Hereditary angioedema

Description

Hereditary angioedema is a disorder characterized by recurrent episodes of severe swelling (angioedema). The parts of the body that are most often affected by swelling are the limbs, face, intestinal tract, and airway. Minor trauma or stress may trigger an attack, but swelling often occurs without a known trigger. Episodes involving the intestinal tract cause severe abdominal pain, nausea, and vomiting. Swelling in the airway can restrict breathing and lead to life-threatening obstruction of the airway. About one-third of people with this condition develop a non-itchy rash called erythema marginatum during an attack.

Symptoms of hereditary angioedema typically begin in childhood and worsen during puberty. On average, untreated individuals have swelling episodes every 1 to 2 weeks, and most episodes last for about 3 to 4 days. The frequency and duration of attacks vary greatly among people with hereditary angioedema, even among people in the same family.

Hereditary angioedema is broadly divided into two types, which are distinguished by levels of a protein called C1 inhibitor (C1-INH) in the blood. These types are known as hereditary angioedema due to C1-INH deficiency and hereditary angioedema with normal C1-INH.

Hereditary angioedema due to C1-INH deficiency is further divided into two types: type I occurs when C1-INH levels are low, and type II occurs when the C1-INH protein is not functioning correctly.

The different types of hereditary angioedema have similar signs and symptoms.

Frequency

Hereditary angioedema is estimated to affect 1 in 50,000 people worldwide. Hereditary angioedema due to C1-INH deficiency accounts for the vast majority of cases.

Causes

Variants (also called mutations) in the *SERPING1* gene cause hereditary angioedema

due to C1-INH deficiency. The *SERPING1* gene provides instructions for making the C1-INH protein, which is important for controlling the immune response and inflammation. The C1-INH protein blocks the activity of certain proteins that promote inflammation.

SERPING1 gene variants that cause hereditary angioedema due to C1-INH deficiency type I lead to reduced levels of C1-INH in the blood, while variants that cause type II result in the production of a C1-INH protein that functions abnormally. When the body does not have enough normal C1-INH protein, it ends up with excessive amounts of a protein fragment (peptide) called bradykinin. Bradykinin promotes inflammation by increasing the amount of fluid that leaks through the walls of blood vessels into body tissues (vascular permeability). The accumulation of fluids in body tissues causes the episodes of swelling seen in individuals with hereditary angioedema due to C1-INH deficiency.

Variants in the *F12* gene cause most cases of hereditary angioedema with normal C1-INH. The *F12* gene provides instructions for making a protein called coagulation factor XII. In addition to playing a critical role in blood clotting (coagulation), factor XII is also an important stimulator of inflammation and is involved in the production of bradykinin.

In people with hereditary angioedema with normal C1-INH, variants in the *F12* gene cause cells to produce a factor XII protein that is easier to activate than normal. As a result, a greater-than-normal amount of bradykinin is released. More bradykinin leads to increased inflammation and leaky blood vessel walls, which causes the episodes of swelling seen in people with hereditary angioedema with normal C1-INH.

Variants in a few other genes are responsible for a small number of additional cases of hereditary angioedema with normal C1-INH. The cause of other cases of hereditary angioedema with normal C1-INH remain unknown.

Learn more about the genes associated with Hereditary angioedema

- F12
- PLG
- SERPING1

Additional Information from NCBI Gene:

- ANGPT1
- HS3ST6
- KNG1
- MYOF

Inheritance

This condition is inherited in an autosomal dominant pattern, which means one copy of an altered gene in each cell is sufficient to cause the disorder. In some cases, an

affected person inherits the variant from one affected parent. Other cases result from a new (de novo) variant in a gene that occur during the formation of reproductive cells (eggs or sperm) in an affected individual's parent or in early embryonic development. These affected individuals have no history of the disorder in their family.

Other Names for This Condition

- C1 esterase inhibitor deficiency
- C1 inhibitor deficiency
- HAE
- HANE
- Hereditary angioneurotic edema

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Angioedema, hereditary, 7 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C5543526/)
- Genetic Testing Registry: Hereditary angioedema type 3 (https://www.ncbi.nlm.nih.gov/gtr/conditions/C1857728/)
- Genetic Testing Registry: Hereditary angioneurotic edema (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0019243/)
- Genetic Testing Registry: Hereditary C1 esterase inhibitor deficiency - dysfunctional factor (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0398776/)

Genetic and Rare Diseases Information Center

- Hereditary angioedema (https://rarediseases.info.nih.gov/diseases/5979/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22Hereditary angioedema%22)

Catalog of Genes and Diseases from OMIM

- ANGIOEDEMA, HEREDITARY, 1; HAE1 (https://omim.org/entry/106100)

- ANGIOEDEMA, HEREDITARY, 3; HAE3 (https://omim.org/entry/610618)
- ANGIOEDEMA, HEREDITARY, 4; HAE4 (https://omim.org/entry/619360)
- ANGIOEDEMA, HEREDITARY, 5; HAE5 (https://omim.org/entry/619361)
- ANGIOEDEMA, HEREDITARY, 6; HAE6 (https://omim.org/entry/619363)
- ANGIOEDEMA, HEREDITARY, 8; HAE8 (https://omim.org/entry/619367)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=(Angioneurotic+Edema%5BMAJR%5D)+AND+((hereditary+angioedema%5BTIAB%5D)+OR+(hereditary+angioneurotic+edema%5BTIAB%5D)+OR+(c1+esterase+inhibitor+deficiency%5BTIAB%5D)+OR+(c1+inhibitor+deficiency%5BTIAB%5D))+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1600+days%22%5Bdp%5D)

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Last updated March 11, 2024