DIAGNOSING

Hereditary Angioedema: A Challenging Diagnosis

Hereditary angioedema (HAE) is a rare disease typically caused by a mutation in the gene for C1 esterase inhibitor (C1-INH). Deficiency or dysfunction of C1-INH leads to overproduction of bradykinin, which ultimately leads to subcutaneous and submucosal edema. In another form of HAE, C1-INH levels are normal (HAE-nC1). In these patients several mutations have been identified; however, most patients have an unknown genetic cause[1]

There are 3 types of HAE[1]

Type I and II can be diagnosed by measuring serum complement levels including C4 and antigenic and functional levels of C1-INH[1]

HAE-nC1 is primarily a clinical diagnosis[1]:

- Currently, there are believed to be at least 4 different genetic mutations in HAE-nC1: FXII, plasminogen, angiopoietin-1, and kininogen 1[1]
- Currently, the only commercially available test is for HAE-FXII[2]
- In Europe, only 20% to 25% of patients with HAE-nC1 have an FXII mutation. It is notable that HAE-FXII appears to be very rare in the United States[2]
- Clinical symptoms are more likely to start in adulthood for these patients versus Type I and Type II patients[3]

Pharming®

Hereditary Angioedema Lab Testing and Codes

If HAE is suspected, diagnostic testing can confirm or rule out Type I and II. Please refer to this as a guide to order these tests.

Diagnostic workup in patients suspected to have HAE may include[4]:

- Serum C4 levels
- C1-INH antigenic level concentration
- C1-INH antigenic function
- C1q levels

If C1 inhibitor complement tests are negative but clinical symptoms strongly indicate HAE, a diagnosis of HAE-nC1 can be considered.

In patients suspected to have HAE-nC1, diagnosis requires evaluation of[5]:

- A history of recurrent angioedema in the absence of concomitant urticaria or use of a medication known to cause angioedema
- Documented normal or near-normal C4, C1-INH antigen, and C1-INH function
- One of the following:
  - A demonstrated F12 mutation associated with the disease
  - A positive family history of angioedema*
  - Documented evidence of lack of efficacy of chronic high-dose antihistamine therapy†

*Positive family history is not a requirement, as *de novo* mutations are possible.

†Cetirizine at 40 mg/d or the equivalent for at least 1 month and an interval expected to be associated with 3 or more attacks of angioedema.

Because HAE is a highly heterogeneous genetic disease and mutations that have not been previously identified are possible, a negative test result cannot be used to exclude the diagnosis.

National Jewish (ADx)[a] 1-303-270-2541

Laboratory Code	Test Name	Normal Range	CPT Code	ICD-10-CM Code
C4	C4 Level	11–61 mg/dL (depending on age)	86160	**D84.1**
C4RAT	Ratio of C4d to C4	Male/Female: C4: 0.112–0.441 mg/mL C4d: 0.52–7.88 mcg/mL Ratio: <25	86160 (x2)	
CEIQ	C1-Esterase Inhibitor Level (C1-INH)	20–37 mg/dL	86160	
CEICHR	C1-Inhibitor (C1-INH) Function, Chromogenic Assay	N/A	86161	
C1Q	C1q Level	83–125 mcg/mL	86160	
INHA	C1-Esterase Inhibitor Autoantibody[†]	<39.0% of STD	83520	
FXII	Factor XII SNP Analysis[‡]	N/A	81403	

[a]Advanced Diagnostic Laboratories, National Jewish Health – Affiliated with the University of Colorado, Denver. https://www.nationaljewish.org/for-professionals/diagnostic-testing/adx/diagnostic-testing. Accessed May 24, 2019.

[†]The presence of autoantibodies against C1-INH may explain why plasma-derived C1-INH replacement therapy is not effective in some patients.[6]

[‡]Informed Consent is required prior to completing. Consent must be obtained by the provider and maintained in the patient medical record.

WAO/EAACI guidelines recommend that all patients suspected to have HAE-1/2 are assessed for blood levels of C1-INH function, C1-INH protein, and C4.[1]

LabCorp[b] 1-800-631-5250, Ext. 2

Laboratory Code	Test Name	Normal Range	CPT Code	ICD-10-CM Code
123020	**Hereditary Angioedema (HAE) (Panel includes all tests below)**	**See below**	**86160 (x2)**	**D84.1**
001834	Complement C4, Serum	13–44 mg/dL (depending on age/sex)	86160	
004648	Complement C1 Esterase Inhibitor, Serum	21–39 mg/dL	86160	
120220	Complement C1 Esterase Inhibitor, Functional	Normal: >67% Equivocal: 41–67% Abnormal: <41%	86161	
016824	Complement C1q, Quantitative	Male: 11.8–23.8 mg/dL Female: 11.8–24.4 mg/dL	86160	

[b]Laboratory Corporation of America® Holdings. https://www.labcorp.com/test-menu. Accessed May 24, 2019.

