Get to know the signs and symptoms of **hereditary angioedema** (**HAE**), and how to identify this rare, genetic disease in your patients.[1-3]

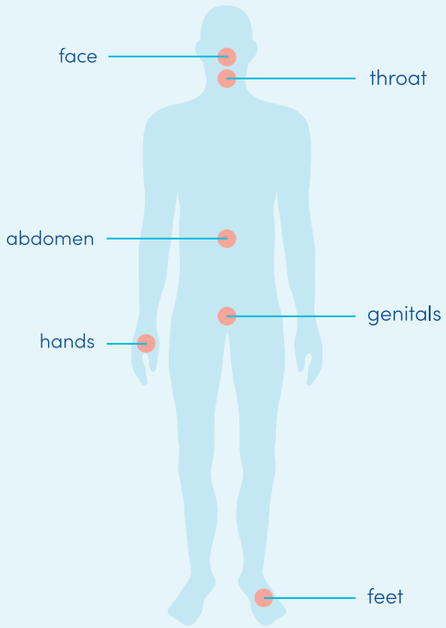
knowHAE
awareness, answers, action

know the symptoms

what is hereditary angioedema (HAE)?

HAE is a rare and potentially fatal autosomal dominant disease affecting approximately 1 in 50,000 people worldwide. HAE is characterised by spontaneous, recurring swelling attacks in various parts of the body, including the skin and gastrointestinal tract. Symptom expression can vary widely—even among family members—often contributing to delays in diagnosis.[1-9]

common attack locations



- **Attacks occurring in the larynx can be fatal due to asphyxiation**[7]
  - 50% of patients will experience at least 1 laryngeal attack in their lifetimes[4]
- **Attacks in the abdomen** are often associated with less visible swelling, extreme pain, vomiting, and diarrhoea[4,7,10]
  - 70% to 80% of patients have reported recurrent abdominal attacks[10]
- **Attacks in the hands or feet** are considered peripheral, but can prevent patients from doing daily tasks, such as using a computer or driving[1,11]

In a study of patients with recurring painful abdominal attacks, **28% of patients went, on average, more than 8 years before noticing any signs of skin oedema.**[10]

often, attacks happen without warning

Because HAE is unpredictable in nature, it can cause substantial emotional, psychosocial, and quality-of-life impairments for patients and their caregivers.[2,11]

who is most likely to have HAE?

There are no known racial, ethnic, or sex differences in prevalence, though women may have more frequent attacks. Age of onset of symptoms may vary, but symptoms can be present in children as young as 2 years old, and have been shown to worsen during puberty.[7,9,12]

triggers

While many swelling attacks occur with no identifiable trigger, some may be associated with[12,13]:

- Certain foods
- Emotional distress
- Physical trauma
- Changes in hormone levels
- Infection
- Medication
- Exposure to cold
- Nontraumatic tissue compression
- Prolonged sitting or standing

prodromes

Before an attack, patients may experience a prickling sensation, tightness in the skin, or a nonpruritic rash called erythema marginatum, as well as[14-16]:

- Fatigue or malaise
- Restlessness
- Nausea
- Joint pain
- Abdominal cramps
- Anxiety or mood changes

"We recommend that all patients with HAE should be educated about possible triggers which may induce HAE attacks."

—The international WAO/EAACI guideline for the management of hereditary angioedema[1]

know the cause

mechanism of disease

C1-INH ↓

Within the kallikrein-kinin system, C1-inhibitor (C1-INH) inhibits the production of bradykinin by controlling plasma kallikrein activity[4,17]

kallikrein ↑

Uncontrolled plasma kallikrein activity leads to excessive bradykinin production[17]

