

Angioedema Types

Type	Description	Common Symptoms (1)	Complement System	Possible Treatment*
Hereditary Type I (HAE-I)	Represents approximately 80 to 85% of HAE cases. C1 inhibitor is considerably below normal due to a defective gene on chromosome 11. There is usually a family history of angioedema, but a number of cases are due to a spontaneous mutation of the gene.	Swelling can occur in the extremities, abdomen, throat and other organs. Swelling of the airway can be fatal. Abdominal swelling usually involves pain, vomiting and diarrhea. Symptoms usually appear early in life, most often by age 13 and may increase in severity after puberty. Episodes may be spontaneous or triggered by physical trauma or emotional stress.	Low levels of C1 inhibitor. C4 is almost always low. C1, C3 and C1q are normal. Abnormal complement (above) is the same whether the condition is hereditary or spontaneous.	C1 inhibitor concentrate (2) is the gold standard acute attack therapy, but is not yet licensed in the US. While some clinicians use 2 units of FFP, there are reports that the therapy could exacerbate an ongoing attack. Androgens such as winstrol (stanozolol), danazol, and oxandrolone are preventive therapies that are not effective acute attack treatments. Fluid replacement, pain management, and maintaining an open airway are the key elements of acute attack therapy.
Hereditary Type II (HAE-II)	Represents approximately 15 to 20% of HAE cases. Similar description to Type I, but C1 inhibitor does not function properly.	Same as HAE-I.	C1 inhibitor level may be normal or elevated, but it is dysfunctional. C1, C3 and C1q are normal, but C4 is almost always low.	Same as HAE-I
Acquired Type I (AAE-I) AAE-I & II are considered very rare; there are few reported cases.	Immune complexes that are usually linked to an underlying lymphoproliferative disorder destroy the function of C1 inhibitor. Angioedema can be an indicator that a lymphoproliferative disease is developing, so early detection needs to be emphasized.	Similar to HAE. The symptoms typically appear in the fourth decade of life or later. Because acquired angioedema is not related to a genetic defect there is an absence of a family history of symptoms.	Low level of C1 inhibitor and C4. C1q is usually reduced, but not always.	Diagnosis and treatment of underlying lymphoproliferative disease often eliminates the root cause. Antifibrinolytics such as tranexamic acid and epsilon-aminocaproic acid for possible prevention of episodes. Androgen therapy may help.
Acquired Type II (AAE-II) AAE-I & II are considered very rare; there are few reported cases.	Autoantibodies are present and destroy C1 inhibitor function. There is no apparent underlying disorder.	Same as AAE-I.	Same as AAE-I. A lab test for autoantibodies may be appropriate.	Antifibrinolytics such as tranexamic acid and epsilon-aminocaproic acid for possible prevention. It is possible that immunosuppressive therapy might be successful.
Idiopathic	Swelling and/or hives persist beyond 6 weeks. Thyroid dysfunction should be considered.	Swelling may occur just about anywhere and may be accompanied by urticaria (hives).	Normal	Primarily antihistamines. DHEA. 1-thyroxine for thyroid dysfunction. Prednisone therapy.
Nonhistaminergic (INAE) May occur in about 1 out of 20 cases of angioedema	Angioedema without urticaria (usually not responsive to H1 antihistamine blockers). Parasites, infections and autoimmune diseases are not present.	Swelling may occur anywhere: face, arms, legs, genitalia, throat, abdomen (but abdomen is less frequent than those with HAE). Symptoms do not change due to menstrual period or pregnancy.	Normal	Antifibrinolytics such as epsilon-aminocaproic acid (available in the US) and tranexamic acid.
Allergic This is the most common form of angioedema.	Swelling and/or hives are a reaction to an outside influence such as food, bee sting, cold, heat, latex or drug. The outside influence provokes a histamine reaction, which leads to swelling and/or the hives.	Swelling occurs most often in the face and throat area. Urticaria (hives) may be present. If condition persists beyond 6 weeks it is considered chronic idiopathic and not an allergic reaction.	Normal	Avoid the substance or behavior that causes the allergic reaction. Antihistamines. Adrenaline (epinephrine) possibly as self-injecting Epi pens for emergencies.
ACE-Inhibitor (Angiotensin-Converting Enzyme Inhibition) Possible cause for 4 to 8% of people with angioedema.	Caused by ACE-Inhibitors for high blood pressure (captopril, enalapril, genzapril, quinapril, ramipril). Swelling may commence anywhere from a few hours to years after first starting medication.	Swelling may occur just about anywhere: throat, face, lips, tongue, hands, feet, genitals, intestines. If urticaria is present it reduces the probability of a link to ACE-Inhibitors.	Normal	Suspension or change of medication.

