Review Article

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Hereditary Angioedema

Susmit Kosta*, Ravindra Kumar**

Abstract

The hereditary angioedema (HAE) resources communally occurrence of angioedema that could be very threat and are recurrently linked with imperative morbidity and even mortality. Sympathetic the pathophysiology of this disease is vital for appropriate diagnosis and management of these patients. The HAE is caused through mutations in the SERPING1 gene and that result in decreased plasma levels of functional C1 inhibitor. In HAE results, the huge numbers of various mutations have been elucidated. All most 15% of patients have a mutation at or near the active site of the reactive mobile loop, resulting in a protein that decreases functional action (type II HAE). In Type I HAE is caused through a diverse range of mutations, a few of which cause the nascent protein to misfold and therefore to be incapable to go in the secretory pathway. A first mediator of swelling in HAE is bradykinin, a product of the plasma contact system. The bradykinin stimulated enlarged vascular permeability via activating the bradykinin B2 receptor, which results in phosphorylation of vascular endothelial cadherin. A regulation of both the bradykinin B2 receptor and peptidases that degrade bradykinin could influence HAE disease sternness. A HAE results from mutations in the SERPING1 gene that directed to a loss of functional C1 inhibitor. The assaults of angioedema result from creation of bradykinin, which works on bradykinin B2 receptors to improve vascular permeability.

Keyword: Angioedema; Morbidity; Nascent protein; Bradykinin.

Introduction

The hereditary angioedema (HAE) is especially atypical and possible severe genetic situation that occur in about 1 in 10,000 to 1 in 50,000 people. It is differentiating by recurrent episodes of angioedema occurring most recurrent in skin and mucosal tissues including the upper respiratory and gastrointestinal tracts. A hallmark of HAE is angioedema without urticarial or pruritus and unresponsiveness to antihistamine therapy. The precise event triggering the non-inflammatory angioedema attacks is unclear, but episodes are self-limiting and typically last longer than 12 hours. Other symptoms include frequent abdominal pain and laryngeal edema. In severe cases, laryngeal swelling may cause asphyxiation and death [1, 2]. Mean age of onset is 11 years old, but symptoms may present at birth [3]. There are three types of HAE. Types I and II are due to mutations in the *SERPING1*/*C1NH* gene and represent ~85% and 15% of cases, respectively. Type I HAE individuals have decreased C1INH (Complement 1 inhibitor) levels and activity compared to type II individuals only displaying impaired activity. Type III HAE is a rare disorder with some cases being due to mutations in the *F12* gene [1, 2]. Genetic testing is helpful in diagnosis of HAE in children younger than one year of age as C1INH levels and function are difficult to interpret and may lead to false positive or negative results [4]. Genetic testing is also helpful in the differential diagnosis of HAE from acquired angioedema, allergic reactions with anaphylaxis, thyroid disorders, trichinosis, and autoimmune conditions such as systemic lupus [2].

Author's Affiliation: *Junior Scientist, ** Scientist & Head, Central Research Laboratory, Sri Aurobindo Medical College and PG Institute, Indore-453555, Madhya Pradesh, India.

Corresponding Author: Susmit Kosta, Junior Scientist, Central Research Laboratory, Sri Aurobindo Medical College and PG Institute, Indore-453555, Madhya Pradesh, India.
E-mail: susbiotech@gmail.com

Inheritance

HAE is inherited autosomal-dominant mutations. Its means only need to inherit one copy of a mutated gene to develop HAE parent. A parent with HAE has a 50% chance of inheriting this disease if one of his or her parents has it. In the atypical cases, a person will develop HAE when neither parent is affected. It means that an impulsive gene mutation has occurred. Even if technically the persons HAE are not inherited, they will be capable to pass it on to their offspring [5-7].

SERPING1 gene

The *SERPING1* gene gives information for making a protein called C1 inhibitor which is a type of serine protease inhibitor (serpin). The *SERPING1* gene belongs to a family of genes called SERPIN (serine or cysteine) peptidase inhibitors [8]. The *SERPING1* gene is located on the long (q) arm of chromosome 11 at position 12.1. More precisely, the *SERPING1* gene is located from base pair 57,597,553 to base pair 57,614,852 on chromosome 11.

Serpins control several types of chemical reactions by blocking the activity of certain proteins. C1 inhibitor is important for controlling a range of processes involved in maintaining blood vessels, including inflammation [9]. C1 inhibitor blocks the activity of several proteins in the blood, including plasma kallikrein and the activated form of factor XII (called factor XIIa). These two proteins are involved in the production of bradykinin. Bradykinin is a protein that promotes inflammation by increasing the permeability of blood vessel walls, allowing fluids to leak into body tissues [10]. C1 inhibitor attaches (binds) to plasma kallikrein and factor XIIa, which prevents them from completing any further reactions. These proteins are cleared from the bloodstream once they are bound to C1 inhibitor [11].

