D J Med Sci 2023;9(3):133-141
doi: 10.5606/fng.btd.2023.134

Review

Diagnosis and treatment modalities for hereditary angioedema in emergency medicine

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ABSTRACT

Hereditary angioedema (HAE), although perhaps a rare occurrence in the professional lives of emergency service professionals, is a dangerous type of angioedema characterized by attacks. The frequency of attack development varies from patient to patient, and due to its ability to affect internal organs, it may progress more severely than other types of angioedema. The diagnosis of HAE is challenging, as it can be confused with many different entities. Considering the often high cost of available medications for attack treatment in developing country emergency departments, they are frequently unavailable. Currently, during attacks, C1 esterase inhibitor concentrate, fresh frozen plasma, high-dose danazol, aminocaproic acid, or tranexamic acid can be used. Recently, lanadelumab has been approved for long-term prophylaxis. It is essential to develop more accessible and practically applicable agents for acute attack treatment in the emergency department to reduce mortality. In this review, we discussed the current approach to HAE and its treatment in the emergency department, as well as new developments in this field.

Keywords: C1 esterase inhibitor, emergency department, hereditary angioedema.

Hereditary angioedema (HAE) was first described by Osler in 1888. Subsequently, the biochemical foundations of HAE have been elucidated, revealing that it occurs due to a deficiency of C1 esterase inhibitor (C1-INH).[1] Hereditary angioedema is generally characterized by the functional deficiency of C1-INH and follows an autosomal dominant inheritance pattern. According to the database, there can be more than 150 mutations observed in the C1-INH gene. It is a disease within the angioedema group where urticaria is not present and is much less common than conditions leading to other forms of angioedema. Hereditary angioedema has two subtypes: those associated with C1 inhibitor deficiency (HAE-C1-INH) and those with normal levels of C1-INH (HAE with normal C1-INH).[2] Hereditary angioedema type 1 is observed in approximately 85% of patients, resulting in a reduction of C1-INH function to 5-40% of normal levels. In type 1, mutations are observed across the gene, leading to truncated and misfolded proteins. This results in a decrease in both functional and antigenic levels of C1-INH. Type 2 is present in 15% of cases; C1-INH may be detected in normal or elevated amounts, but it is functionally impaired. The mutation occurs in exon 8 of the active region or its vicinity. This leads to the formation of a mutated protein that is secreted but non-functional. The specific genetic mutations responsible for the condition have been identified to be linked to the factor XII, angiopoietin-1, and plasminogen genes. Clinically, type 1 and type 2 cannot be distinguished, but they arise from different mutations. Patients with unknown mutations constitute a distinct group. In some research, there is mention of type 3 HAE that is dependent on estrogen. Angioedema occurs only during pregnancy and estrogen therapy. This hereditary condition is not associated with C1-INH. It is believed to result from a genetic mutation in factor XII. Acquired angioedema (AAE), on the other hand, is related

Received: December 03, 2023
Accepted: November 15, 2023
Published online: December 19, 2023

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Cite this article as:
Işık B, Erbaş O. Diagnosis and treatment modalities for hereditary angioedema in emergency medicine. D J Med Sci 2023;9(3):133-141. doi: 10.5606/fng.btd.2023.134.

to the consumption (type 1) or inactivation (type 2) of C1-INH. Both HAE and AAE can be life-threatening. The true prevalence of HAE is unknown. In some European countries, the reported prevalence, calculated by dividing the number of diagnosed HAE patients by the general population, is 1:10,000-1:50,000. In Türkiye, it is believed that the prevalence of HAE is higher than estimated due to the frequency of consanguineous marriages. Hereditary angioedema with normal C1-INH levels is more associated with estrogen and is more commonly observed in women.[3] In other types of angioedema, there is no significant gender difference in terms of frequency.

