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HAE frequently asked questions

Q: What is Hereditary Angioedema (HAE)?

A: Hereditary Angioedema (HAE) is a rare genetic disorder characterized by episodes of swelling (edema attacks) in different areas of the skin or the internal organs. In particular, it occurs in the upper respiratory tract and intestine.^{1,2} Episodes affecting the larynx or tongue are particularly dangerous and can cause death by suffocation if untreated.^{2,6-8}

Q: How many people are affected by HAE?

A: Exact figures regarding the incidence of HAE are not available. It is estimated that about 1 in 10,000 to 1 in 50,000 people are affected worldwide.^{1,9}

Q: When do the symptoms of HAE first occur?

A: Most patients experience their first attack during childhood or adolescence, and then continue to suffer from subsequent attacks throughout the duration of their lives.²

Q: How do the symptoms of HAE manifest themselves?

A: An episode of HAE involves an acute swelling of the skin or mucous membranes, primarily affecting the limbs, face and neck as well as the buttocks and genitalia. Although this swelling of the skin is almost never associated with itching, it causes a feeling of tension, the severity of which ranges from unpleasant to painful. The facial swelling can be disfiguring. Swelling can also occur in the wall of the intestine. This swelling is associated with colicky pain and can cause diarrhea, vomiting and circulatory disorders. In extreme cases, even intestinal paralysis and intestinal obstruction are possible.^{1,2,5,10} The most feared complication of HAE is swelling in the larynx (laryngeal edema) or upper respiratory tract, which can cause death by suffocation if left untreated.^{2,6-8}

Q: How often do episodes of HAE occur?

A: The frequency, duration and severity of attacks vary considerably. Approximately 22 per cent of patients report a frequency of greater than one attack per month; 40 per cent of patients experience on average 6 to 11 attacks per year; and the remaining 22 per cent are infrequently symptomatic.¹

Q: How long does an episode of HAE last?

A: In most cases, the symptoms of HAE are transient, progressing over 12 to 36 hours, and then subsiding gradually over the next two to five days. However, some patients may experience attacks that

last over a week.^{1,5} Although HAE episodes are self-limiting, the unpredictable occurrence of attacks places considerable strain on patients, often restricting their ability to lead normal lives. Untreated, patients with HAE lose up to 100 to 150 workdays per year and have a morbidity approaching 50 per cent.¹¹

Q: Why can certain episodes of HAE be life threatening?

A: If an episode of HAE involves laryngeal attacks this may lead to airway obstruction and have the potential to cause death by asphyxiation.^{2,6-8} Amongst HAE patients suffering from edema of the larynx, the estimated mortality rate of untreated attacks is as high as 40 per cent if the attack is not treated adequately.¹⁰ If the mucous membranes in the larynx start to swell, immediate medical treatment is required. It may be necessary to intubate the patient or make an emergency incision in the windpipe (tracheotomy) if appropriate treatment is not available.

Q: What causes HAE?

A: HAE is caused by a genetic defect on chromosome 11, which leads to a deficiency of the protein C1-esterase inhibitor (C1-INH). This protein is part of a system known as the complement system, which is involved in the complex interaction leading to immune and inflammatory reactions in the body. Among other things, C1-INH controls release of the tissue hormone bradykinin. If either C1-INH concentration or activity is decreased, bradykinin concentrations may increase and an episode of swelling can occur. There are two types of HAE. Type I is the most common (approximately 85 per cent of cases) and involves a C1-INH deficiency resulting from insufficient production of the enzyme. Type II affects approximately 15 per cent of patients and involves normal or even elevated C1-INH concentrations but reduced C1-INH activity (function). Recently, a rare third form of the disease has been discovered. Unlike the other two subtypes of HAE, this subtype is not associated with a C1-INH deficiency. It affects mostly women and is reported to be associated with a mutation of factor XII.^{12,13,14}

Q: What triggers an episode of HAE?

A: Episodes of HAE often occur without an obvious trigger. However, in some cases, a cause can be identified. For instance, infections, minor injuries and mechanical stimuli such as pressure can induce an attack.

Dental procedures or surgery to remove the tonsils are particularly critical, as they can cause swelling in the larynx. Emotional and mental stress can also trigger an attack.

