Molecular Mechanisms and Treatment of Hereditary Angioedema

Bruce Zuraw, MD

UC San Diego

Hereditary angioedema (HAE) overview

-First described by Osler in 1888 based on familial inheritance and recurrent angioedema

- Must make a clear distinction between HAE and allergic or recurrent idiopathic angioedema

- HAE:

  - Characterized by recurrent attacks of angioedema (especially larynx, mouth, face, abdomen, extremities, GU)

  - Autosomal dominant inheritance

  - Prevalence estimated to be 1:50,000

  - No known ethnic or gender differences

  - Disease severity is highly variable

  - Significant risk of morbidity and mortality

HAE due to C1 inhibitor deficiency

- Type I: low antigenic and functional levels of C1 inhibitor (C1INH)

  - first described by Virginia Donaldson (Am J Med 35:37, 1963)

  - ~85% of HAE patients

  - Failure to secrete C1INH protein

- Type II: normal antigenic with low functional levels of (C1INH)

  - first described by Fred Rosen (Science 148:957, 1965)

  - ~15% of HAE patients

  - Dysfunction of mutant protein

- Both type I and type II HAE result from mutations in SERPING1; however involve distinct and different regions of the gene

HAE with normal C1 inhibitor deficiency

- Associated with factor XII mutation

  - co-sorts with disease but not proven to be causative

    - 20-25% of patients in Europe; much less in USA
    - unlikely to be a true gain of function mutation; possibly activation
- Unknown
- Subtle differences from HAE due to C1INH deficiency
- Reduced penetrance

Mediator of swelling in HAE is bradykinin

- C1INH regulates multiple plasma proteolytic cascades including classical complement, intrinsic coagulation, kallikrein-kinin, and fibrinolytic pathways
- Multiple lines of evidence have showed that the swelling in HAE results from insufficient control of the kallikrein-kinin pathway with generation of bradykinin
- Bradykinin increases vascular permeability predominantly through its effect on the vascular endothelial cell adherens junction, especially VE-cadherin

Diagnosis of HAE

- Complement assays remain primary modality
- C4 is excellent screening tools
- C1INH antigenic and functional levels complete most evaluations
- Diagnosis of HAE with normal C1INH not well defined

Treatment of HAE

- Rational drug development targeting contact system
- On demand: C1INH concentrates, ecallantide, icatibant
- Prophylaxis: anabolic androgens, antifibrinolytics, C1INH concentrates
- Additional novel treatments in the pipeline