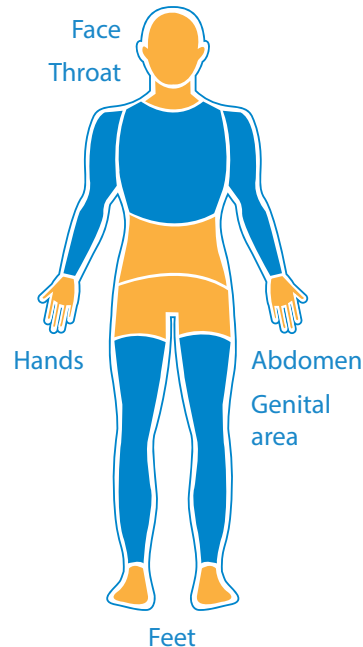


# What is Hereditary Angioedema (HAE)?

HAE is a rare inherited condition characterized by painful, recurring attacks of swelling in parts of the body including:<sup>1,2</sup>



It is the result of a problem with a protein called C1 esterase inhibitor.

There are three types of hereditary angioedema:

## Type I

- 85% of cases<sup>3</sup>
- C1-INH is decreased or not present<sup>4</sup>

## Type II

- 15% of cases<sup>3</sup>
- C1-INH is not working properly<sup>4</sup>

## Type III

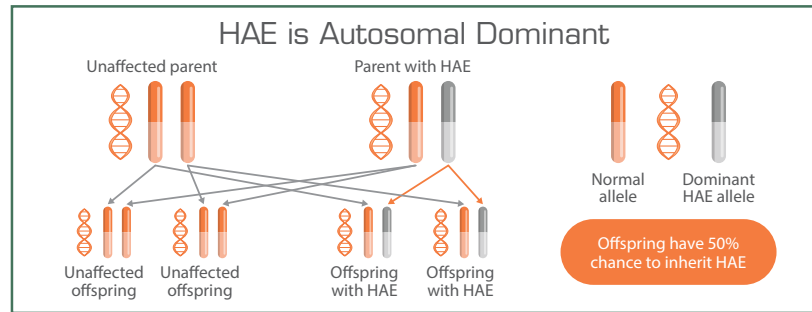
- Rare; prevalence is unknown<sup>5</sup>
- Diagnosed by genetic testing<sup>6</sup>

# What is Hereditary Angioedema (HAE)?

HAE is characterized by painful, unpredictable, recurrent attacks of swelling and/or edema affecting the hands, feet, face, abdomen, urogenital tract, and the larynx.<sup>1,2</sup>

HAE is a rare, autosomal dominant disease.<sup>1,2</sup> Patients with HAE generally inherit one normal gene and one abnormal gene (heterozygous).

The child of an affected parent has a 50% chance of inheriting the abnormal gene. It is important to note that spontaneous mutations may also occur, and it is estimated that 20% to 25% of all HAE cases occur in patients with no family history of the disease.<sup>1</sup>



Adapted from National Organization for Rare Disorders (NORD), 2010.

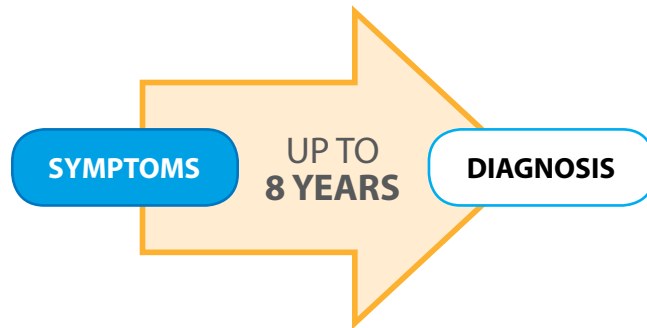
## Three forms of HAE have been defined:

Type <sup>5</sup>	C1-INH protein <sup>5</sup>	C1-INH function <sup>5</sup>	Prevalence <sup>5,7</sup>
Type I HAE (HAE-1)	Low	Low	85% of cases; autosomal dominant
Type II HAE (HAE-2)	Normal or elevated	Low	15% of cases; autosomal dominant
Type III HAE (HAE-3)	Normal	Normal	Unknown, rare