*Patients with the slightest hint of throat swelling should seek immediate treatment to ensure that their airway is not compromised. The medical literature and practitioner experience confirms that corticosteroids (Prednisone), antihistamines, and epinephrine are not effective in treating angioedema created by C1-inhibitor deficiency.

NOTES:

1. The presence of urticaria associated with angioedema could suggest a diagnosis other than HAE or AAE.
2. C1 inhibitor concentrate is undergoing clinical trials in the United States that may lead to FDA approval. It is currently available in other countries.

A Brief Description of the Complement System: The Complement is part of our immune system. It involves a series of complex proteins (C1 thru C9 in addition to C1 inhibitor) that act in "concert" to clear foreign organisms from our bodies. C1 inhibitor essentially monitors the complement system and prevents it from having a "runaway" reaction. When C1 inhibitor is not present at an adequate level, or is dysfunctional, the system "overreacts" resulting in swelling. Angioedema Basics was compiled based upon current research and medical knowledge. The emphasis has been on presenting the information in language that is not technical and is primarily for those that are trying to understand the different types of angioedema.

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What is Hereditary Angioedema?

Hereditary Angioedema (HAE) is a very rare and potentially life threatening genetic condition that occurs in about 1/10,000 to 1/50,000 people. HAE symptoms include episodes of edema (swelling) in various body parts including the hands, feet, face, and airway. In addition, patients often have bouts of excruciating abdominal pain, nausea, and vomiting that is caused by swelling in the intestinal wall. Airway swelling is particularly dangerous and can lead to death by asphyxiation.

HAE patients have a defect in the gene that controls a blood protein called C1-inhibitor. 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 disease fighting, inflammatory response, and coagulation. Because defective C1-inhibitor does not adequately perform its regulatory function, a biochemical imbalance can occur and produce unwanted peptides that induce the capillaries to release fluids into surrounding tissues, thereby causing edema.

HAE is called hereditary because the genetic defect is passed on in families. A child has a 50 percent chance of inheriting this disease if one of his or her parents has it. The absence of family history does not rule out the HAE diagnosis, however. Scientists report that as many as 20 percent 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.

Because the disease is very rare, it is not uncommon for patients to remain undiagnosed for many years. Many patients report that their frequent and severe abdominal pain was inappropriately diagnosed as psychosomatic, resulting in referral for psychiatric evaluation. Unnecessary exploratory surgery has been performed on patients experiencing gastrointestinal edema because abdominal HAE attacks mimic a surgical abdomen. Before therapy became available, the mortality rate from airway obstruction was reportedly as high as 30%.

For more information about the HAE Association or any of the clinical trials currently being conducted please email us at: generalinfo@hereditaryangioedema.com or phone us toll free at 866-580-8178.

What causes Hereditary Angioedema attacks?

Most attacks occur spontaneously with no apparent reason, however anxiety, stress, minor trauma, surgery, and illnesses such as colds and flu have been cited as triggers. Trauma to the oral cavity caused by dental procedures make HAE patients particularly vulnerable to airway attacks. Patients have also reported swelling in extremities following typing, prolonged writing, pushing a lawn mower, hammering, shoveling, and other physical activities.

In women, menstruation and pregnancy seem to have a major effect on disease activity. Some women patients report a definite increase in the number of attacks during their menstrual periods. During pregnancy, some patients note an increase in the frequency of attacks, while others have reported a decrease. Use of oral contraceptives and hormone replacement therapy is associated with an increase in the frequency and severity of attacks.

How is Hereditary Angioedema diagnosed?

Most cases of angioedema are not HAE because swelling attacks are typically caused by something other than C1-inhibitor deficiency, usually an allergic reaction. Laboratory analysis of blood samples or genetic testing is required to establish the HAE diagnosis. There are two specific blood tests that confirm HAE:

1. C1-inhibitor quantitative (antigenic)
2. C1-inhibitor functional

Traditionally, HAE has been classified into two types. The most common form of the disease—Type I—is characterized by low quantitative levels of C1-inhibitor and affects about 85% of patients. Type II HAE affects the other 15% of patients who have normal or elevated levels of C1-inhibitor, but the protein does not function properly. Several investigators have noted a familial (and therefore inherited) angioedema, exclusively in women with normal levels of C1INH, that is correlated with conditions creating high estrogen levels—for example, pregnancy or the use of oral contraceptives. This estrogen-dependent/estrogen-related inherited angioedema is often referred to as HAE III. A recent paper in the American Journal of Human Genetics implicates a mutation in the gene for human coagulation Factor XII as the potential cause for swellings in these patients.

At what age do attacks of Hereditary Angioedema start?

