Chapter 11

# Hereditary Angioedema

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**Abstract**

Hereditary angioedema (HAE) is an autosomal dominantly inherited orphan disease manifested by recurrent unpredictable nonpitting and nonpruritic swelling attacks without urticarial plaques. HAE is caused by a deficiency of the C1 esterase inhibitor (C1-inh) or decreased function of C1-inh. Type 1 HAE, the most common form, occurs due to C1-inh deficiency and is seen with low-serum C1-inh levels. In type 2 HAE, the function of C1-inh is impaired, and in HAE with normal C1-inh serum levels, the function of C1-inh is normal. HAE episodes can affect various sites in the body such as the larynx, face, extremities, gastrointestinal tract, and urogenital area. Acute episodes can be treated with C1-inh concentrates, a kallikrein inhibitor, called ecallantide and bradykinin B2 receptor antagonist, icatibant. Depending on the frequency, severity, and location of the episodes, long-term prophylaxis regimens with plasma-derived C1-inh concentrates, antifibrinolytics, or 17$\alpha$-alkylated androgens can be used. C1-inh concentrates or 17$\alpha$-alkylated androgens should be administered before dental procedures and minor or major surgical interventions to provide short-term prophylaxis. In conclusion, HAE is a rare life-threatening disease of which clinical presentation is highly variable and early accurate diagnosis significantly prevents mortality and morbidity.

**Keywords:** hereditary angioedema, C1-inhibitor, bradykinin, complement, orphan disease

## 1. Introduction

Hereditary angioedema (HAE) is a rare disease, clinically characterized by recurrent unpredictable nonpitting and nonpruritic swelling episodes involving different mucosal or cutaneous surfaces of the body such as the larynx, face, extremities, gastrointestinal tract, and urogenital area [1]. In the late 1880s, Osler described the hereditary feature of angioedema for the first time [2]. In the 1960s, a deficiency in a type of serine proteinase inhibitor, C1 esterase inhibitor (C1-inh), was discovered as the cause of HAE, and a few years later, the second form was

defined as non-functioning C1-inh. These diseases are called type I and type II HAE, respectively [3, 4]. These laboratory abnormalities in C1-inh are the result of the mutations found in the C1-inh gene called SERPING1 [5]. In the 2000s, a third form of HAE was defined and in these patients characteristic clinical signs and symptoms are seen; however, the level and the function of C1-inh are normal with no mutations on the SERPING1 gene [6, 7]. However, mutations in the F12 gene were found in approximately 25% of these patients. A strong association between this type of HAE and conditions causing increased levels of estrogen such as pregnancy and the usage of oral contraceptives was determined [7, 8]. Therefore, at first, this type was called estrogen-dependent or type III hereditary angioedema [6]. After affected male relatives were reported, it was renamed as hereditary angioedema with normal C1-inh [9].

HAE is rarely seen, and its estimated prevalence ranges from 1:30,000 to 1:80,000 in the general population [10]. The most common form of HAE is the first type, which is responsible for 85% of the patients [10]. HAE is an autosomal dominant disease generally affecting all generations in a family, although a quarter of patients do not have a family history. Patients are similarly affected independent of gender and ethnicity [11]. Mortality rates range from 14 to 33% mostly because of poorly treated laryngeal episodes, which indicates the significance of early diagnosis and appropriate management [12, 13].

## 2. Clinical presentation

Symptoms primarily develop when the serum level of C1-inh is below 35% but are not usually correlated with serum C1-inh levels. Symptoms can be expected from birth in a heterozygote individual with a serum level of C1-inh around 50% [14]. Although signs and symptoms can start at any age, including after 70, they are primarily seen starting around the second decade of life when the level of C1-inh usually decreases and then continues to occur lifelong [14, 15].

Angioedema episodes can affect any cutaneous or mucosal sites of the body such as the face, larynx, extremities, gastrointestinal tract, and urogenital area [1]. A typical HAE episode worsens within the first 24 h, begins to improve after 48–72 h, and lasts approximately 72–96 h [11, 14]. Apart from visible angioedema, fluid extravasation on the gastrointestinal tractus through the intestinal wall or peritoneum leads to abdominal pain attacks. Nausea and emesis may accompany them [16]. The majority of the patients experience gastrointestinal angioedema during their lives and the abdominal attacks accompany 50% of the overall attacks [17]. Due to these abdominal attacks, unnecessary operations like appendectomy and diagnostic laparotomy are sometimes performed [16]. Fever or leucocytosis is not observed during a typical attack unless the cause is an infection [18]. Sometimes, fluid extravasation can be so severe that it causes hypotension or ascites [19]. The most severe complication is angioedema in the larynx and/or oropharynx, which can prevent air passage leading to asphyxiation or even death. Fortunately, this seems less frequent [16]. More than 50% of the patients experience laryngeal edema at least once in their lifetime [20].