# How is a diagnosis of HAE confirmed?

HAE is difficult to diagnose. Literature reports that the time lapse between first symptoms and final, correct diagnosis can be up to 8 years for type I and longer for type II.<sup>8</sup>

Ultimately, a diagnosis of HAE requires a detailed personal and family history, and laboratory measure of certain blood proteins.<sup>4</sup>



# How is a diagnosis of HAE confirmed?

Requires quantitation of C4 and quantitation of C1-INH by protein and function. A low C1q level (seen in ~70%) is associated with acquired C1-INH deficiency<sup>9</sup>

## Laboratory Evaluation of Angioedema<sup>9</sup>

Type	C4 <sup>†</sup>	C1-INH protein	C1-INH function <sup>‡</sup>	C1q <sup>§</sup>
Type I	↓	↓	↓	N
Type II	↓	N or ↓	↓	N
Type III	N	N	N	N
ACE inhibitor	N	N	N	N
Idiopathic	N	N	N	N
Acquired C1-INH deficiency	↓	↓	↓	↓

Adapted from Kaplan et al.

<sup>†</sup> Decreased in 95% of patients with type I and type II HAE.

<sup>‡</sup> Symptoms typically occur when functional activity is 35% or less.

<sup>§</sup> Decreased in approximately 70% of patients with acquired C1-INH deficiency.

Markedly reduced in rare type I HAE patients with homozygous deficiency.

ACE = Angiotensin-converting enzyme

INH = Inhibitor

N = Normal

# What causes HAE?

When your body experiences trauma, hormonal change, stress, or other triggers, the normal swelling is controlled by C1-INH. If this protein is absent or not functioning properly, abnormal swelling occurs.<sup>4</sup>

## How does this happen?

Low levels of C1-INH may increase a naturally occurring hormone called bradykinin.<sup>10</sup>

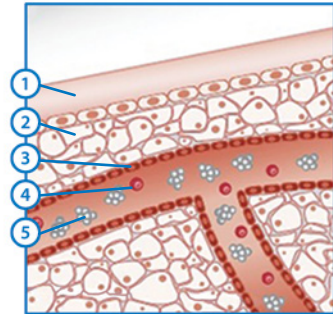
If bradykinin levels are increased, fluids can pass through the vessel walls into the surrounding tissue causing the local swelling of an HAE attack.<sup>10</sup>

Swelling attacks are often divided into three types:<sup>9</sup>

1. Peripheral – swelling under the skin of hands, feet and face
2. Abdominal – swelling in the abdomen
3. Episodes that can make breathing difficult – swelling in the airways

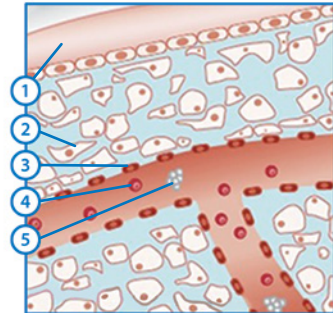
### Normal levels of C1 inhibitor

1. Skin
2. Tissue cell
3. Blood vessel wall
4. Red Blood cell
5. C1 inhibitor



### Levels of C1 inhibitor in a person with HAE

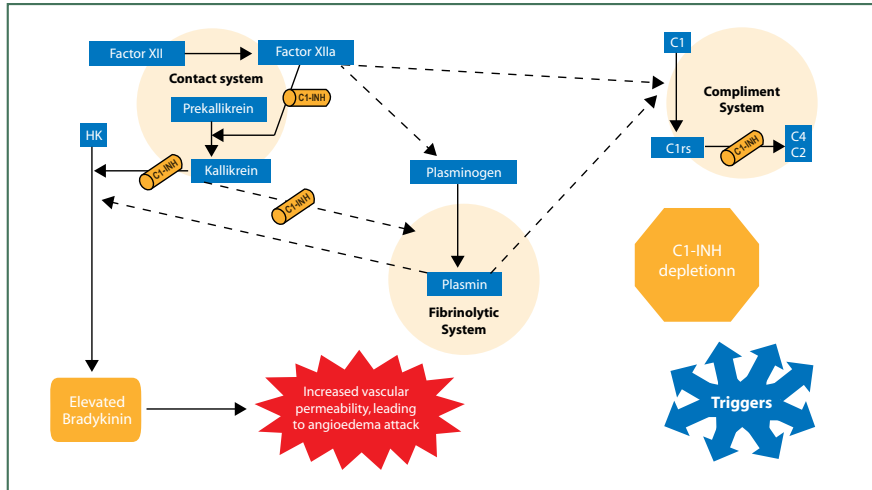
1. Skin
2. Tissue cell
3. Blood vessel wall
4. Red Blood cell
5. C1 inhibitor