Symptoms and bigns

In approximately 50% of patients, initial symptoms manifest between the ages of two and 10. Almost all patients remain symptomatic until the age of 20. However, there are cases where individuals either never develop symptoms throughout their lifetime (5%), or experience symptoms only after the initiation of medication, with symptoms not recurring after discontinuation of the medication. In HAE-C1-INH patients, erythema marginatum appears to be a prodrome for an attack and is considered the most distinctive symptom of an attack.[4] The resulting cutaneous angioedema appears asymmetric, disfiguring, and non-pitting in appearance.[5] Unlike urticaria commonly seen in allergies, angioedema also involves the mucosal layer. As described by Frank et al.,[6] the edema typically does not pit until the terminal stage of an attack. Intestinal edema is commonly observed, and it can have a severe course. The only symptom that may arise during an attack is abdominal pain due to intestinal wall edema. An abdominal angioedema attack can lead to unnecessary surgical interventions by being misdiagnosed as acute abdomen.[7]

Pathophysiology

Generally, the mechanisms involved in angioedema are mediated by histamine or bradykinin. Histamine-mediated angioedema is most commonly associated with allergy-related conditions such as foods, drugs, insect stings, and idiopathic factors. Acquired angioedema with C1 inhibitor deficiency or HAE results from the accumulation of bradykinin through the kinin-kallikrein system, leading to the onset of the disease.[8] C1 inhibitor, a member of the serpin family, is the primary inhibitor of various complement proteases (C1r, C1s, and mannose-binding lectin-associated serine proteases 1 and 2) and contact system proteases. It is also a smaller inhibitor of kallikrein, coagulation factor XIIa, and fibrinolytic protease plasmin, as well as coagulation protease factor XIa. During HAE attacks, activation of these plasma proteolytic cascades occurs due to C1-INH deficiency and dysfunction. While many vasoactive substances are produced, studies have demonstrated that bradykinin, a nanopeptide generated by activation of the contact system, is the predominant mediator of increased vascular permeability during HAE attacks by binding to the bradykinin B2 receptor on vascular endothelial cells.

The kallikrein-kinin system, or simply the kinin system, in which C1-INH plays a role, is a hormonally regulated pathway that has been studied to a limited extent and is not fully understood. It consists of blood proteins involved in inflammation, blood pressure control, coagulation, and pain. Key mediators include bradykinin and kallidin, which lead to vasodilation and affect various cell types. Kinins are known inflammatory mediators that cause the dilation of blood vessels and increased vascular permeability. Kinins are small peptides produced from kininogen by kallikrein and cleaved by kininases. C1 inhibitor is a serine protease inhibitor (serpin) protein. The C1-INH is the primary physiological inhibitor of plasma kallikrein, fXIa, and fXIIa. Additionally, C1-INH inhibits proteinases in the fibrinolytic, coagulation, and kinin pathways. Deficiency in C1-INH leads to the uncontrolled activation of plasma kallikrein, resulting in the production of the vasoactive peptide bradykinin.[9] And bradykinin accumulates. The HAE-C1-INH has an autosomal dominant genetic inheritance, arising from mutations in the SERPING1 gene, which codes for C1-INH, a serine protease with various functional domains.[10] Although C1-INH is a crucial regulatory inhibitor for the contact activation system, kallikrein-kinin system, coagulation system, and complement system in the plasma, its deficiency does not have clinically pronounced effects on the coagulation system.[1]

The contact activation system and the kallikrein-kinin system are intertwined pathways, and the main proteins influencing both pathways are factor XII (FXII), plasma pre-kallikrein, and

high molecular weight kininogen. Mutations in these proteins can lead to quantitative and/or functional deficiencies in C1-INH, as they play roles in the steps of these pathways. In cases of HAE with normal C1-INH levels, mutations in proteins interacting within the pathways should be investigated since C1-INH is present in normal amounts. Hereditary angioedema with normal C1-INH levels is associated with mutations in other proteins, ultimately resulting in excessive bradykinin production.[3,11] The activation of the contact system begins with the conversion of pre-kallikrein to kallikrein by active FXII; this, in turn, leads to the release of bradykinin by cleaving high molecular weight kininogen. Bradykinin binds to the B2 receptor, structurally expressed in endothelial cells, interfering with endothelial connections, increasing vascular permeability, and ultimately causing angioedema. Due to its role in complement system activation, C1-INH deficiency leads to a decrease in plasma C4 levels.[12] In cases of HAE with normal C1-INH levels, mutations in FXII can also contribute to the pathogenesis. Mutations in FXII result in increased activation by plasmin, leading to the production of activated factor XII that is effective on pre-kallikrein. Consequently, the mutated FXII rapidly activates after being cleaved by plasmin and evades C1-INH inhibition. Mutations in coagulation factor XII (FXII) are the most common in these cases. Other recently identified mutations occur in plasminogen (HAE-PLG),[13] angiopoietin-1 (HAE-ANGPT1), and kininogen-1 (KNG1) genes.[14] In the case of mutations in the ANGPT1 gene, the loss of protein function results in a decrease in the activation capacity of the angiopoietin-1 receptor expressed in endothelial cells. This, in turn, will ultimately impact vascular permeability.[11] With a mutation in the KNG1 gene, there is the formation of an abnormal bradykinin that has a longer half-life and, consequently, is more active.[14] In the pathophysiology of AAE, consideration should be given to the consumption of C1-INH, with the most common causes being lymphoproliferative and autoimmune diseases.[11] In these cases, the C1-INH protein is degraded by the immune system. The clinical presentation is similar to HAE, but the onset of symptoms is later, and there is no family history. Triggers in the bradykinin pathway may include medications such as angiotensin-converting enzyme inhibitors (ACEI). The use of these drugs prevents the degradation of bradykinin protein. The ACE inhibitors, a group of antihypertensive agents, account for approximately 0.1 to 0.5% of angioedema cases seen in the emergency department that can lead to AAE.[15] Gliptins, including sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin, which are used in the treatment of type 2 diabetes, are potential triggers for angioedema. These drugs act by inhibiting the dipeptidyl peptidase-4 enzyme, which plays a crucial role in the breakdown of bradykinin and substance P.[16]