Hormonal factors are another known cause of HAE attacks. For example, the frequency of episodes can be higher in women taking products containing estrogen (“the pill”), products for menopausal complaints, or who have their menstruation. A class of blood pressure lowering drugs known as ACE (angiotensin converting enzyme) inhibitors are contraindicated in HAE patients as they have also

been shown to trigger HAE attacks in some patients. HAE patients should therefore avoid taking this type of medication.

Q: What does the fact that HAE is a hereditary disease mean?

A: The defect on chromosome 11 that is responsible for HAE is equally common in men and women and can be passed on by both sexes. As HAE is an autosomal dominant hereditary disease, there is a 50 per cent risk of a child inheriting the disease from the affected parent. Male and female offspring are at equal risk of inheriting HAE.

Q: How can you tell if the larynx is starting to swell?

A: The larynx can swell both spontaneously and after an injury to the oral mucosa, e.g. during dental treatment. The first signs will be difficulty swallowing, voice changes and hoarseness. Increasing swelling in the larynx then leads to breathlessness, which can cause suffocation in extreme cases. If a patient experiences these symptoms, he or she should seek medical help immediately.

Q: How is HAE diagnosed?

A: If the patient has recurrent episodes of edema affecting the limbs, face, neck or buttocks and lasting several hours to days, HAE should be considered as a diagnosis. HAE can also be the cause of recurrent colicky pain in the abdominal cavity. If a family history is already known to include cases of HAE, it is very reasonable to suspect HAE the first time it occurs in another family member. Failure to respond to drugs administered for allergic reactions, such as antihistamines, corticosteroids and adrenaline, is also used to distinguish HAE from allergic edema. However, the diagnosis of HAE is confirmed by special blood tests in which the concentration and activity of C1-INH and the concentrations of other proteins in the complement system are measured. The concentration and/or activity of C1-INH are reduced in patients with HAE.

Q: What does HAE mean for a pregnancy and vice versa?

A: In principle, women with HAE can have children. HAE does not impair fertility. However, women who are being treated with androgens should stop taking them, as this treatment can impair female fertility. Episodes of HAE can increase or decrease during pregnancy, as can the severity of the edema. Your doctor will follow you closely during this time and discuss appropriate treatment with you.

Q: Why does it often take years to diagnose HAE?

A: HAE is a rare and relatively unknown disease. In addition, the symptoms of an episode of HAE are similar to those of much more common diseases, e.g. an allergy or appendicitis. This makes it difficult to diagnose HAE correctly. HAE can also be confused with other forms of angioedema, e.g. allergic angioedema. However, the drugs used to treat this form of angioedema, such as cortisone and antihistamines, have no effect on the symptoms of HAE. Diagnosing HAE is particularly difficult if the

patient suffers predominantly from gastrointestinal attacks. If HAE is suspected, the diagnosis can be confirmed quickly by a blood test.

Q: What treatment options for HAE are available?

A: There are three established treatment options for HAE: acute treatment, long-term prophylaxis and short-term prophylaxis.

Q: When is acute treatment of HAE necessary?

A: The aim of acute treatment is to stop progression of the edema and to resolve the symptoms. This applies particularly to episodes in the larynx, which can cause death if left untreated.

Q: What options are available for acute treatment?

A: The recommended options for acute treatment vary from country to country due to the fact that drugs for specific treatment are not licensed in all countries. In these cases acute treatment may be limited to more unspecific drugs such as tranexamic acid or even just painkillers. In countries where it is available, Icatibant or C1-INH concentrate can be used for the treatment of acute attacks. Icatibant must be administered by subcutaneous injection by a healthcare professional, C1-INH concentrate must be administered intravenously.

Q: What is the aim of long-term prophylaxis?

A: Long-term prophylaxis is indicated in patients whose quality of life is clearly reduced by the disease. These are usually patients in whom episodes occur more than once a month or who are at high risk of developing laryngeal edema. The aim is to reduce the frequency and/or the severity of HAE attacks.

Q: When is short-term prophylaxis necessary?

A: Short-term prophylaxis is usually performed before surgical procedures or dental treatment. In countries in which C1-INH concentrate is available, it is administered 60 to 90 minutes before the procedure as an intravenous infusion. In all other countries in Europe high-dose treatment with androgens is administered for 5-7 days beforehand.

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