bradykinin ↑

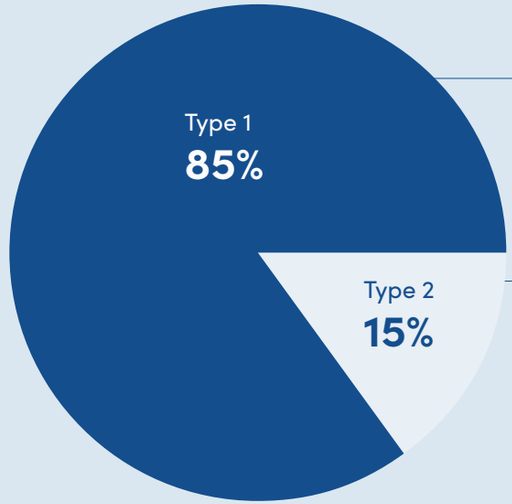
Bradykinin is a peptide that is the predominant mediator of enhanced vascular permeability in HAE attacks[17]

HAE attack

When C1-INH is deficient or dysfunctional, the bradykinin-forming pathway is no longer inhibited and an increased level of bradykinin is released, causing an HAE attack[4,17]

Even between attacks, patients have elevated levels of plasma kallikrein activity.[18]

while there are several forms of HAE, Type 1 and Type 2 are the most common[1,7]



C1-INH deficiency (Type 1 HAE, HAE-1): characterised by low antigenic and functional C1-INH levels.[1,19]

C1-INH dysfunction (Type 2 HAE, HAE-2): characterised by normal or elevated antigenic, but low functional, C1-INH levels.[1,19]

HAE Type 1 and Type 2 are caused by 1 of more than 450 different mutations in the *SERPING1* gene, which codes for C1-INH. In approximately 1 in 4 patients, a *de novo* mutation of *SERPING1* is responsible for the disease.[1]

Other forms of HAE that do not involve mutations of *SERPING1* include[1,19]:

- *F12* gene mutation (HAE-FXII)
- *Angiopoietin-1* gene mutation (HAE-ANGPTI)
- *Plasminogen* gene mutation (HAE-PLG)
- Unknown gene mutation (HAE-unknown)

Attack history is *not* a predictor of future attack frequency, severity, or location[4,6]

know the difference

HAE is often misdiagnosed, even among patients with a family history[8]

In a real-world registry study of patients with HAE Type 1 or Type 2, nearly 50% of patients had initially received 1 or more misdiagnoses (185/418).[8]

Common misdiagnoses include, but are not limited to[8,11]:

- Allergic angioedema
- Appendicitis
- Nonallergic angioedema
- Arthritis
- Biliary disorder
- Gastroesophageal reflux disease
- Peptic ulcers

