HAE Disease Fact Sheet

Hereditary Angioedema (HAE) is a rare, potentially life threatening inherited disorder with symptoms of severe, painful, and recurring attacks of edema (swelling). HAE patients often suffer for many years and may be subject to unnecessary medical procedures and surgery prior to receiving an accurate diagnosis. While HAE cannot yet be cured, intelligent use of available treatments can help patients lead a relatively normal life.

What is HAE?

- HAE affects between one in 10,000 and one in 50,000 people worldwide.\(^1\)\(^2\)
- HAE is hereditary because the genetic defect is passed on in families. If a parent has HAE, their child has a 50 per cent chance of inheriting the disorder.\(^1\) The absence of family history does not rule out the HAE diagnosis, however, scientists report that as many as 25 per cent of HAE cases result from patients who had a spontaneous mutation of the C1-inhibitor gene at conception. These patients can pass the defective gene to their offspring.\(^3\)
- People with HAE experience attacks of severe swelling that affect various body parts including the hands, feet, face, airway (throat) and internal organs.
- Swelling of the throat is the most dangerous aspect of HAE because the airway can be closed and cause death by suffocation. Throat attacks must be treated as an emergency and patients must seek prompt medical attention as soon as throat involvement is suspected. Studies reveal that more than 50 per cent of patients will endure at least one throat attack in their lifetime.\(^4\)\(^5\)
- Almost all HAE patients experience abdominal attacks.\(^6\) Swelling in the abdomen involves severe and excruciating pain, vomiting, and diarrhea.\(^1\)\(^7\)\(^8\) Approximately one third of patients with undiagnosed HAE undergo unnecessary surgery during abdominal attacks because the symptoms mimic a surgical emergency.\(^1\)
- Swelling of the face, hands, feet and other body parts is disfiguring, extremely painful and debilitating. It is not uncommon for HAE attacks to involve more than one body part.
- Untreated, an average attack lasts for between 24 and 72 hours, but some attacks may go on for over a week.\(^7\)
- The majority of patients experience their first attack during childhood or adolescence.\(^5\) Most attacks occur spontaneously with no apparent reason. However, anxiety, stress, minor trauma, certain medical, surgical and dental procedures and illnesses such as colds and flu have been cited as triggers. ACE Inhibitors (a blood pressure control medication) and estrogen-derived medications (birth control pills and hormone replacement drugs) have also been shown to cause HAE attacks.
- Patients often report a “tightness” sensation at the site where the swelling then occurs thirty minutes to several hours later. In some cases, this sensation can be felt 12 to 24 hours before the swelling begins. Approximately one quarter of HAE patients experience a flat, non-itching red blotchy rash both before and during an attack.\(^4\)
What causes HAE?

HAE patients have a defect in the gene that controls a blood protein called C1-inhibitor, and therefore the disorder is also commonly referred to as C1-inhibitor deficiency. The genetic defect results in production of either inadequate or nonfunctioning C1-inhibitor protein. Normal C1-inhibitor helps to regulate the complex biochemical interactions of blood based systems involved in fighting disease, inflammatory response and coagulation. Because the defective C1-inhibitor does not adequately perform its regulatory function, a biochemical imbalance can occur and produce an unwanted peptide — called bradykinin — that induces the capillaries to release fluids into surrounding tissues, thereby causing swelling.

As shown in Table 1 there are two forms of HAE. The most common form of the disease — Type I — is characterized by low quantitative levels of C1-inhibitor and affects about 85 per cent of patients. Type II HAE affects the other 15 per cent of patients who have normal or elevated levels of C1-inhibitor, but the protein does not function properly. The two types are symptomatically indistinguishable and affect men and women equally. Several investigators have noted a familial (and therefore inherited) angioedema in patients with normal levels of C1-inhibitor. Often found under the designation of ‘HAE Type III’, this form of angioedema is yet to be fully understood.