Although the precipitating factors of attacks are not well determined in all attacks, some episodes of HAE can be triggered by factors such as stress, trauma, infection, angiotensin-converting enzyme inhibitors (ACEIs), estrogen-containing hormones, oropharyngeal surgery,

and minor medical procedures like tooth extraction [21–23]. Sometimes, the usage of ACEI or estrogen-containing drugs can trigger the symptoms in patients with a silent disease [14]. Prodromal symptoms can precede the attacks; the most frequent symptoms are erythema marginatum, which is a nonurticarial erythematous rash and tingling on the angioedema site. Fatigue, malaise, irritability, hyperactivity, mood changes, and nausea are other preceding factors [21, 24].

The severity of HAE is variable and usually unpredictable. While some patients do not experience any attacks in their lives, others experience swelling up to twice a week. Similarly, the attacks of some patients can be so severe that treatment in an intensive care unit may be needed while the attacks of other patients can be so mild that treatment is unnecessary [15, 17]. The disease severity and the course of the disease cannot be predicted according to the initial symptoms [9].

Types I and II HAE are very similar in their clinical presentation; however, HAE with normal C1-inh differs from the other two types with respect to some features. In HAE with normal C1-inh, abdominal attacks are less frequently seen and angioedema on the face, lips, and tongue are the major symptoms. It predominantly affects females, rarely starts under the age of 10, symptoms recur less frequently, and asymptomatic intervals are more common [21].

## 3. Pathogenesis

C1-inh is a broad-spectrum serine proteinase inhibitor, which regulates the activity of various proteases comprising those of the contact system, the intrinsic coagulation pathway, and the fibrinolytic pathway [5]. C1-inh is produced primarily in the liver and inhibits the plasma kallikrein, a type of protease that cleaves high-molecular-weight kininogen (HMWK) to produce bradykinin and also inhibits activated coagulation factor XII (FXII), which in turn enhances the activation of the contact system by activating the plasma kallikrein [10].

Trauma as well as surgical interventions causing a negatively charged endothelial surface and a deficiency in the serum level of C1-inh leads to the development of FXIIa in significant amounts. FXIIa induces the transformation of prekallikrein to kallikrein, which in turn leads to the cleavage of high-molecular-weight kininogen to bradykinin [10, 14] (**Figure 1**).

The major mediator responsible for angioedema is a type of nanopeptide called bradykinin. Bradykinin is formed secondary to the activation of the contact system. It leads to an increase in vascular permeability by binding to the B2 receptor on the vascular endothelial cells, and this in turn causes the development of edema, ascites, and hypotension [25, 26].

C1-inh is encoded by the SERPING1 gene which is located on the 11th chromosome. Around 300 different mutations of the SERPING1 gene were identified in both type I and type II HAE patients. Approximately a quarter of patients with C1-inh deficiency do not have a family history, indicating the occurrence of de novo mutations. In type I HAE, various types of mutations involving nonsense, missense, insertion, or deletion mutations developed throughout SERPING1 leading to a decrease in the serum level of C1-inh [10, 27]. By contrast, almost all

