PIA. for any information we have regarding hospitals near your holiday destination. You may also check the HAE International web site www.haei.org for contact details of national HAE Patient Associations who may be able to offer specific advice.
- Some countries will have a reciprocal prescribing arrangement with the UK for patients spending some time in residence.
- Do phone the PIA to discuss any areas of difficulty regarding safety while travelling.
- When you first arrive at your holiday destination check out the best and quickest way to obtain the required medical support in an emergency.

Having set up your best emergency support.....Relax.....and HAVE A GREAT HOLIDAY.

SPECIAL CONSIDERATIONS FOR HAE PATIENTS REGARDING DENTAL CARE.

Dental treatment can precipitate angioedema in HAE patients. It is very important that your Dentist has a full understanding of the issues involved in the dental care of a HAE Patient.

You will need to discuss your dental care and your own situation with your Consultant HAE Specialist. In virtually all cases, local care with your high street dentist is most desirable.

Patients with Hereditary Angioedema should be aware that infection or minor trauma can precipitate an attack of angioedema.

- Good dental hygiene is especially important to avoid areas of infection if at all possible.
- Prompt treatment is needed for gum infections or abscesses.
- Regular dental inspections are important to seek to avoid major procedures.
- Dental work can trigger an attack of facial or laryngeal oedema. Attacks are unpredictable. Extensive dental work may be carried out without complication, and conversely minor work can precipitate an attack. Attacks do not usually occur immediately but most often in the hours/days following dental work.

Patients should have rapid access to C1 inhibitor concentrate in the event of an attack, irrespective of whether or not they have received preventative treatment.

- The patient should discuss the level of prophylaxis needed prior to dental care with their Consultant and with their Dentist. Advice should take account of the proposed dental procedure and previous reactions experienced by the patient.

Examination, radiographs, crown cementation and suture removal do not generally require prophylaxis.

Hygiene treatments, restorations and taking impressions; the clinician may consider giving large doses of danazol or tranexamic acid for 5 days before and after the procedure or a single

dose of C1 inhibitor concentrate before the procedure.

Extractions, other surgery, or where the patient is considered at high risk of an attack, C1 Inhibitor concentrate may be needed and should be given prior to treatment.

PATIENT CHECK LIST

Ask to be referred to a HAE Specialist

Ask your Specialist to talk to you about :

- Setting up a HAE management program
- What to do if you have a swelling of your face or throat or if you have an abdominal attack.
- Keeping C1 Inhibitor Concentrate at home in your fridge.
- Information about testing family members.
- HAE in adolescence
- Contraception
- Pregnancy
- Hormone replacement therapy
- Dental care
- Operations
- Infections
- Travel
- Medic Alert bracelets

Contact details

The Primary Immunodeficiency Association (PIA)

Phone: 0207 976 7640

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web site: www.pia.org.uk

International HAE Association (HAEI)

web site: www.haei.org

USA HAE patient association

web site: www.hereditaryangioedema.com

For further details about UK Guidelines for Management of Hereditary Angioedema and Acquired Angioedema please go to www.pia.org.uk and click on 'Consensus Document'.

A PATIENT'S VIEW

Ann Price recalls her family's experience of hereditary angioedema over four generations.

The story of hereditary angioedema in our family is a very positive one. Although it started with much ignorance, fear, pain and mismanagement, we now understand the disorder and have confidence and enough control over the situation to live full and active lives. We hope that in the future, with the availability of new therapies and the advances in gene therapy, the prospects will be still brighter. I have told our story to encourage those who have had to struggle - and perhaps continue to struggle - with many years of misdiagnosis and inadequate treatment.

Let me start by introducing our family as we are today. I am a 52-year-old part-time nurse. My husband John, also 52, is a health and safety specialist. We have three children: Helen, who is 24 and has just qualified as a doctor, David who is 23 and studying medicine, and Edward, aged 13.