# What causes HAE?

HAE is caused by mutations of the C1-Inhibitor (C1-INH), a key plasma protease inhibitor.<sup>9</sup> Normally, C1-INH regulates the complement, fibronolytic, and contact systems by blocking pathways and preventing the systems from becoming overactive.<sup>1</sup>

- In HAE patients, there is insufficient C1-INH to properly control the cascades. The result is an overproduction of bradykinin,<sup>1</sup> which is considered to be the major mediator of HAE attacks<sup>11</sup>



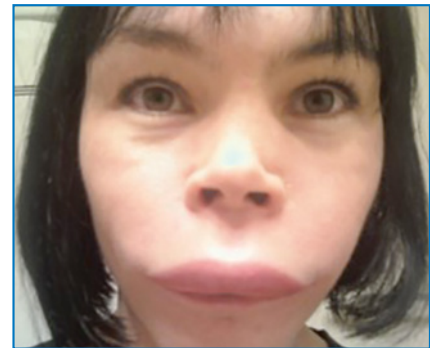
Adapted from National Organization for Rare Disorders (NORD), 2010.

Attacks of angioedema are often divided into three types:<sup>9</sup>

1. Peripheral (cutaneous)
2. Gastrointestinal
3. Angioedema episodes that can potentially compromise breathing

## What is a peripheral attack?

- Peripheral attacks can be painful, debilitating, and disfiguring<sup>2</sup>
- As the word 'peripheral' suggests, these attacks are associated with swelling of the skin, typically on the hands, feet and face<sup>9</sup>



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## What is a peripheral attack?

- Painful, debilitating, and disfiguring<sup>2</sup>
- Characterized as swelling of the extremities and facial structures<sup>9</sup>



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## What is an abdominal attack?

- Often the most painful of HAE attacks
- Swelling of the intestinal wall<sup>6</sup>
- Attack may involve vomiting, diarrhea, and cramping, and can appear to be a surgical emergency<sup>6</sup>



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# What is an gastrointestinal attack?

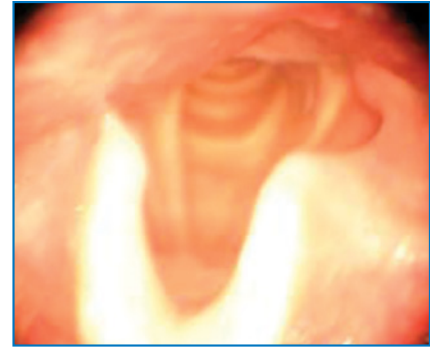
- Painful attacks<sup>9</sup>
- Due to edema of the bowel wall<sup>9</sup>
- Patient experiences severe cramping abdominal pain, nausea, vomiting and, occasionally, diarrhea<sup>9</sup>
- Can lead to unnecessary surgery and delay in diagnosis, as well as to narcotic dependence due to the frequent, severe pain<sup>6</sup>



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## How can an attack potentially compromise breathing?

- Laryngeal edema attacks are the most serious type of HAE attack because they can result in the inability to breathe and possibly death<sup>6</sup>
- During a laryngeal edema attack, the tongue or throat swells up,<sup>6</sup> stopping air from getting in
- Over half of HAE patients will experience one of these attacks during their lifetime<sup>12</sup>
- If you experience a laryngeal attack, seek immediate medical attention<sup>9</sup>

