

# A guide for diagnosing hereditary angioedema (HAE)

## Clinical presentation and differential diagnosis of bradykinin-mediated angioedema

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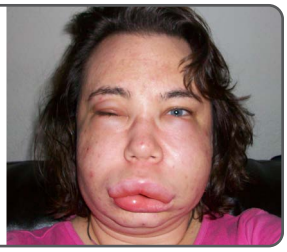
# Approaching the diagnosis of suspected HAE

**1** **If a patient presents with angioedema**

Manage airways and anaphylaxis risk per local protocols. For angioedema that does not respond to epinephrine, corticosteroids, or antihistamines, proceed with suspicion of bradykinin-mediated angioedema.[1]



**2** **Discuss personal history of recurrent angioedema and family history of HAE[2]**

**3** **Assess for key characteristics of bradykinin-mediated angioedema[1,2]**

| Timing of attack onset | Symptom presentation | Treatment response |
|---|---|---|
| • Gradual worsening over several hours<br>• Lasts 3 to 5 days | • Pain rather than itching<br>• Abdominal and cutaneous swelling and pain<br>• Erythema marginatum (a nonpruritic rash pathognomonic of HAE) | • No response to epinephrine corticosteroids, or antihistamines |

**4** **To confirm clinical suspicion, continue with diagnostic workup for bradykinin-mediated angioedema to determine** if patient has HAE type 1, HAE type 2, or HAE due to normal C1 esterase inhibitor (HAE-nl-C1INH)[2,3]

**5** **Upon confirmation of HAE (ICD-10 code D84.1), testing first-degree relatives is strongly encouraged[2-4]**

# When to suspect HAE

HAE should be suspected in all patients who present with recurrent noninflammatory episodes of angioedema and a lack of treatment response to antihistamines and corticosteroids.[2,5]

## Thorough evaluation of clinical history for differential diagnosis of HAE

Begin by looking at the patient's clinical history. Look for evidence of medications known to cause angioedema—this may indicate drug-induced angioedema. If further evaluation shows recurrent angioedema in the absence of urticaria, consider the following suggestive factors[2]:

### AGE OF PRESENTATION[2,6]

- Mean age is **8 to 12 years**, though HAE can occur as early as the first year of life
- HAE types 1 and 2 are more likely to occur in early childhood vs HAE-nl-C1INH
- While some patients with HAE may present later in life, later presentation should lead to suspicion of acquired angioedema

### FAMILY HISTORY[7]

- About **75%** of patients inherit the mutations
- The remaining **25%** of patients present with a spontaneous mutation with no family history of HAE

### TRIGGERS[2,8,9]

- While attacks can occur without the presence of a trigger, **well-known provocateurs** of angioedema attacks include estrogen, mental stress, infections, physical exertion, mechanical trauma, medical procedures, angiotensin-converting enzyme inhibitors, dental work, and surgical procedures



### HALLMARK SYMPTOM PRESENTATION[10]

- Many patients experience cutaneous swelling in the extremities (~98% of patients), recurrent and painful abdominal symptoms from gastrointestinal angioedema (~93% of patients), and risk to the airway from laryngeal edema (reported in more than 50% of patients)

### TIMING OF ATTACK ONSET[2,11-14]

In HAE, **attacks progress** to maximal severity **over several hours**. The swelling is protracted and, if untreated, **can last 3 to 5 days**.

Prior to an attack, many patients with HAE experience a period of prodrome. **HAE prodrome is a set of signs, symptoms, or perceptions that occur several hours or up to a day before an HAE attack**.

Prodromal symptoms include unusual fatigue, numbness, headaches, muscle aches, joint pain, tightness or prickling/tingling sensation in the skin, or erythema marginatum (nonpruritic rash).

### TREATMENT RESPONSE[2]

Treatment response can also be a helpful indicator. **Antihistamines, corticosteroids, and epinephrine** are not proven treatments for HAE and **do not show treatment response**.

# Diagnostic workup of HAE

If the patient's clinical history reinforces your suspicion of HAE, initiate core laboratory testing.[3]

## 3 main lab parameters for bradykinin-mediated HAE[2,3,7,15]

**1. Complement C4**

- Depletion may be observed due to persistent increased activation of the complement system in HAE
- However, C4 has limited sensitivity and specificity as a marker for HAE
- Guidelines recommend against using C4 as the only parameter for diagnosing HAE