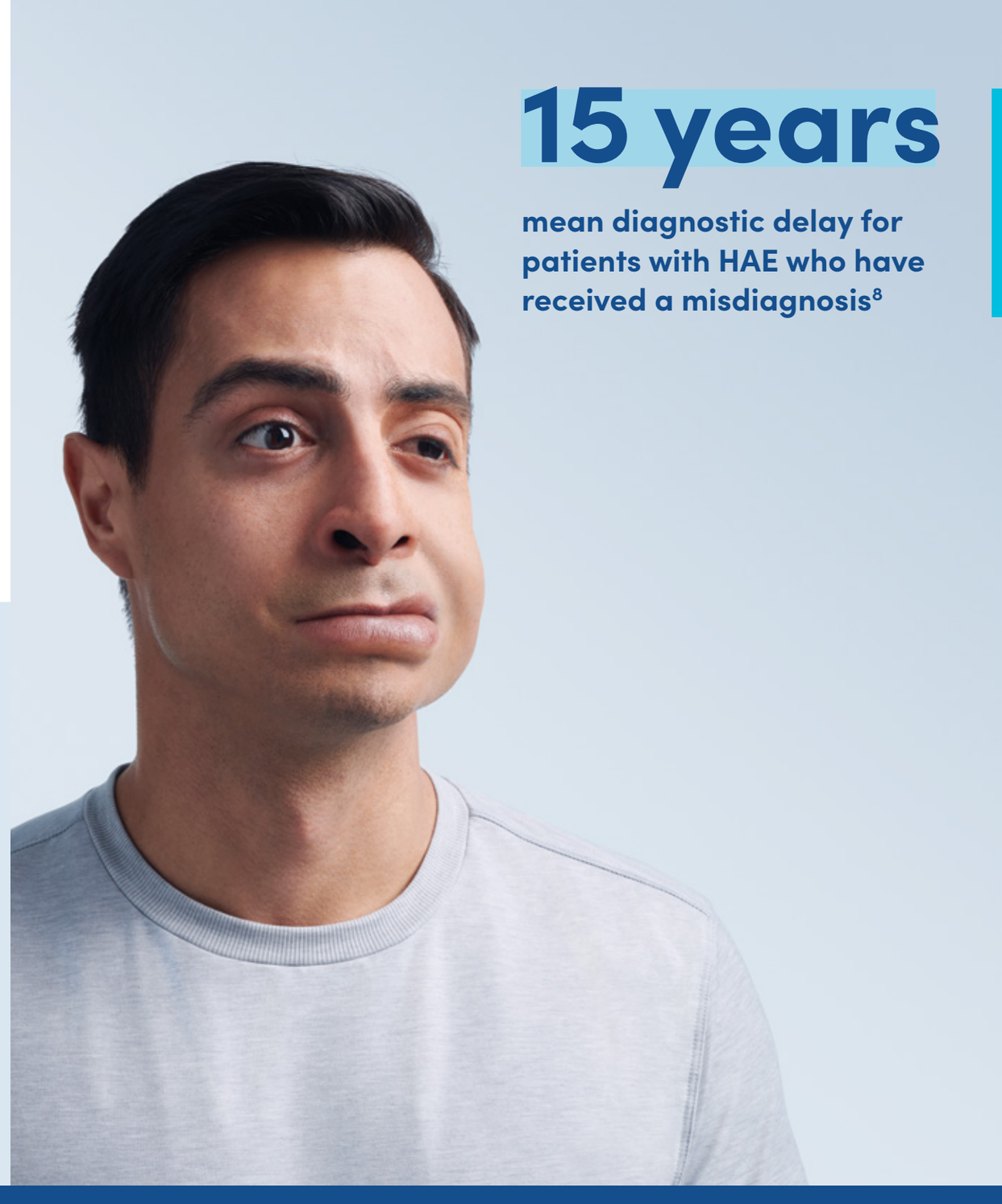
delays in diagnosis can have serious consequences

Nearly 1 out of 5 undiagnosed HAE patients have undergone unnecessary surgeries, such as appendectomies and laparotomies.[2,20,21]

Delays in diagnosis can also lead to increased risk of death from laryngeal attacks.[21]

> **In a retrospective study of families with a history of HAE, nearly 1 in 10 patients had died of asphyxiation, the majority of whom were undiagnosed[21]***

*In a retrospective study of 728 patients from 182 families analysing death cases among patients with HAE-C1-INH.



15 years

mean diagnostic delay for patients with HAE who have received a misdiagnosis[8]