More than 350 mutations in the *SERPING1* gene have been found to cause HAE types I and II. Mutations that cause type I occur throughout the gene and lead to reduced levels of C1 inhibitor in the blood [12]. Mutations that cause type II usually occur in a specific region of the gene called exon 8 and result in the production of a C1 inhibitor that functions abnormally. Without the proper levels of functional C1 inhibitor, the activity of plasma kallikrein and factor XIIa cannot be blocked and excessive amounts of bradykinin are produced. Excess fluids leak through blood vessel walls and accumulate in body tissues, leading to the recurrent episodes of swelling seen in individuals with HAE type I and type II [8-11].

Type I and II HAE are inherited in an autosomal dominant manner through mutations in the SERPING1 gene. In rare cases, homozygous deficient patients have been described. In a study of 87 Spanish individuals with either type I or II HAE, missense, short insertions or deletions, nonsense, large deletions or insertions, and splicing variants represented 32%, 19%, 15%, and 11% of causative variants and occurred throughout the gene [5]. Similar frequencies have been observed in other large population studies of patients with HAE [8, 9]. Mutations in the SERPING1 gene are not fully penetrant with about 10% of heterozygous individuals being asymptomatic [5]. De novo mutations occur in about a quarter of cases [10].

A rare variant Type III HAE with similar clinical manifestations to type I and 2 but normal C4 and C1 INH antigenic levels and function has been described. Subsets of these patients have a mutation in Hageman factor (i.e. coagulation factor XII protease) but the underlying mechanism in the majority of these patients is unknown [13-15].

Pathophysiological role of C1INH

In HAE patients have a defect in gene. It controls the blood protein that's called C1 Inhibitor. The genetic defect results in production of either inadequate or non-functioning C1-Inhibitor protein. Normal C1-Inhibitor facilitates to regulate the complex biochemical interactions of blood-based systems involved in disease hostile, inflammatory response and coagulation. Because defective C1-Inhibitor does not sufficiently perform its regulatory function, a biochemical imbalance can occur and produce not needed peptides which induce the capillaries to liberate fluids into surrounding tissue, thereby causing edema [16] (figure 1).

The mutation in C1 inhibitor C1INH genes is able to cause the HAE. While the occurrence of 1 normal gene and 1 mutated gene would advise that patients should have 50% chance of the normal level of C1INH, the actuality is that patients generally have approx 20% chance of the normal C1INH level. Actually, patients with 50% chance of the normal C1INH level do not swell. The cause for the much lower C1INH level in most patients has been a mystery [17-19].

The mutated misfolded C1INH protein interferes secretion of the normal C1INH protein. This provides a feasible justification for the low C1INH levels in HAE and thus for the severity of the disease [20]. The C1INH might also be amenable to

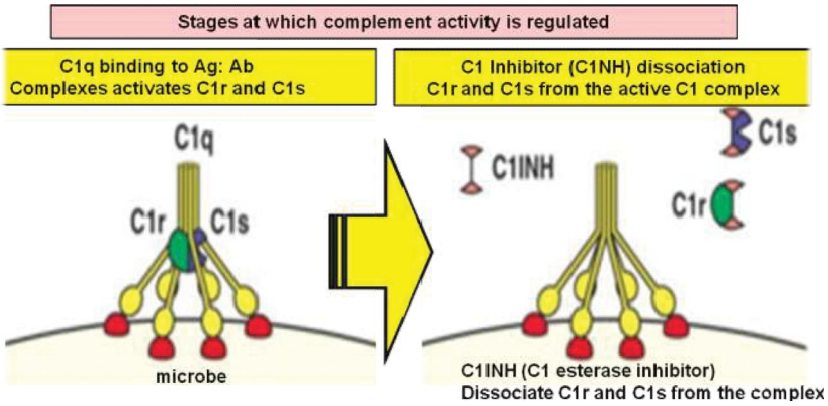

Fig. 1: *Regulation:* Classical Pathway

therapeutic intervention. The idea that obtained defects in secretion of wild type C1INH might influence disease severity offered a novel basis for understanding HAE and a chance to investigate new molecular therapeutic interventions [21]. HAE with normal C1 inhibitor (HAE-nlC1INH) is clinically similar to HAE because of C1INH deficiency (HAE-C1INH). HAE-nlC1INH has also been referred to as HAE type III [22-23]. Angioedema attacks in patients with HAEnlC1INH might react to the same medicines used for HAE-C1INH. Establishing a diagnosis of HAE-nlC1INH, while, is regularly difficult or impossible because of the lack of a diagnostic test. The mainly serious question facing angioedema care is whether we can recognize those patients who will or will not react to BK-acting medications and therefore potentially elucidate which patients truly have HAE-nlC1INH [24-26]. In HAE-C1INH the mediator of swelling has been shown to be bradykinin that is generated during activation of the contact system (figure 2).