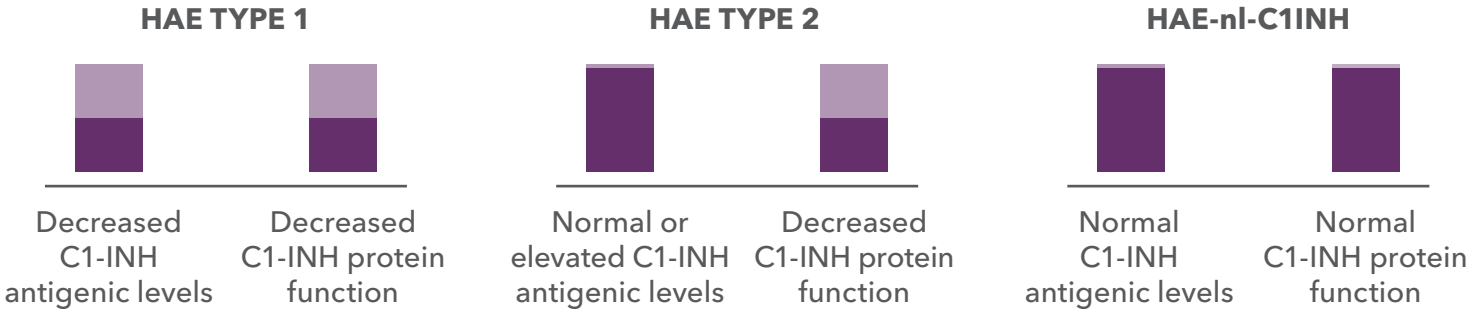
**2. C1-INH antigenic levels**

**3. C1-INH protein function**

## There are 2 test options to consider depending on availability[2,16,17]

The **enzyme-linked immunosorbent assay (ELISA)** may show equivocal results while the **chromogenic test** may confirm functional deficiency (also considered to be more reproducible than the ELISA test).

## Interpreting C1-INH lab results[2,3,18]




## Optional genetic testing[2,3,19]

- Mutations in the *SERPING1* gene account for most cases of HAE due to C1-INH
  - Genetic testing for HAE continues to be a topic of ongoing research
  - Mutations in the following genes have been identified in some patients with HAE-nl-C1INH: coagulation factor XII (*FXII*), angiopoietin-1 (*ANGPT1*), plasminogen (*PLG*), kininogen-1 (*KNG1*), myoferlin (*MYOF*), and heparan sulfate glucosamine 3-O-sulfotransferase-6 (*HS3ST6*); however, the genetic cause is still unknown in the majority of cases
- Genetic testing can help confirm a diagnosis of HAE in patients without a clear family history, but genetic testing alone cannot definitively rule out HAE

**PRO TIP**

If lab results are inconclusive and you still strongly suspect that your patient has HAE, consider running the tests again while symptoms are present.[2,3]

# Checklist for when you suspect HAE in your patients

Use this checklist to help navigate the diagnostic process when you have a high index of suspicion for HAE based on your patient's symptoms.

## Patient history

Ask your patient the following questions to evaluate clinical history.

**1. Have you ever had swelling episodes before? If answer is yes:**

- When did you experience your first episode? _____
- How long do the episodes last? _____
- How frequently do you have episodes? _____
- Are there any symptoms you experience prior to an episode? _____
- What symptoms do you experience during an episode? _____
- Does the swelling resolve or worsen after several hours? _____
- Did you take any of the following medications? Did they work for you?

☐ Antihistamines _____ ☐ Corticosteroids _____ ☐ Epinephrine _____

**2. Do you have any family history of swelling episodes?**

☐ Yes ☐ No

**3. Has anyone in your family been diagnosed with HAE?**

☐ Yes ☐ No

## Testing and results

**1.** Go through your patient's chart and clinical history to evaluate symptom presentation. If your findings result in a **high index of suspicion for HAE**, test for complement C4 level, C1-INH protein function, and C1-INH antigenic level[2,3]

| **Results** | ☐ Decreased C1-INH antigenic levels<br>☐ Decreased C1-INH protein function | ☐ Normal or elevated C1-INH antigenic levels<br>☐ Decreased C1-INH protein function | ☐ Normal C1-INH antigenic levels<br>☐ Normal or close-to-normal C1-INH protein function |
|---|---|---|---|
| **Interpretation** | **HAE TYPE 1** | **HAE TYPE 2** | **HAE-nl-C1INH** |

**2. Additional considerations if lab results do not confirm HAE but index of suspicion remains high[2,3]:**

- ☐ Run lab tests again
- ☐ Consult an HAE specialist
- ☐ Explore available genetic testing options
- ☐ Run the C1q test to help rule out acquired angioedema

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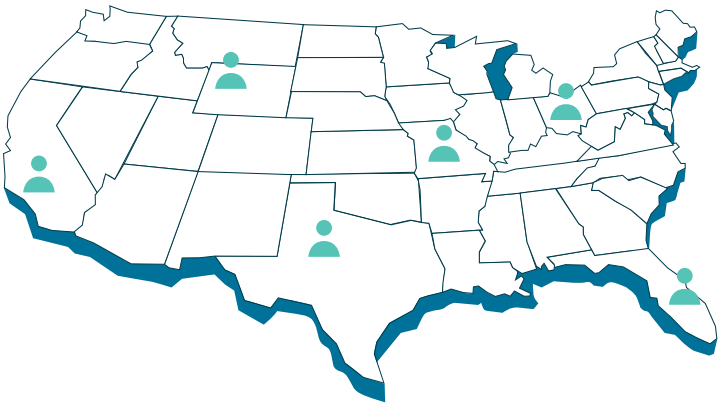
# Why is streamlining the diagnosis of HAE so critical?

**HAE in the United States**



**~6000 affected**

- **The journey to a diagnosis of HAE is long for patients in the United States**
- There are ~6000 patients in the United States living with HAE[2]
- A 2016 study showed that nearly half of all patients with **HAE have reported prior misdiagnoses**[20]
- Even though the first symptoms of swelling manifest by a median age of 11 years, **the median diagnostic delay is approximately 8 years from symptom onset**[21]

## Early symptom presentation and unmet diagnostic needs have resulted in[7,21]

Longer diagnostic delays

More attacks per year

Greater perceived HAE severity

More negative overall life impact

More hospital admissions

Significant morbidity and potential mortality

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