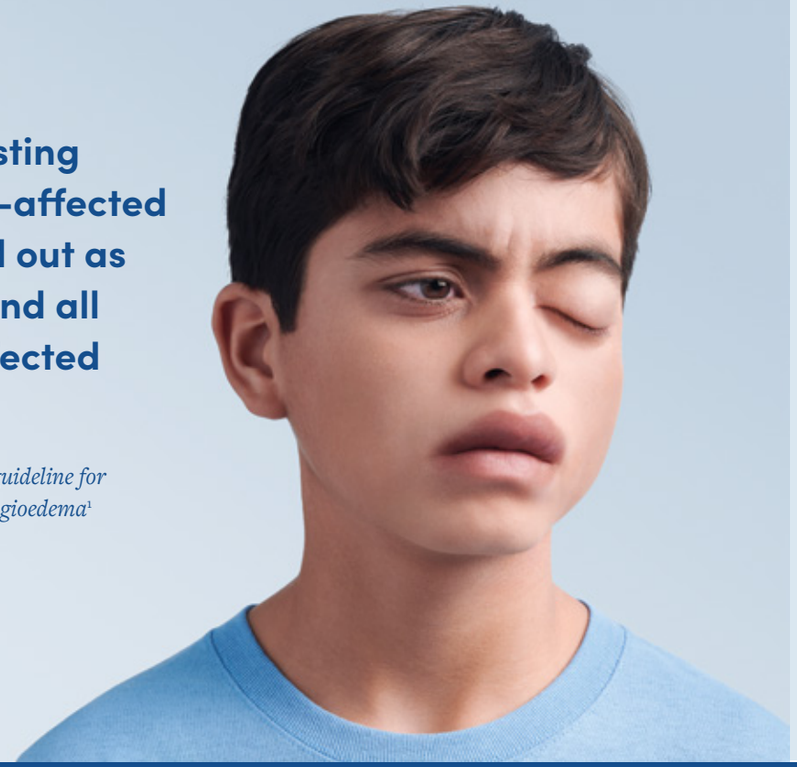
know how to diagnose

Knowing how to distinguish HAE from other angioedema can help with early therapeutic intervention. When evaluating a patient, it is important to note[1]:

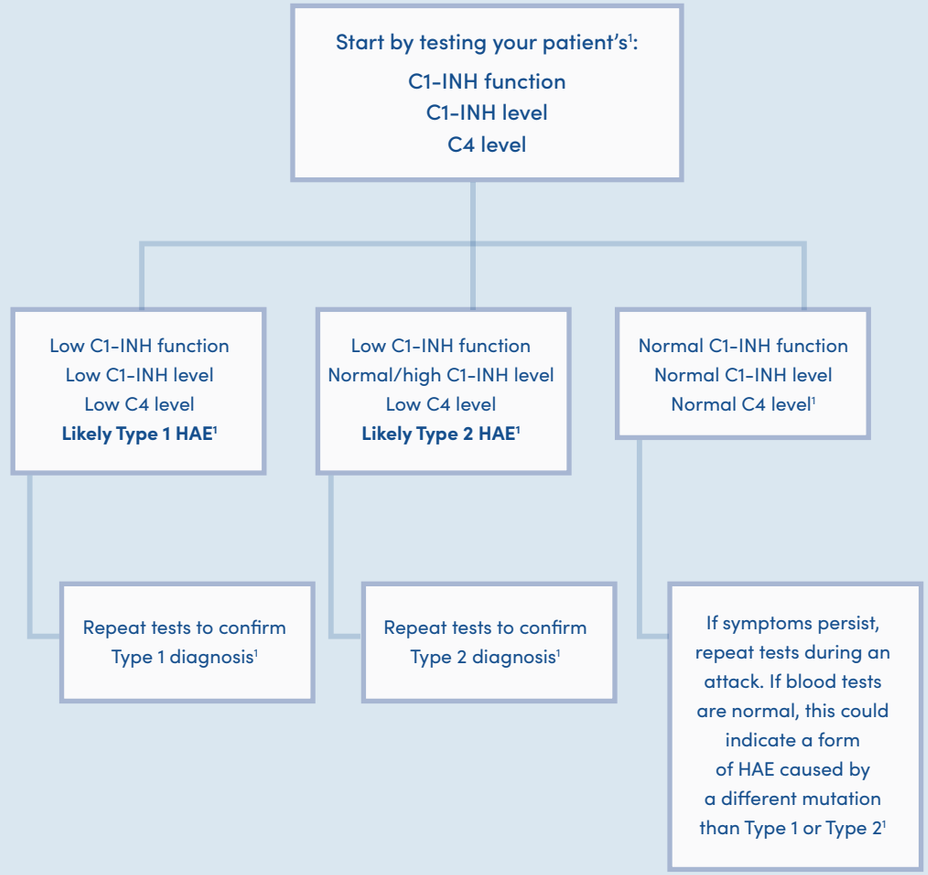
- Recurrence of attacks
- Onset of symptoms during childhood or adolescence
- Family history
- Presence of prodromes, painful abdominal symptoms, or occurrence of upper airway oedema
- Absence of urticaria or wheals
- Lack of response to treatments such as glucocorticoids, epinephrine, or antihistamines

"We recommend testing children from HAE-affected families be carried out as soon as possible and all offspring of an affected parent be tested."

