Understanding hereditary angioedema (HAE), an unpredictable and potentially life-threatening disease[1,2]

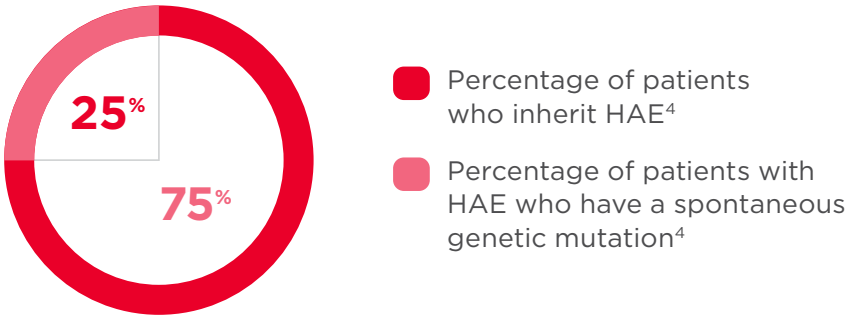
HAE is a rare, genetic disease that can be life threatening[1-3]

HAE is a genetic disease characterized by **recurrent attacks of angioedema** without urticaria or pruritus.[1,3]

The two most common types of HAE are Type I and Type II. They are similar in clinical presentation but result from different C1 esterase inhibitor (C1-INH) mutations.[3]

- ~85% of patients have Type I, which is characterized by a deficiency in C1-INH[3]
- ~15% of patients have Type II, which is characterized by dysfunctional C1-INH[3]

Most cases of HAE are inherited



There is a need to improve diagnostic delays in HAE[5]

8.4

In a 2017 survey of 445 patients with HAE, people with HAE on average experienced a delay of 8.4 years in getting an accurate diagnosis.[5]

47.1%

In a 2015 survey of 106 patients with HAE Type I or II, one-fourth were diagnosed within 1 year of onset of HAE symptoms, but almost half (47.1%) experienced a delay of ≥10 years between their initial onset of symptoms and their diagnosis.[6]

Misdiagnoses may contribute to diagnostic delays and result in unnecessary treatments, potentially increasing the risk of death.[7]

Lab tests to confirm a diagnosis of HAE

To confirm an HAE diagnosis, laboratory testing is necessary. Patients should have the following measured[8,9]:

- Serum levels of C4
- Antigenic and functional C1-INH levels

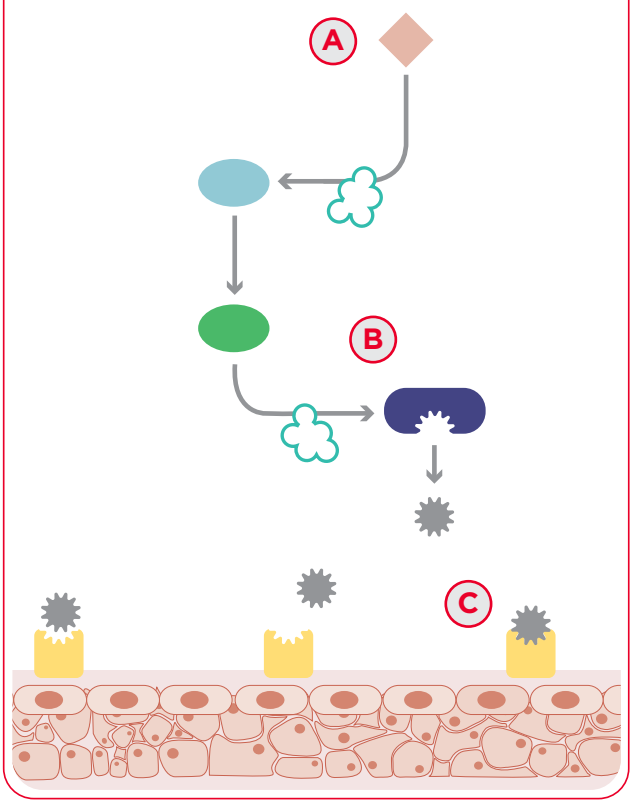
Testing results for HAE types I and II[9,10]

Angioedema Type	C4 Level	C1-INH Level	C1-INH Function
Type I HAE	Low	Low	Low
Type II HAE	Low	Normal-High	Low

Causes of HAE attacks

Most cases of HAE are caused by a deficiency or dysfunction of C1-INH, resulting in the inability to regulate the kallikrein-kinin system.[3]

Kallikrein-kinin system



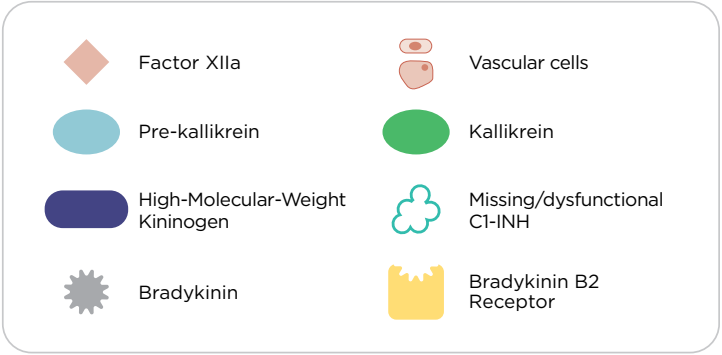
Adapted from Zuraw 2008 and Kaplan 2010.[3,12]

Increased bradykinin levels trigger an HAE attack[9,11]