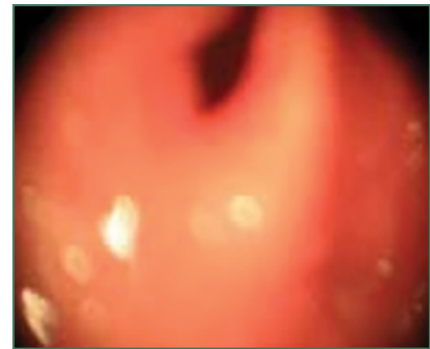
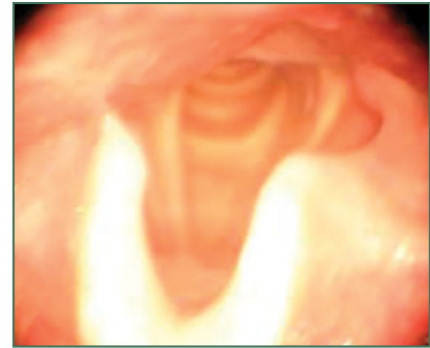


Courtesy of Bas M, et al. *Allergy*. 2006;61(12):1490-1492.

# How can an attack potentially compromise breathing?

Breathing may be compromised due to:

- Laryngeal edema, and/or severe tongue/pharyngeal edema such that secretions cannot be handled<sup>9</sup>
- Over 50% of patients with HAE will experience at least one upper airway attack with risk for asphyxiation during their lifetime<sup>12</sup>
- Patients experiencing a laryngeal attack should always seek immediate medical attention<sup>9</sup>



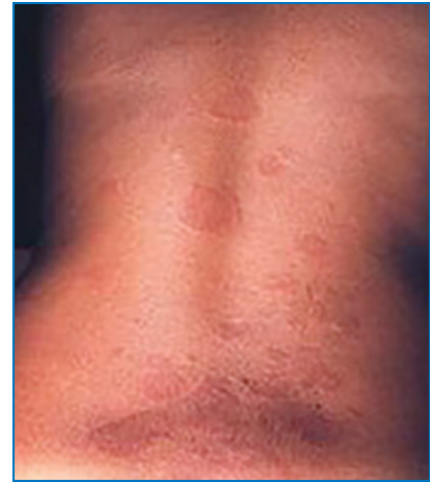
Courtesy of Bas M, et al. *Allergy*. 2006;61(12):1490-1492.

## Is there any way to tell if I am going to have an attack?

It's difficult to predict an HAE attack. However, in some patients, there are signs that can occur several hours and even up to one day before an attack, including:<sup>12</sup>

- Fatigue
- Irritability
- Weakness
- Nausea
- Pink rings or a rash

Every patient is different so it is important to learn to recognize your signs.

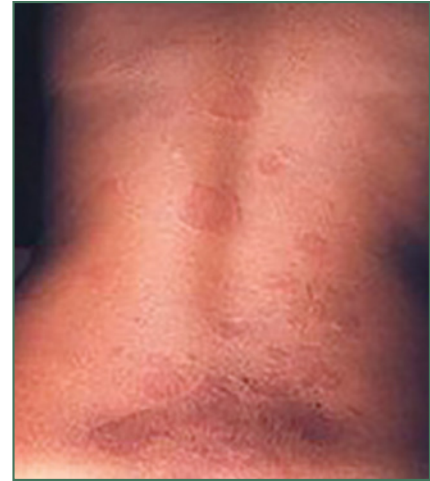


Courtesy of Binotto MA, et al. *Images Paediatr Cardiol* 2002;4(2):12-31.

# How can patients tell if they are going to have an attack?

In some patients, these symptoms may precede an angioedema attack by several hours, and include:<sup>12</sup>

- Fatigue
- Irritability
- Weakness
- Nausea
- Erythema marginatum (pink rings on the trunk and inner surfaces of the limbs)



Courtesy of Binotto MA, et al. *Images Paediatr Cardiol* 2002;4(2):12-31.

# What triggers an HAE attack?

HAE is an unpredictable disease. Attacks can occur spontaneously for no apparent reason. However, in some patients, certain triggers have been identified:

- Minor trauma
- Surgery, such as the anesthetic injection during a dental procedure<sup>1</sup>
- Severe emotional stress<sup>1,9</sup>
- Infection<sup>1,9</sup>
- Hormonal influences such as birth control pills or the onset of puberty, menstruation, or menopause have increased the frequency of attacks<sup>1,9</sup>

It is important to learn and recognize your triggers.