The age of HAE onset varies considerably, however, in one study, half of the patients reported onset of their symptoms by the age of seven, and over two thirds became symptomatic by the age of thirteen. There also seems to be an increased frequency of attacks during puberty or adolescence.

How long do Hereditary Angioedema attacks last?

Patients often report tingling or tightness at the site where edema will occur thirty minutes to several hours later. In some cases, this sensation can be present twelve to twenty four hours before the onset of swelling. Approximately one fourth of HAE patients experience a flat, non itching red blotchy rash both before and during an attack. The edema itself usually lasts for twenty four to seventy two hours, but the length of an attack can range from four hours to four or more days.

When are Hereditary Angioedema attacks considered serious?

Swelling of the extremities is uncomfortable and, according to some patients, can be painful and debilitating depending on the location of the edema. Attacks that involve the face and throat must be taken seriously and medical treatment should be sought without delay. Swelling of the throat can close the air passage and cause death by suffocation. The symptoms of an impending airway obstruction include difficulty swallowing and a change in voice pitch.

Abdominal attacks cause severe pain, nausea, vomiting, and watery diarrhea. Some patients require hospitalization for low blood pressure, dehydration, and pain management. As noted above, abdominal attacks can mimic a surgical abdomen and many patients have been subjected to unnecessary exploratory surgery.

How is Hereditary Angioedema treated?

There are three types of therapy for HAE patients.

1. Long term preventive treatment
2. Short term preventive treatment
3. Treatment of acute attacks

Clinicians generally recommend long term therapy for patients who experience more than one attack per month, or who believe that the disease significantly interferes with their life style. The present drugs of choice for long-term therapy are 17 alpha alkylated androgens such as danazol, and oxandrolone (Oxandrin). 17 alpha alkylated androgens produce an increase in C1-inhibitor levels, but the exact mechanism of how they do so has not been precisely defined.

Winstrol (stanozolol) was a widely used HAE therapy until the company producing the product ran into manufacturing problems and decided to discontinue manufacturing the drug. To accommodate anyone who would like to continue using Winstrol (stanozolol), the HAE Association has made arrangements for patients to purchase the drug from pharmacies equipped to make the drug in-house.

Some patients report success with a class of drugs called anti-fibrinolytics (epsilon aminocaproic acid is available in the US), but their use has largely been abandoned because androgens have proven to be much more effective.

The medical literature and practitioner experience confirms that corticosteroids (prednisone), antihistamines, and epinephrine are not effective in treating angioedema caused by C1-inhibitor deficiency. Short-term therapy is necessary for patients who do not require ongoing preventive treatment, but are facing dental procedures or elective surgery. Current practice calls for daily high dose androgen therapy (600-800 mgs of danazol) for at least five days prior to surgery and four days afterward. For emergency procedures, fresh frozen plasma can be used to prevent attacks. There have been reports of acute attacks getting worse after fresh frozen plasma was administered. The threat of this complication only exists during an acute attack, and is not a concern when fresh frozen plasma is given as a preventive measure.

Currently, there is no approved treatment for acute HAE attacks available in the United States. Some clinicians use fresh frozen plasma effectively, but (as noted above) this therapy is considered controversial because of reports that it caused attacks to worsen. C1-inhibitor concentrate is the treatment of choice for acute attacks of HAE, and has been available to patients in Europe for over a decade. C1 inhibitor concentrate treatment resolves the angioedema in thirty minutes to two hours with complete remission in twenty-four hours. C1-inhibitor concentrate is not available in the United States. To the dismay of US HAE patients, a poorly designed C1-inhibitor concentrate phase III clinical trial sponsored by a major multinational pharmaceutical company did not result in a US license for this life saving product. C1INH concentrate can be purchased under the FDA's Personal Importation guidelines. As noted on our website, <http://www.haea.org>, The HAE Association provides patients with technical assistance on personal importation of C1INH concentrate.

The absence of an effective acute attack therapy limits clinicians to providing supportive care. Maintaining an open airway is the primary concern for patients with laryngeal edema. Because gastrointestinal edema usually involves excruciating pain and frequent vomiting, therapy should include aggressive pain management and fluid replacement. Clinicians report that Zofran, compazine, and phenergan are effective in reducing nausea and vomiting, while either morphine, dilaudid, darvocet, or other narcotics can be used to relieve attack related abdominal pain.

Unfortunately, the HAE literature in the mid seventies made reference to patients who developed narcotic dependency and this observation was repeated in subsequent papers. Many HAE patients have noted that physicians are often wary of prescribing pain medicine for painful abdominal attacks, and this could be due to reports contained in the literature. Any notion that the HAE population suffers from widespread narcotics addiction has been discredited by the experience of researchers who have treated relatively large numbers of patients.