A. HAE attacks are initiated when the kallikrein-kinin cascade is activated.[4,12]

B. In response to this activation, plasma kallikrein activity increases the cleavage of high-molecular-weight kininogen (HMWK) to produce bradykinin[9,12]

C. Excessive bradykinin, after binding to bradykinin B2 receptors, causes an increase in blood vessel permeability. This allows fluid to pass through the blood vessel walls causing subcutaneous or submucosal swelling.[9,11,12]



HAE attacks are unpredictable and can be life threatening[1,2]

HAE attacks typically cause swelling of the skin/subcutaneous tissues and gastrointestinal tract, some of which may be painful and functionally disabling.[3]

Skin/subcutaneous tissue:

- Typically affects face, extremities, and genitals[13]
- Facial swelling can extend to laryngeal edema[2,a]

Gastrointestinal tract:

- May present with mild to severe abdominal pain accompanied by vomiting and/or diarrhea[13]
- Untreated abdominal attacks may require, on average, between 24 and 50 hours of bed rest[14,b]

Upper airway, including larynx and oropharynx

- In the past, untreated laryngeal attacks resulted in mortality rates up to 30%[13]
- 50% of patients experience at least 1 laryngeal episode during their lifetime[2,c]

HAE attacks can migrate to other parts of the body during a single attack.[3,13]

HAE attacks can occur without warning[1,2]

Some HAE attack triggers have been identified and may include:

- Stress[13,15]
- Physical trauma, surgery, or a dental procedure[15,16]
- Infection[13,15]
- Hormonal influence[15]
- Mechanical pressure[13]

Many patients experience prodromes before an HAE attack, including[17-19]:

- A tingling sensation
- Erythema marginatum, a mild, nonpruritic rash
- Fatigue
- Nausea
- Muscle aches
- Neurologic symptoms

[a]In a survey of 158 patients.[2]
[b]In a survey of 23 patients.[14]
[c]In a survey of 209 patients.[2]

HAE can impact a patient's life in a variety of ways

Burden of illness may include[5]:

- Anxiety and depression
- Dissatisfaction with care (perception of effectiveness, tolerability, and convenience of treatment)
- Impairment of daily activities (work, education, and social)
- Economic costs
- Decreased health-related quality of life (physical, psychological, social, and somatic functioning and well-being)

In a 2017 survey of 445 subjects, over the course of one year[5]:

13% Approximately 13% of patients visited a hospital and stayed an average of 1 week

14% Approximately 14% of patients required intubation following a laryngeal attack

According to a 2017 survey of 445 subjects, anxiety and depression are common comorbidities, affecting approximately 35% and 21% of patients with HAE, respectively. The severity of anxiety and depression worsened with more frequent HAE attacks.[5]

In a 2020 questionnaire covering a 7-day period, a higher frequency of HAE attacks was also associated with lower energy levels and greater difficulty performing basic daily activities[5]:

34% 34% of patients reported that their physical health or emotional problems interfered with their ability to participate in social activities at least some of the time[5]

In that questionnaire, patients reported that HAE-related symptoms affected their work productivity and their ability to perform nonwork-related activities[5]

Considerations for HAE management to prevent and reduce severity of HAE attacks

The goal of long-term preventive treatment is to decrease the overall number, severity, and burden of HAE attacks. The goal of acute therapy is to minimize morbidity and prevent mortality from an ongoing HAE attack. There are a number of other factors to consider when discussing expectations and goals with patients.[9]

Management guidelines from the US Hereditary Angioedema Association (HAEA) Medical Advisory Board (MAB) recommend 4 guiding principles to treatment approach[9]**:**

- Availability of effective acute therapy
- Early treatment to prevent attack progression
- Treatment of attacks irrespective of site swelling
- Incorporation of long-term preventive treatment based on individualized decision-making, reflecting a physician-patient partnership

Crafting a management plan

For both adults and children, a goal of treatment should be to help the management of HAE as much as possible.[9]

HAE management plans should be individualized with treatment tailored to each patient's[9]:

- Medical needs
- Preferences
- Life circumstances
- Tolerance of and response to specific medications

A collaborative physician-patient relationship with frequent communication is important to facilitate shared decision-making and maintain optimal treatment over time[9]

As is the case with any chronic disease in childhood, young patients and their caregivers should be educated about HAE[9]

Components of a detailed HAE management plan

Consideration of long-term preventive treatment

According to guidelines, decisions when considering long-term preventive treatment should take into account the patient's quality of life and treatment preferences in the context of attack frequency, attack severity, comorbid conditions, and access to emergent treatment.[9]

Preventive treatments can help prevent or reduce the frequency and severity of HAE attacks.

Your patient's needs and disease may change over time and they may need a reminder that their management plan can change, too. Guidelines recommend reviewing management plans for patients with HAE, including the need for preventive treatment.[5,9]

Access to effective acute treatment

Patients with HAE should have access to at least 2 doses of an on-demand medication to treat acute attacks.[9]

All attacks, irrespective of location, should be considered for treatment as soon as they are clearly recognized.[9]

Partner with your patients to better understand how HAE is affecting them to develop a management plan

- HAE is a rare, genetic disease that can be life threatening[1-3]
- HAE can impact a patient's life in a variety of ways[5]
- Goal of HAE treatment should be to reduce or prevent the frequency and severity of HAE attacks[9]
- Patients should be evaluated for prevention on a regular basis[9]
- All patients with HAE should have access to at least 2 doses of an on-demand medication to treat acute attacks and are strongly encouraged to administer their prescribed acute therapy at the first sign of an HAE attack, regardless of the location or severity of the attack[9]

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