# What triggers an HAE attack?

Most acute episodes of angioedema appear to be spontaneous, however, there are predisposing circumstances that trigger the response. These may include:

- Trauma<sup>1,9</sup>
- Surgery<sup>1,\*</sup>
- Anesthesia<sup>1</sup>
- Dental procedures<sup>1</sup>
- Severe emotional stress<sup>1,9</sup>
- Infection<sup>1,9</sup>
- Fluctuating hormone level (particularly increased estrogen)<sup>9</sup>
- Menstruation<sup>1</sup>
- Oral contraceptive use<sup>1</sup>

\*Attacks after surgery are common and usually occur 4 to 30 hours after the procedure.<sup>5</sup>



# Can HAE be managed?

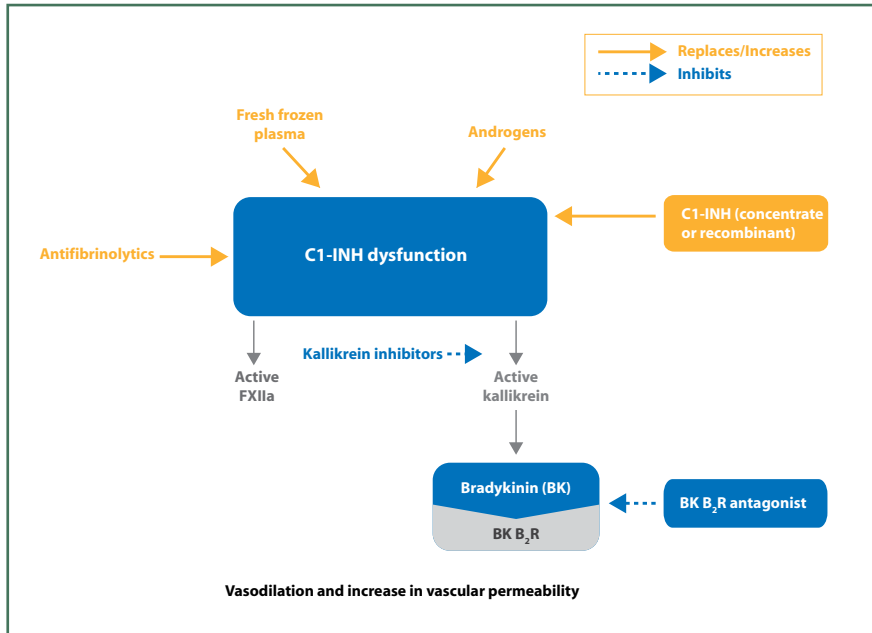
Once a diagnosis of HAE is established, it is crucial that the disease continue to be properly managed.<sup>13</sup> This includes:<sup>3</sup>

- Immediate treatment of acute or serious attacks<sup>3</sup>
- Short-term treatments to help prevent attacks<sup>3</sup>
- Long-term treatments to reduce the frequency and severity of recurrent attacks<sup>3</sup>

# Can HAE be managed?

Optimal management of HAE includes treatment of acute attacks, short-term prophylaxis to prevent an attack, and long-term prophylaxis to minimize the frequency and severity of recurrent attacks.<sup>3</sup>

HAE targeted therapies include C1-esterase inhibitors, kallikrein inhibitors, and bradykinin receptor antagonists.<sup>13</sup>



## Where can I go for more support?

Along with the advice that you will receive from your doctor, it is important that you receive additional support as well.

HAE Canada is a patient group that can be a valuable resource for HAE patients.

They can connect you to others living with HAE, so you can share your unique experiences living with this rare and unpredictable disease.

For more information, visit [www.haecanada.org](http://www.haecanada.org).



**Hereditary Angioedema (HAE) Canada**  
**Angioédème Héritaire (AEH) Canada**

## Where can patients go for more support?

Encourage patients to reach out to HAE Canada for emotional support, to help raise HAE awareness, and to feel that they are not alone.

[www.haecanada.org](http://www.haecanada.org)



**Hereditary Angioedema (HAE) Canada**  
**Angioédème Héritaire (AEH) Canada**

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