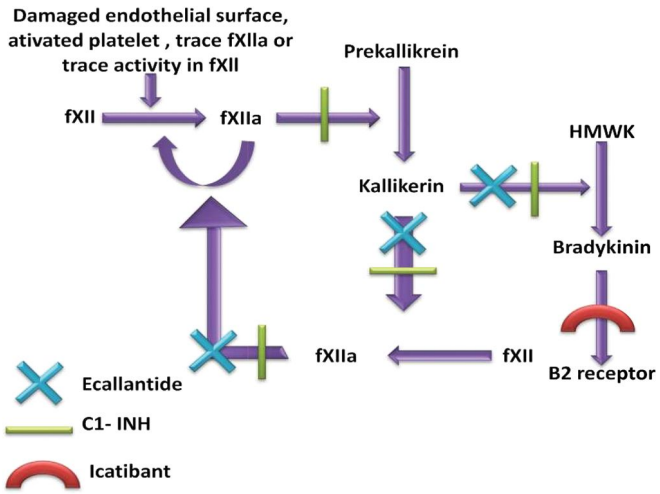

Fig. 2: Functioning C1-INH inhibits the formation of bradykinin. ACE inhibitors impair the degradation of bradykinin.

Clinical presentation and diagnosis

Clinical manifestations of HAE usually emerge during childhood [27-28] However, the low prevalence of HAE and the potential confusion with other disorders often delays diagnosis. If a patient's medical history and / or a positive family history of disease lead to the suspicion of HAE, diagnosis can be confirmed by measuring complement and C1INH activity [7,29]. As HAE patients typically display substantial reductions in plasma levels of C4, testing for C4 can be used as an initial screening tool. If C4 levels are found to be low, or if these levels are normal but clinical suspicions of HAE remain, functional C1INH levels should then be measured for definitive diagnosis [30].

Current therapies and treatment of acute HAE attacks

Current therapies for HAE are divided into management of acute attacks and short- and long-term prophylaxes. Long-term prophylaxis may be initiated in patients who have severe, frequent episodes of angioedema. Medications in this category include androgens, plasma-derived C1-INH (pdC1-INH), and tranexamic acid. Short-term prophylaxis can be considered for surgeries, especially those requiring endotracheal intubation and/or manipulation of the upper airway, [31] stressful periods, pregnancy, and childbirth. Prophylactic treatment options at the time of pregnancy would likely involve pdC1-INH because of the better safety profile. In the pediatric population, tranexamic acid would likely be the treatment of choice for long- and short-term prophylaxes, especially when pdC1-INH is unavailable. One needs to use androgens with caution during childhood because of potential adverse side effects. Of note, long-term prophylaxis has been shown to decrease the number of attacks that patients have; however, they have not been proven to place patients in complete remission [32].

Plasma derived C1-INH and recombinant form of human C1 INH has recently approved for acute treatment of HAE in adults and adolescents. Cinryze C1-inhibitor may be used for preventing HAE attacks. Berinert C1-inhibitor may be used treating acute abdominal, facial or laryngeal HAE attacks. Both drugs are administered intravenously and are approved for home infusion.

Burke et al [31] describe a case involving a 49-year-old woman with known HAE who was receiving Cinryze™ for short-term prophylaxis for a procedure and who developed an acute HAE attack 1.5 hours postoperatively. She was successfully treated with ecallantide [31]. Further research is needed to determine whether ecallantide can be used in short-term prophylaxis for perioperative procedures. Currently, ecallantide and two pdC1-INH medications (Cinryze™ and Berinert) are approved for use in children ≥ 12 years, while icatibant is only approved for those who are ≥ 18. Ruconest, a recombinant C1-INH, can also be used in adolescents and adults. Both icatibant and ecallantide are administered subcutaneously, giving them a theoretical advantage of easier administration over intravenous agents [33].While icatibant and pdC1-INH medications can be self-administered, ecallantide and Ruconest cannot because they both have the risk of anaphylaxis.

Conclusion

HAE is a rare but potentially life-threatening inherited disorder that has a significant impact on the quality of life and productivity of affected individuals. HAE due to C1 esterase inhibitor deficiency has been intensively studied, and nearly all steps in its pathogenesis are known, from the causative gene defect all the way to the clinical presentation of angioedema. Bradykinin is the main mediator in this pathway. New treatment options (icatibant; C1-inhibitor concentrate for self-administration and long-term treatment) have helped patients considerably. In recent years, a new type of hereditary angioedema has been described, resulting not from a lack of C1 inhibitor, but rather from mutations of coagulation factor XII or other, as yet unidentified genetic abnormalities. There are major differences in the pharmacological treatment of the different diseases that cause angioedema. In an emergency, when severe upper airway obstruction can be lifethreatening, immediate treatment is needed to keep the upper airway open.

The highly variable clinical presentation of HAE can lead to significant delays in diagnosis, leaving many patients untreated. Diagnosis may be made based on clinical and patient factors (ie, repeated episodes of cutaneous swelling and of abdominal pain and vomiting, onset of symptoms at puberty or young adulthood, family history of such episodes) and confirmed with laboratory assessments of complement proteins. In patients with recurrent angioedema, the diagnostic classification of the underlying disorder as a particular type of hereditary or acquired angioedema is a prerequisite for appropriate treatment.

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