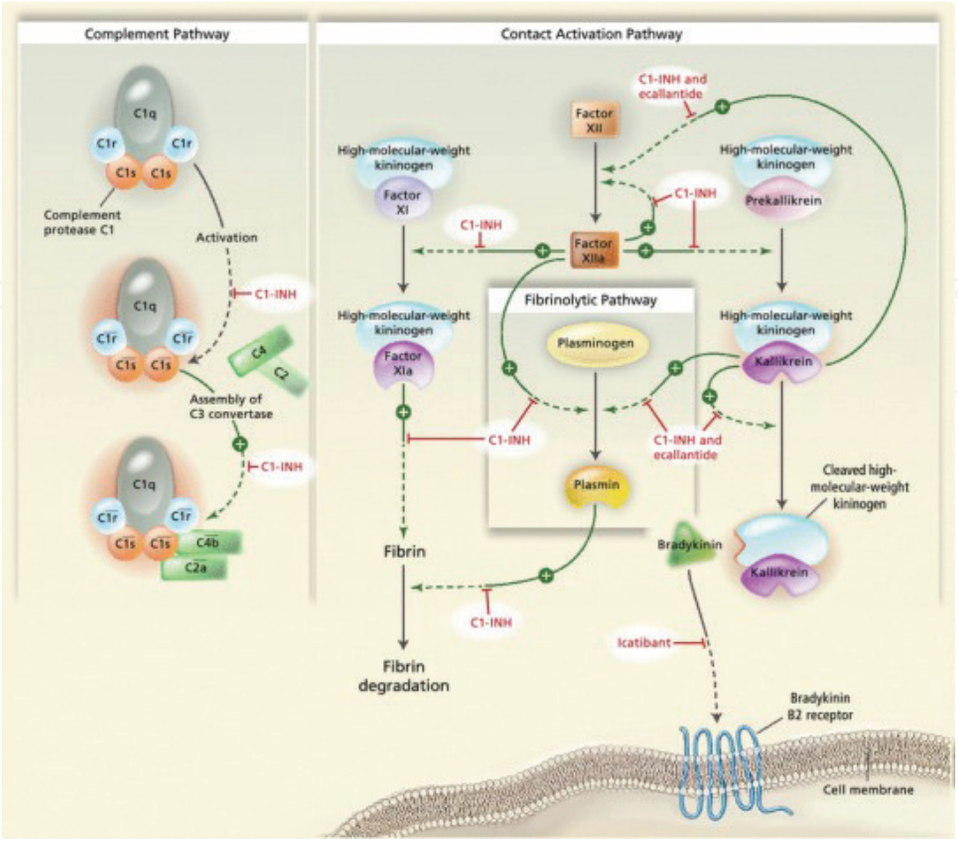


**Figure 1.** The role of C1-inh in the plasma cascade and complement pathway and the pathogenesis of the HAE [14]. (With permission from Massachusetts Medical Society).

of the mutations in type II HAE are missense at or near the active site causing the production of a defective protein, which cannot act properly [10]. In patients with HAE with normal C1-inh, the SERPING1 gene is not mutated, but in some of these patients mutations on the FXII gene, which is located on the fifth chromosome, can be detected. The pathomechanism of angioedema in these patients is not well defined. One of the detected mutations on factor XII leads to a gain of function, which is thought to cause the increase in the production of bradykinin [28]. However, this hypothesis was not confirmed in another study [29]. Since bradykinin antagonist drugs are effective in uncontrolled patients, it can be assumed that this type of angioedema is also bradykinin mediated [10].

## 4. Diagnosis

Low awareness of the disease among both doctors and the public can lead to more than a 10-year delay in the diagnosis and also result in a misdiagnosis such as allergies, systemic lupus erythematosus, and appendicitis [30–32]. HAE patients usually have a typical medical history with episodes of angioedema without urticarial plaques on their skin and/or abdominal pain attacks without inflammatory signals. Such a clinical presentation accompanied by a family history is highly suggestive of the diagnosis, but laboratory tests are recommended to confirm

the diagnosis [9]. Serum C4 level is the screening test for HAE, which is decreased both during and between episodes in almost all of patients (98%). Interestingly, C4 can seldom be observed at a normal level between episodes [20]. Serum C1 and C3 levels are not affected by the disease. If C4 levels are normal during an episode, the diagnosis of type I, type II HAE, and acquired angioedema is excluded. After measuring C4, C1-inh must be measured in the serum to accurately diagnose the HAE type. In type I HAE, both serum C1-inh and C4 levels are detected below the normal ranges (the reference range of C4 is 15–50 mg/dl and of C1-inh is 16–33 mg/dl), whereas in type II HAE serum C1-inh is normal but the function of C1-inh is impaired. These tests can indicate a false negative in children younger than one, so the tests must be repeated to confirm the diagnosis [9]. In the third HAE type, HAE with normal C1-inh, serum C4- and C1-inh levels are normal and the diagnosis is challenging. Its diagnosis depends on recurrent angioedema attacks without urticaria or abdominal pain attacks and possibly a family history. However, clinical presentation is highly variable, which often leads to a misdiagnosis, and genetic tests including FXII mutations rarely support the diagnosis [33]. In **Table 1**, differential diagnoses of angioedema including both hereditary and sporadic diseases based on laboratory are shown.