—The international WAO/EAACI guideline for the management of hereditary angioedema[1]



if you suspect it's HAE...



know the treatment options

While availability differs by country, there are now a range of therapies to treat and prevent HAE attacks in both paediatric and adult patients. According to the 2017 World Allergy Organization/ European Academy of Allergy and Clinical Immunology (WAO/EAACI) Treatment Guideline, HAE can be managed with on-demand and preventive treatments.[1,6]

on-demand treatment

- All attacks should be considered for on-demand treatment and treated as early as possible. Any attack potentially affecting the upper airway should be treated[1]
- Attacks can be treated with C1-INH concentrate, ecallantide,* or icatibant (a bradykinin receptor antagonist)[1]
- All patients should have on-demand treatment for 2 attacks, to be carried with them at all times[1]

*Ecallantide (plasma kallikrein inhibitor) can be used to treat attacks, but is only approved for use in the United States.

preventive treatment

Short-term prophylaxis

- Preprocedural prophylaxis with C1-INH concentrate is recommended for all medical, surgical, and dental procedures associated with any mechanical impact to the upper aerodigestive tract[1]

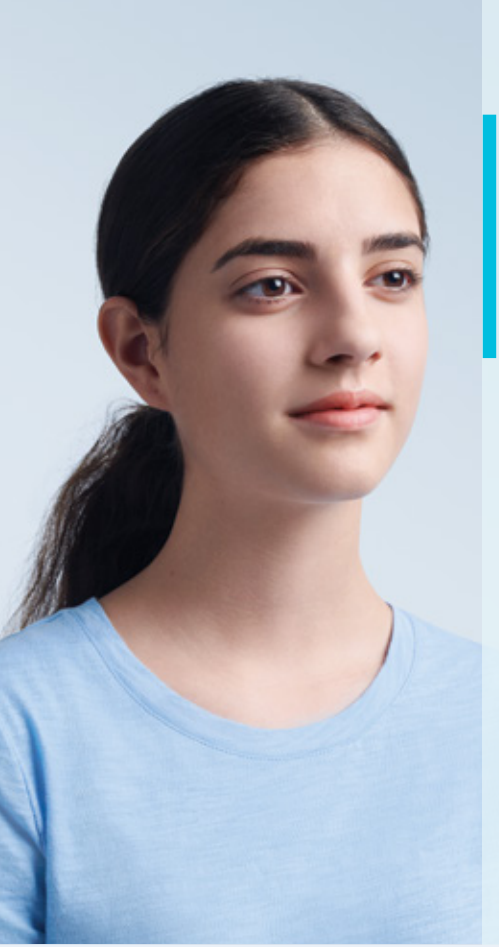
Long-term prophylaxis

- Consider for patients who face events in life that are associated with increased disease activity[1]
- Patients should be evaluated for long-term prophylaxis at every visit, taking into account disease burden and patient preference[1]
- Dosage and treatment interval should be adapted as needed to minimise burden of disease[1]

Androgens, recommended as second-line treatment, must be regarded critically, especially in light of their adverse androgenic and anabolic effects, drug interactions, and contraindications.[1]

Get an overview of the latest WAO/EAACI recommendations on how to manage HAE.

visit **knowHAE.com** to download the **HAE management guideline fact sheet**



there's always more to know about HAE

now it's easier than ever to stay in the know:

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Takeda

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