

A guide for diagnosing hereditary angioedema (HAE)

Clinical presentation and differential diagnosis of bradykinin-mediated angioedema

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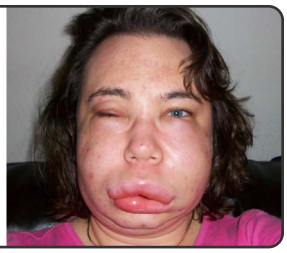
Approaching the diagnosis of suspected HAE

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]**

Timing of attack onset[1]

- Gradual worsening over several hours
- Lasts 3 to 5 days

Symptom presentation[1,2]

- Pain rather than itching
- Abdominal and cutaneous swelling and pain
- Erythema marginatum (a nonpruritic rash associated with HAE)

Treatment response[1]

- 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[2,3,7,15-17]

1. Complement C4 (CPT code 86160)

- 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

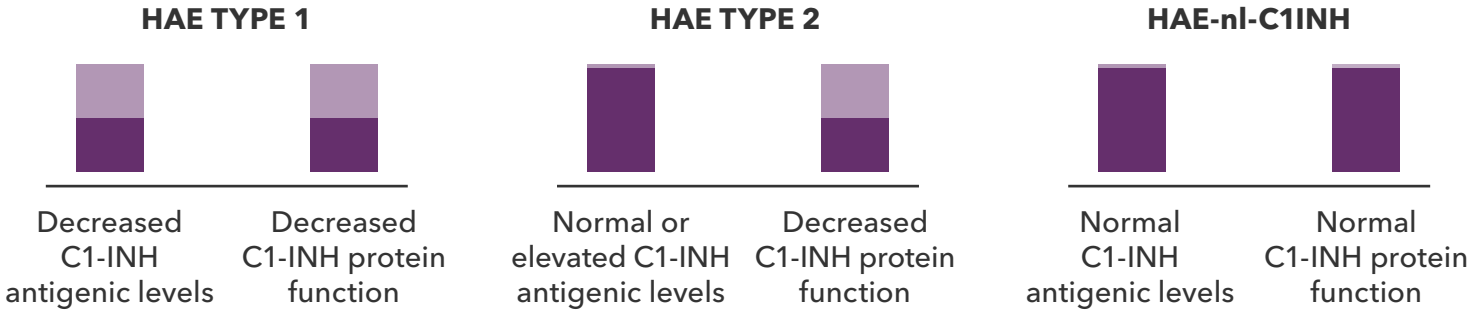
2. C1-INH antigenic levels (CPT code 86160)

3. C1-INH protein function (CPT code 86161)

There are 2 test options to consider depending on availability[2,18,19]

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[2,3,20]



Optional genetic testing[2,3,21]

- 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. Review 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]

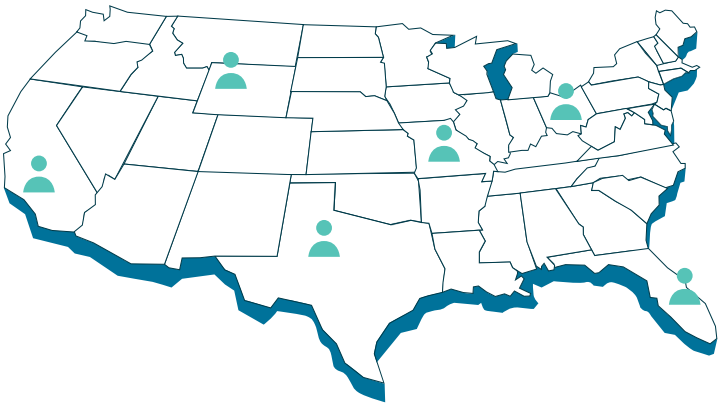
Results	☐ Decreased C1-INH antigenic levels ☐ Decreased C1-INH protein function	☐ Normal or elevated C1-INH antigenic levels ☐ Decreased C1-INH protein function	☐ Normal C1-INH antigenic levels ☐ Normal or close-to-normal C1-INH protein function
Interpretation	**HAE TYPE 1**	**HAE TYPE 2**	**HAE-nl-C1INH**

2. Additional considerations if lab results do not confirm HAE but index of suspicion remains high[2,3,16]:

- ☐ Run lab tests again
- ☐ Consult an HAE specialist
- ☐ Explore available genetic testing options
- ☐ Run the C1q test (CPT code 86160) to help rule out acquired angioedema

Why is streamlining the diagnosis of HAE so critical?

HAE in the United States



~8,000-10,000

- **The journey to a diagnosis of HAE is long for patients in the United States**
- There are ~8,000-10,000 patients in the United States living with HAE[22]
- A 2016 study showed that nearly half of all patients with **HAE have reported prior misdiagnoses**[23]
- 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**[24]

Early symptom presentation and unmet diagnostic needs have resulted in[7,24]

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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