Quest Diagnostics[c] 1-800-222-0446

Laboratory Code	Test Name	Normal Range	CPT Code	ICD-10-CM Code
17706	**Hereditary Angioedema (HAE) (Panel includes all tests below)**	**See below**	**86160 (x2), 86161**	**D84.1**
353	Complement C4c	14–57 mg/dL (depending on age/sex)	86160	
298	C1 Esterase Inhibitor, Protein	21–39 mg/dL	86160	
297	C1 Inhibitor, Functional	Normal: ≥68% Equivocal: 41–67% Abnormal: ≤40%	86161	
981	Complement Component C1q	5.0–8.6 mg/dL	86160	

[c]Quest Diagnostics Incorporated. https://testdirectory.questdiagnostics.com/test/home. Accessed May 24, 2019.

HAE should be suspected in patients who present with some of the following[1]:

- Recurrent angioedema attacks
- A positive family history (present in ~75% of patients with HAE)*
- Onset of symptoms in childhood/adolescence*
- Recurrent and painful abdominal symptoms
- Occurrence of upper airway edema
- Presence of prodromal signs or symptoms before swellings
- Absence of urticaria (wheals)
- Failure to respond to antihistamines, glucocorticoids, or epinephrine

**These factors are more common for patients with suspected HAE Type 1 and 2, compared to HAEn-C1.*

Misdiagnosis of HAE is common—as many as 66% of patients are misdiagnosed as per a 2016 study of 663 HAE patients[7]

Incorrect diagnosis may include:

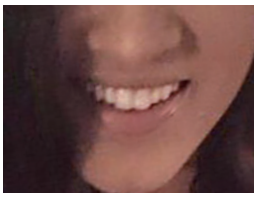
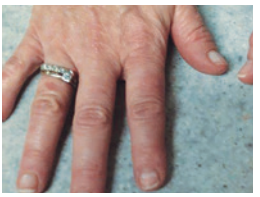
- Allergic[8]
- Gastrointestinal[9]
  - Appendicitis, irritable bowel syndrome, recurrent pancreatitis
- Psychosomatic[10]

In a 2015 survey of 143 HAE patients, nearly half reported a delay of ≥10 years between initial symptoms and diagnosis[11]

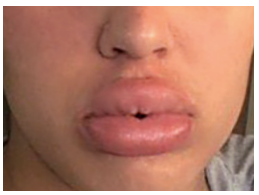
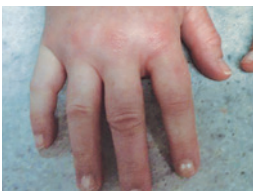
Swelling due to HAE does not respond to antihistamines, glucocorticoids, or epinephrine[1]

Below are a series of images showing the impact of HAE swells on several patients

Without swelling


During swelling


Facial, hand, and abdominal swelling during an HAE attack.

REFERENCES: 1. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-the 2017 revision and update. *Allergy*. 2018;73 (8):1575-1596. **2.** Zuraw BL. Hereditary angioedema with normal C1 inhibitor: four types and counting. *J Allergy Clin Immunol.* 2018;141(3):884-885. **3.** Bork K. Diagnosis and treatment of hereditary angioedema with normal C1 inhibitor. *Allergy Asthma Clin Immunol*. 2010;6(1):e1-8. **4.** Henao MP, Kraschnewski JL, Kelbel T, Craig TJ. Diagnosis and screening of patients with hereditary angioedema in primary care. *Ther Clin Risk Manag*. 2016;12:701-711. **5.** Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. *Allergy Asthma Proc*. 2012;33(suppl 1): S145-S156. doi:10.2500/aap.2012.33.3627. **6.** Bork K, Staubach-Renz, P, Hardt J. Angioedema due to acquired C1-inhibitor deficiency: spectrum and treatment with C1-inhibitor concentrate. *Orphanet J of Rare Dis.* 2019;14(1):65. **7.** Zanichelli A, Longhurst HJ, Maurer M, et al. Misdiagnosis trends in patients with hereditary angioedema from the real-world clinical setting. *Ann Allergy Asthma Immunol.* 2016;117(4):394-398. doi:10.1016/j.anai.2016.08.014. **8.** Lunn ML, Santos CB, Craig TJ. Is there a need for clinical guidelines in the United States for the diagnosis of hereditary angioedema and the screening of family members of affected patients? *Ann Allergy Asthma Immunol.* 2010;104(3):211-214. **9.** Berger J, Carroll MP Jr, Champoux E, Coop CA. Extremely delayed diagnosis of type II hereditary angioedema: case report and review of the literature. *Mil Med*. 2018;183(11-12):e765-e767. **10.** Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. *Arch Intern Med*. 2001;161(20): 2417-2429. **11**. Banerji A, Li Y, Busse P, et al. Hereditary angioedema from the patient's perspective: a follow-up patient survey. *Allergy Asthma Proc*. 2018;39(3):212-22.

OTH-US-2019-0004
Printed in USA.

Pharming®