Laboratory

Confirmation or exclusion of the diagnosis will require laboratory tests. In nearly all patients with HAE, there is consistently a low level of antigenic C4 along with normal antigenic C1 and C3 levels. Measuring C4 levels is a suitable but costly screening test to exclude HAE; however, in rare cases, C4 levels can be normal between attacks. All forms of HAE lead to abnormal activation of the complement system. A screening test for both type 1 and 2 is the complement component C4. The C4 level is consistently low, whether the patient is experiencing an attack or not.[17] Hereditary angioedema can be differentiated from AAE with a useful test, the C1q protein, which is normal in HAE and low in AAE. It's important for emergency physicians to be aware that HAE is the only condition causing C4 deficiency in cases presenting with angioedema symptoms without urticaria. If deficiency is detected in the screening test, the next step is to measure C1-INH levels. Serum tryptase levels, taken 30 minutes to 6 hours after the onset of symptoms in anaphylactic shock, are found to be high, while in HAE attacks, tryptase levels are normal. However, measuring tryptase levels is not a test commonly used in the emergency department for acute and life-threatening attacks.[18] Hereditary angioedema attacks in the abdomen are known to typically cause a significant increase in the patient's white blood cell count, usually ranging from 13,000 to 30,000. As symptoms begin to decrease, the white blood cell count gradually decreases and returns to normal once the attack subsides.

Clinic

Recurrent episodes lasting more than 24 hours, unresponsive to antihistamines, not accompanied

by urticaria, occasionally causing abdominal pain in a colicky fashion due to laryngeal edema or intestinal edema, with a family history, and exhibiting asymmetric distribution- in such cases, consideration should be given to the diagnosis of HAE.[19]

Hereditary angioedema can be preceded by a prodromal period with symptoms such as weakness, headache, gastrointestinal signs, and a tingling sensation. Angioedema occurring in the skin can cause swelling that matches the color of the skin in the hands, arms, legs, face, trunk, neck, and genital area. Allergic angioedemas typically develop within minutes and reach their maximum size, whereas in HAE, the progression of angioedema is slow, taking up to 24 hours to reach its maximum size. Angioedema that has started in one area may reoccur in another area before complete resolution. The presence of urticaria associated with angioedema in both the current and previous attacks strongly suggests histaminergic angioedema while moving away from a diagnosis of HAE. Clinical data often include a family history of angioedema, edema lasting three to five days, lack of response to conventional treatment, recurrent airway edema, and episodes of abdominal pain without an apparent cause, sometimes accompanied by a history of unnecessary abdominal surgeries.[20] Hereditary angioedema has been very rarely reported in the literature to coexist with familial Mediterranean fever.[21] In the case of abdominal angioedema, the leakage of fluid into the interstitium or peritoneal cavity can lead to severe hypotension. Laryngeal edema statistically may occur once in the lives of half of the patients, and approximately one-third of patients are lost due to this reason.