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<th>Table 1: Hereditary angioedema subtypes</th>
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How does HAE affect patients?
Untreated patients have attacks every 7 to 14 days on average, with a frequency ranging from virtually never to every three days. There is considerable variation in the severity of HAE, even among affected family members. Because a typical attack lasts several days before it subsides, people with HAE may be debilitated by their symptoms for up to 100 days, or more than three months, of the year. HAE imposes a substantial humanistic burden and patient’s quality of life is significantly diminished by missed days of work, school, and leisure activities. HAE patients suffer from decreased physical and mental health, including depression. In addition, HAE can cause patients to withdraw from education, work and social activities.

“Patients with the deficiency of C1-inhibitor are not just an interesting model for study... they are critically ill. Many have ancestors that died suddenly from suffocation. Patients live in constant dread of life threatening laryngeal obstruction.”

What are the costs of HAE?
The economic burden associated with HAE has a significant effect on patients, healthcare systems and society. A recent study conducted in the United States of America showed the substantial economic costs associated with both acute attacks and the ongoing chronic (long term) nature of the disorder. The study indicated that total costs for an HAE patient could be as high as $100,000 each year, and that almost all costs increase with disease severity.

However, the study may underestimate the real costs of HAE. The study was performed before acute therapy was available in the US. Over two thirds of patients in the study did not seek immediate medical help for attacks, probably because of their past experience of frequent misdiagnosis and limited treatment options. Nor did the study take into account the cost of inappropriate procedures or other unnecessary treatments commonly experienced by people with HAE.

How is HAE diagnosed?
It is important that HAE patients receive an accurate diagnosis early in life. Various studies reveal that the risk of death, mainly due to suffocation during laryngeal attacks, can be as high as 30-40 per cent in undiagnosed patients. Delays in diagnosis are common in patients with Hereditary Angioedema. The average time between the onset of symptoms and the diagnosis was 22 years as of 1977 and was still more than 10 years as of 2005. The diagnosis should be suspected in any patient who presents with recurrent angioedema or abdominal pain in the absence of hives, which could suggest allergic angioedema.

The diagnosis is complicated because HAE is extremely rare and most physicians may never see a patient with the disorder. In addition, most cases of angioedema are caused by an allergic reaction. Abdominal attacks may be mistaken for conditions such as appendicitis and often results in unnecessary exploratory surgery. Often, patients are misdiagnosed as having psychosomatic symptoms and are inappropriately referred for psychiatric evaluation.
Treatment of HAE – Because HAE is a non-allergic form of angioedema, symptoms do not respond to treatments for allergic reactions, such as antihistamines, corticosteroids and epinephrine. In the past, treatment was limited to tranexamic acid and pain medicines (including morphine) for acute attacks (attacks that are in progress), and anabolic steroids (such as danazol) for long-term attack prevention. Anabolic steroids are effective in reducing attack frequency in many patients, but are associated with significant side effects. Because anabolic steroids are male hormones, their side effects can be particularly severe in female patients. In addition, these drugs cannot be given to pregnant women and children.

- **Cinryze™** brand of C1-inhibitor has been FDA-approved for preventing HAE attacks. Cinryze™ is delivered intravenously and is approved for home infusion.
- **Berinert®** brand of C1-inhibitor has been FDA-approved for treating acute facial and abdominal HAE attacks. Berinert® is delivered intravenously.
- **Kalbitor®** brand of plasma kallikrein inhibitor has been FDA-approved to treat acute HAE attacks in patients 16 years of age and older. Kalbitor® is delivered through subcutaneous injections.
- **Firazyr®** brand of bradykinin receptor antagonist has been FDA-approved for treating acute HAE attacks in patients 18 years and older. Firazyr® is delivered by subcutaneous injection and is approved for self-administration.

The medical literature and practitioner experience confirm that corticosteroids (prednisone), antihistamines and epinephrine are not effective in treating angioedema caused by C1-inhibitor deficiency.

Patients typically receive treatment for attacks at a clinic or hospital. However, several studies have suggested that home treatment can be safe and reduce the severity and duration of attacks. Self-treatment can help patients regain control of and improve the quality of their lives, and avoid costly admission the hospital.¹
References