

Hereditary Angioedema - C1-INH Deficiency

Clinical Background

Hereditary angioedema (HAE) is an episodic swelling disease associated with the deficiency or malfunction of C1-esterase inhibitor.

Epidemiology

- Incidence – 1/50,000
- Age
 - Congenital form – onset usually in childhood
 - Acquired form – onset occurs later
- Sex – M:F, equal

Risk Factors

- Genetics
- Pressure applied to an extremity
- Stress
- Ingested estrogens, pregnancy
- Lymphoproliferative disorder

Inheritance

- Autosomal dominant inheritance
- Mutations in *C1-INH* gene

Pathophysiology

- C1-esterase inhibitor (C1-INH) is a multispecific, protease inhibitor
- It regulates the enzymes of the complement, coagulation, fibrinolytic and kinin-forming systems, including
 - C1r and C1s subunits of activated first component of complement
 - Activated Hageman factor (factor XIIa) and Hageman factor fragments
 - Activated plasma thromboplastin antecedent (PTA or factor XIa)
 - Kallikrein (Fletcher factor)
 - Plasmin
- HAE is a hereditary quantitative deficiency in C1-INH
 - Type 1 or null – 85%
 - Type 2 or dysfunctional – 15%
 - Deficiency of functionally active component may lead to life-threatening angioedema
 - Rare type 3 defect (familial angioedema) associated with similar clinical presentation but normal C1-INH levels
- Acquired C1-INH deficiency is a qualitative (functional) deficiency of inhibitor
 - Acquired deficiency is associated with a variety of diseases, including lymphoid malignancies

Clinical Presentation

- Symptoms typically begin in childhood, worsen in puberty and have an unpredictable course throughout adulthood
- Transient but recurrent attacks of non-pruritic, deep-seated swelling of various tissues occur throughout the body without the presence of urticaria
 - Typically involves arms, legs, hands, trunk, face, mouth, larynx, airway, genitals and tongue

- Gastrointestinal tract often involved, with recurrent episodes of cramping abdominal pain, nausea and emesis
- Most frequent cause of death is airway obstruction secondary to laryngeal edema
- Presence of autoimmune diseases is higher in these patients
 - Especially glomerulonephritis
- Typical and predictable course
 - Many attacks, preceded by prodrome (tingling sensation)
 - Swelling gradually increases over the first 24 hours then gradually subsides over the next 48-72 hours

Treatment

- Therapy for congenital defect is non-virilizing androgen treatment, which partially corrects the biochemical defect
- Aminocaproic acid
 - May be used for preoperative prophylaxis
 - Contraindicated in patients with thrombotic tendencies
- C1 inhibitor concentrate
 - Not yet licensed in U.S.

Diagnosis

- Indications for testing
 - Recurrent angioedema, laryngeal edema, or abdominal pain in the absence of urticaria
 - Family history
- Laboratory testing
 - Initial testing – C1 through C4
 - C2 and C4 – usually low even when an attack is not ongoing
 - C1 and C3 – usually normal.
 - C-1 esterase
 - Type 1 – low antigenic and functional levels
 - Type 2 – normal antigenic level but low functional level
 - Type 3 – normal antigenic and functional levels
 - Genetic testing not necessary
 - If diagnosis confirmed by above testing, consider C1Q testing
 - Normal C1Q – suggests hereditary form
 - Low C1Q – suggests acquired form

Differential Diagnosis

- Allergic urticaria or angioedema
- Idiopathic or cold-induced angioedema
- Angiotensin-converting enzyme (ACE)-associated angioedem
- Nonsteroidal anti-inflammatory drug (NSAID)-associated angioedema
- Angioedema with urticarial vasculitis

Lab Tests

Indications for Laboratory Testing

Tests generally appear in the order most useful for common clinical situations. For test-specific information, refer to the test number in the ARUP Laboratory Test Directory on the ARUP Web site at www.aruplab.com.

Test Name and Number	Recommended Use	Limitations	Follow Up
C-1-Esterase Inhibitor Panel 0050139 Method: Immunoturbidimetric/ Enzyme-Linked Immunosorbent Assay/Nephelometry	Determine C1 esterase inhibitor levels Diagnose hereditary angioedema (HAE) Panel tests for C1-esterase inhibitor levels and functional complement C4		May want to test for C2 and C4 levels to confirm C1 esterase deficiency and rule out complement deficiency
C1Q Binding Assay 0050301 Method: Enzyme-Linked Immunosorbent Assay	Differentiate hereditary from acquired angioedema		

Additional Tests Available

Test Name and Number	Comments
Complement Component 2 0050148 Method: Radial Immunodiffusion	Help diagnose HAE
Complement Component 3 0050150 Method: Immunoturbidimetric	Help diagnose HAE
Complement Component 4 0050155 Method: Immunoturbidimetric	Help diagnose HAE
C1-Esterase Inhibitor 0050140 Method: Nephelometry	

C1-Esterase Inhibitor Functional

0050141

Method:

Enzyme-Linked Immunosorbent Assay

Guidelines

Bowen T, Cicardi M, Farkas H, Bork K, Kreuz W, Zingale L, Varga L, Martinez-Saguer I, ygoren-Pursun E, Binkley K, Zuraw B, Davis A III, Hebert J, Ritchie B, Burnham J, Castaldo A, Menendez A, Nagy I, Harmat G, Bucher C, Lacuesta G, Issekutz A, Warrington R, Yang W, Dean J, Kanani A, Stark D, McCusker C, Wagner E, Rivard GE, Leith E, Tsai E, MacSween M, Lyanga J, Serushago B, Leznoff A, Wasserman S, de Serres J. Canadian 2003 International Consensus Algorithm For the Diagnosis, Therapy, and Management of Hereditary Angioedema. *J Allergy Clin Immunol*. 2004; 114 (3) 629-637.

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General References

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Diagnostic Algorithm(s)

PDF algorithm(s) available at www.arupconsult.com.

C1-INH Deficiency Testing Algorithm

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Comprehensive Review: November 2009

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