Diagnosis

Unfortunately, some patients succumb to their condition without receiving a diagnosis, and others may lose their lives due to the closure of the upper airways. The primary reason for this exceptionally prolonged diagnostic process is the low awareness of HAE. Until a correct diagnosis is reached, many HAE patients visit the emergency department an average of five times a year, shuttling between numerous family physicians and clinics, including internal medicine, pediatrics, and pediatric clinics. According to the literature, three major clinicals, one minor clinical, and three laboratory findings are defined for diagnosis. According to guidelines, a diagnosis can be made with one major clinical finding and one laboratory finding. A family history is not a prerequisite for diagnosis, and in approximately 25% of cases, family history is absent as it arises from spontaneous mutations. Major clinical findings are defined as *(i)* Non-urticarial, non-inflammatory angioedema lasting more than 12 hours, *(ii)* Recurrent laryngeal edema, and *(iii)* Self-limiting abdominal pain attacks not related to an organic cause. The sole clinical finding accepted is a family history of recurrent laryngeal edema, abdominal pain, or angioedema. As a laboratory criterion, the identification of genetic mutation (C1-INH) or a decrease of more than 30% in C1-INH antigen level or function in a child above one year of age is established. While these criteria can be used for the diagnosis of C1-INH-HAE (type 1 and 2), different laboratory criteria can be utilized for the diagnosis of nC1-INH-HAE. In the presence of unexplained recurrent angioedema without urticaria, if C1-INH level/function (along with complement C4 level) is normal, a diagnosis requires the identification of genetic mutations (F12, PLG, ANGPT-1) or demonstrating an unresponsive response to antihistamines with a family history.[22] Diagnosis of HAE is generally challenging to establish in the emergency department as specific laboratory tests for diagnosis are often not readily available. Nevertheless, if C4 levels can be measured during an attack, it may contribute to the diagnosis. It is estimated that almost all of these patients experience a decrease in C4 levels during an attack; therefore, if C4 levels are normal, HAE without C1-INH can be ruled out.[15] Currently, in many hospitals in Türkiye, laboratory methods for the diagnosis of HAE with C1-INH, such as the measurement of C4 and C1-INH antigen levels, as well as mutation detection, may not be feasible. However, the main challenge in making a diagnosis lies in the rarity of the condition, which often leads to physicians not considering HAE during emergency situations and lacking sufficient knowledge about the disease.[23] At high levels during an attack, tryptase can confirm the degranulation of mast cells, indicating allergic

angioedema. On the other hand, normal levels of tryptase during an attack do not exclude anaphylaxis.[19]

In HAE or bradykinin-induced angioedema cases such as AAE-C1-INH or ACEI use, high levels of tryptase are not observed. If a patient presents after the development of edema in the intestinal endothelium and seeks clarification of the etiology of abdominal pain through abdominal ultrasound or computed tomography, thickening of the bowel walls, and the presence of free fluid in the abdomen and Douglas pouch may be notable. The self-resolution of the abdominal pain attack, followed by repeated imaging methods, reveals a return to normal thickness of the bowel walls due to the absorption of fluid. The lack of response of angioedema attacks to antihistamines, adrenaline, and cortisone is also significant in the diagnosis of hereditary angioedema. Genetic tests, including analysis for mutations in SERPING1, factor XII, PLG, and ANGPT-1, confirm the diagnosis.[2]

Triggers

Trauma, stress, infection, surgical and dental procedures, endoscopic interventions, menstrual periods, pregnancy, alcohol consumption, extreme temperature changes, physical exercise, ACEI use, and exposure to estrogen are the main triggers for the onset of attacks.[24] Since both minor and major surgical procedures fall under the category of trauma, it is necessary to initiate medication for these patients before any intervention. Given that airway compromise can suddenly arise during the perioperative period, anesthesiologists must be able to recognize this condition, as it is of vital importance. Stress management can also improve the course of the disease.