My own symptoms first occurred when I started taking the contraceptive pill at the age of 23. I immediately experienced severe bouts of gross oedema about once a week, involving arms, legs, face and gut. It was very frightening. Only at this stage was I told the family history of this weird condition. My grandfather had HAE severely over many years and he died at the age of 39. My father suffered severely until he was 30, when his symptoms suddenly ceased, never to return. Several aunts and uncles were affected. My mother regarded the condition as "all down to nerves" and "all in the mind". My doctor prescribed massive doses of antihistamines to no effect.

My symptoms continued, but gradually decreased over the next few years. Doctors were emphatic that there was no connection with the pill, but when I discontinued it the oedema stopped completely.

When I became pregnant with my first child, Helen, I had regular oedema from four months, but all symptoms ceased after her birth. The same pattern occurred during my second and

third pregnancies, although the symptoms were more severe. However, between the pregnancies I was free of symptoms.

Our third son, Andrew, appeared to be a very bonny, healthy baby but our lives were devastated when he tragically died in infancy.

It was at this time that my GP spent an afternoon researching into HAE at the postgraduate medical library on our behalf. Subsequent blood tests revealed that Helen and David were, like me, deficient in a substance in our blood called C1-inhibitor (C1INH). However, they were symptom-free at the time. Because of these diagnoses I was determined to find some answers. As a nurse I had access to medical literature and our GPs were supremely helpful. We found a specialist consultant in London. Gradually over the next few years more information and treatment became available.

Two years after Andrew we had Edward, who also has HAE.

In 1983 C1INH was being produced in Holland and towards the end of my pregnancy with Edward, I was the first patient in this country to have C1INH injections. It was like a miracle. What had been a three-day session of very acute abdominal pain, vomiting and diarrhoea was relieved within an hour of the injection.

The availability of C1INH has been the central factor in transforming the lives of our family.

Without treatment, for instance, Helen would not have been able to manage a career and she would have experienced a lot of severe pain and distress. Her symptoms had increased in severity since the age of 14. She suffered severe incapacitating abdominal symptoms for three days out of every seven to ten days. At first she was given high doses of Danazol, but the androgenic properties of this were prohibitive.

She is now controlled by self-injecting two vials of C1INH intravenously as soon as abdominal or throat symptoms develop. Thanks to this replacement therapy Helen has been able to qualify as a doctor. She now lives a normal and happy life and has travelled all over the world.

David developed problems in adolescence, but his condition appears to be less marked and he is maintained relatively symptom-free on small daily

doses of Danazol. He always keeps C1INH available in case of severe symptoms or laryngeal emergencies.

Edward has the deficiency but is at present without symptoms. However, we always have our safety net, in the form of C1INH, at the ready.

The main points of our management at present are:

- Maintaining a sensible, positive attitude to HAE.
- Making available letters and leaflets explaining HAE.
- Wearing "Medicalert" bracelets.
- Taking C1INH injections before any medical or dental treatment.
- Taking Danazol for preventative therapy.
- Always having available C1INH in case of emergencies.

Because of the small risk attached to blood products we still look forward to the day when gene therapy will provide an actual cure for our condition.



The Primary Immunodeficiency Association is a national charity founded in 1990. It is led by a Chair and Board of Trustees who oversee the work of a London-based national office staff, directed by a Chief Executive.

**THE MISSION OF THE PiA IS TO IMPROVE
THE QUALITY OF LIFE OF ALL PEOPLE
WITH PRIMARY IMMUNODEFICIENCIES**

To achieve this we have the following aims:

- To promote awareness and early diagnosis of the various primary immunodeficiencies
- To ensure that all those affected have access to the best possible treatment
- To provide information and support to people with primary immunodeficiencies
- To encourage and support original research

The PiA has a Medical Advisory Panel of clinical immunologists and a Research Grants Committee which award grants to doctors and other researchers looking for improved treatments and a cure for primary immunodeficiencies.



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