Treatment

Although rare, AAE and HAE are significant due to the possibility of fatal outcomes if not appropriately treated.[25] In the approach to treatment, preventing or reducing attacks by avoiding triggering factors can be considered as a primary strategy if feasible. If there is no specific treatment option available, symptomatic control will be the cornerstone of treatment. 17α-alkylated androgens and antifibrinolytic drugs are not suitable for attack treatment because they are not effective for several days. The most crucial point for the emergency physician is to first differentiate an HAE attack from other confusable histaminergic and bradykininergic angioedema-related attack types in patients presenting to the emergency department. Making this distinction is crucial for both the patient and the physician.[19,26] According to international guidelines, a wait-and-see approach can be applied in cases of angioedema occurring in the trunk and extremities, excluding the involvement of the face and neck. However, in attacks involving the respiratory tract and abdomen, a wait-and-see approach is not expected, and prompt attack treatment is initiated. Nowadays, the perspective that every attack should be treated has also come to the forefront.[27] Additionally, it should not be forgotten by emergency physicians that medications such as antihistamines, adrenaline, and corticosteroids are ineffective in these attacks. The goal of treatment is to control the attack by preventing the accumulation or effects of kinins, which are the end product of the plasma contact (kallikrein-kinin) system and indirectly contribute to HAE attacks. This is attempted by replacing the deficient C1-INH protein in the body and/or preventing the production or overactivity of bradykinin through the plasma coagulation system (via F12/PLG).[28] For this purpose, C1 inhibitor concentrates, bradykinin synthesis and receptor inhibitors are used in the treatment. In a study involving a case series of 51 patients who underwent a total of 70 dental or other surgical procedures, the attack rate 48 hours post-procedure was found to be 2.9% in those receiving prophylaxis with recombinant human C1 inhibitor and 76.9% in those not receiving prophylaxis.[29] The results reported in another study involving plasma-derived C1 inhibitors are similar. Here, the rates of sudden attacks are 6% in those receiving treatment and 68.9% in those not receiving treatment.[30] These studies seem to indicate the effectiveness of the treatment. The management of HAE has undergone a transformation in recent times with the emergence of disease-specific treatments. When approaching a patient experiencing an HAE attack affecting the airways, tongue, and/or smaller tongue, the first step is to ensure airway patency. In unstable patients at high risk of asphyxiation, endotracheal intubation should not be delayed. In the early stages of airway obstruction in HAE, there may

be no drop in oxygen saturation. If hypotension or dehydration is present, fluid replacement should be initiated.[31] Plasma-derived C1 inhibitors, recombinant human C1 inhibitors, bradykinin B2 receptor antagonists (icatibant), and kallikrein inhibitors (ecallantide) are commonly used agents today. These agents are expensive, and three of these products (plasma-derived C1 inhibitor, recombinant human C1 inhibitor, and ecallantide) carry a rare risk of anaphylaxis. The goal of acute attack treatment is to prevent morbidity and potential mortality associated with the attack at that moment. Administration of C1 inhibitor concentrate to the patient without delay is essential in cases of edema in the neck, nape, face, and upper airways. Currently, there are two C1 inhibitor concentrates available in Türkiye. One of them (Cinryze) is in 500 IU vials as a dry powder and should be administered at a dose of 1000 IU IV in adults during an acute attack. The other C1 inhibitor concentrate (Berinert) is also in 500 IU vials as a dry powder and is used intravenously at a dose of 20 IU/kg during an acute attack. It has been demonstrated that C1-INH concentrates are effective and safe in the treatment of any type of HAE attack due to C1-INH deficiency in both children and adults.[32] Recombinant human C1-INH (Ruconest®), obtained from the purification of transgenic rabbit milk. Studies have shown its effectiveness and safety without any adverse thrombotic events, but it should be used with caution in those allergic to rabbits.[33] Icatibant, a bradykinin receptor antagonist, is available in ready-to-use injectors at 30 mg/3 mL. It should be administered subcutaneously in the abdominal region during an acute attack. Icatibant, designed for patients to self-administer during an acute attack, is similar to adrenaline autoinjectors used in histaminergic angioedema. In Türkiye, Icatibant is available under various brand names such as Bradikant, Estereban, Heact, and Icatin. They act by blocking the effects of bradykinin in endothelial cells or by increasing C1-INH levels.[25] Icatibant (Firazyr®) is a synthetic molecule resembling bradykinin, and it acts as a competitive and selective antagonist to the bradykinin B2 receptor.[34] Hereditary angioedema attacks respond more quickly with early use of icatibant, so it is recommended to administer it within the first 6 hours after the onset of symptoms.[35] It is safe for home use. The recommended dose is 30 mg for adults and 0.4 mg/kg for those aged two to 17 years. It is administered subcutaneously, only in the abdominal area. Additional injections can be given every 6 hours, up to a maximum of three injections within 24 hours. The fourth class of drugs used to treat attacks includes kallikrein inhibitors, such as Ecallantide (Kalbitor®), approved for use in the United States. The recommended dose is 30 mg subcutaneously, but it is not approved for home use due to observed anaphylaxis in approximately 3% of patients.[36]

Until now, there has been no randomized clinical trial comparing the efficacy of these drugs. Therefore, for greater effectiveness, it is recommended to use the available treatment option as soon as possible after the onset of an acute attack.

Another alternative for C1-INH replacement that has been used for many years is the infusion of fresh frozen plasma, ranging from two to four units for adults and 10 mL per kg for children. However, this strategy has not yet been tested for efficacy and safety in clinical trials for HAE and should be reserved as a last resort for situations where no other drug is available for the attack. Additionally, the administration of fresh frozen plasma not only reveals C1-INH but also the substrates affected by this inhibitor, which may not provide sufficient efficacy and could even worsen the condition. To date, very few strategies have been licensed for use in the pediatric population. Berinert®, approved without age restrictions at a dose of 20 IU/kg, and the use of icatibant from the age of two has recently been approved.[37] There is limited research on the safety and efficacy of medications for treating attacks during pregnancy, postpartum, and breastfeeding. During pregnancy, childbirth, postpartum, and breastfeeding, the preferred treatment is pdC1-INH concentrate. When pdC1-INH concentrate is not available, fresh frozen plasma can be used as an alternative. pdC1-INH concentrate used for attack treatment can also be used for prophylaxis. Recently, an immunobiological agent, lanadelumab, which blocks kallikrein and consequently bradykinin formation, has been approved for long-term prophylaxis.[38] The first human monoclonal antibody targeting plasma kallikrein and produced using laboratory cells instead of human plasma.[39]

Agents of this kind are often not available in low-income countries or in small hospitals and pharmacies due to their high cost. Studies have shown that in their place, heparins, especially low-molecular-weight heparin, have been successful in both prophylactic treatments and acute attacks of hereditary angioedema.[40] In a study involving 34 patients with HAE and a total of 256 attack histories, the administration of nadroparin after the onset of prodromes resulted in a complete response rate of 90%.[41]

Antifibrinolytic drugs like androgens were commonly used in the past but have been abandoned today due to being perceived as less effective compared to newly developed drugs. Nevertheless, they can be used when no other option is available. The effect of danazol treatment begins within an average of one to two days. Therefore, it is not considered a good option for attack treatment. They have been used in patients receiving long-term prophylaxis treatment as a general approach. Androgens also affect C1-INH protein synthesis by increasing it from the liver. Danazol treatment is initiated with a partially high dose (400 mg/day), if necessary, increased up to 600 mg, and attempts are made to reduce the dose to 50 mg/day, five days/week at monthly intervals. Anabolic androgens are taken orally and are cheaper drugs. However, they lead to complications such as muscle cramps, psychiatric problems, obesity, and hyperlipidemia. Danazol treatment is more effective in AAE.[42]

In the follow-up phase, a patient who presents to the emergency department can be admitted to the internal medicine department once the attack begins to regress. Intubated cases need to be monitored in intensive care conditions until the vital danger has passed. If the patient's diagnosis is unknown, it is appropriate to refer them to a healthcare center with an Allergy and Immunology department for diagnosis, issuing a committee report, and conducting further follow-ups. Weak androgens such as danazol (50-600 mg/day twice a day), stanazol (2 g three times a day), C1-INH concentrate (25 U/kg once or twice a day), antifibrinolytic treatment (12-25 mg/kg/day) can be prescribed for long-term prophylactic treatment.[43]

Prognosis

It is estimated that untreated HAE attacks lead to death in 25 to 40% of cases due to asphyxia.[44] Patients should be informed about the severity of their condition, indicating that if they experience more than one angioedema attack per month or have a life-threatening single attack, their treatment may need to be lifelong. Hereditary angioedema poses life-threatening risks during pregnancy, with the frequency and severity of attacks increasing towards the end of pregnancy. Patients should be educated about this aspect as well. However, it is rare for an attack to occur during childbirth. In individuals with HAE, there is an increased incidence of other autoimmune diseases, primarily glomerulonephritis. Patients should be encouraged to carry a medical alert card that provides information about their condition.

In conclusion, the molecular and biochemical characteristics of HAE, factors initiating and terminating attacks, and the most appropriate strategies to manage attacks are not fully understood. Ongoing research is exploring new drug developments. Proper management of HAE in the emergency department prevents fatal outcomes and unnecessary surgeries. Limited knowledge among healthcare professionals about hereditary angioedema, especially when attacks involve internal organs, can lead to misdiagnoses, highlighting the need to increase awareness in this area. Considering its potential mortality and distinctive treatment, HAE should always be kept in mind during diagnosis, and healthcare providers should stay updated on new developments in its treatment.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Author, literatüre research, data collection: B.I.; Literature research, data collection: O.E.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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