| Type of angioedema | C1-inh antigenic level | C1-inh functional level | C4 level | C1q level |
|---|---|---|---|---|
| HAE-1 | Low | Low | Low | Normal |
| HAE-2 | Normal | Low | Low | Normal |
| HAE with normal C1-inh | Normal | Normal | Normal | Normal |
| ACID | Low | Low | Low | Low |
| Angioedema due to ACEI | Normal | Normal | Normal | Normal |
| Nonclassified angioedema[a] | Normal | Normal | Normal | Normal |

ACEI, angiotensin-converting enzyme inhibitor; ACID, acquired angioedema due to C1-inh deficiency; HAE-1, hereditary angioedema type I (due to C1-inh deficiency); HAE-2, hereditary angioedema type II (due to C1-inh defect); C1-inh, C1 inhibitor.



[a]Nonclassified implies that no cause has been identified [34]. http://dx.doi.org/10.1016/j.anai.2012.10.008

**Table 1.** Differential diagnosis of angioedema according to laboratory results [34].

## 5. Management

Angioedema and abdominal pain episodes do not respond to antihistamines, corticosteroids, and epinephrine, which are effectively used in histaminergic angioedema. The management of HAE comprises prophylaxis and treatment of acute attacks [35]. Moreover, patients should be educated about their disease and some preventive measures must be taken, such as

avoiding known triggering factors like estrogen-containing pills and ACEI [30]. All patients are at risk for life-threatening episodes independent from their previous attacks. Therefore, all patients should have a written action plan that includes what to do in a severe attack [21].

### 5.1. Treatment of acute attacks (on-demand treatment)

For the treatment of acute attacks, C1 inhibitor concentrates, B2 receptor antagonist, icatibant, and an inhibitor of kallikrein synthesis, ecallantide, are used (**Table 2**, **Figure 1**) [34].

The faster intervention leads to a quicker response; therefore, patients should be treated as early as possible in attacks [21]. If these drugs cannot be provided in a health-care facility, fresh-frozen plasma can be substituted. However, it can possibly worsen an attack because of the presence of bradykinin in the plasma [36]. Furthermore, symptomatic treatment including intravenous fluid replacement, anti-emetics, and analgesics can be effective in relieving the symptoms [14]. Patients experiencing angioedema in the oropharyngeal or laryngeal region should be closely observed for the possibility of the impairment of the air passage since tracheostomy or intubation may be needed [21].

| Drug | EMA and FDA indications | Recommended dosage | Mechanism | Potential adverse effects |
|---|---|---|---|---|
| Plasma-derived nanofiltered C1-inh | | | | |
| Berinert-P® | Acute attacks | 20 U/kg IV | Deficiency replacement | Theoretical: transmission of infectious agent |
| Cinryze® | Long-term prophylaxis in the US and Europe Short-term prophylaxis and on demand in Europe | 1000 U IV every 3–4 days | Deficiency replacement | Theoretical: transmission of infectious agent |
| Recombinant human C1-inh (Rhucin®) | Acute attacks | 50 U/kg IV | Deficiency replacement | Uncommon: risk of anaphylaxis in rabbit-sensitized individuals |
| Ecallantide | Acute attacks | 30 mg SC (administered as three injections of 10 mg/ml each) | Inhibits plasma kallikrein | Uncommon: antidrug antibodies, injection-site reactions, risk of anaphylaxis |
| Icatibant | Acute attacks | 30 mg SC | Bradykinin B2-receptor antagonist | Common: injection-site reactions |

EMA, European Medicines Agency; FDA, Food and Drug Administration; IV, intravenous; SC, subcutaneous [34]. http://dx.doi.org/10.1016/j.anai.2012.10.008.



**Table 2.** Drugs used for acute attacks in HAE [34].

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### 5.2. C1-inh concentrates

There are three kinds of C1-inh concentrates: Cinryze® (Shire ViroPharma Inc., Lexington, USA) and Berinert® (CSL Behring GmbH, Marburg, Germany) are both plasma-derived C1-inh, and Ruconest® (Pharming, Leiden, Netherlands) is a recombinant human C1-inh and was approved in 2014 by the Food and Drug Administration (FDA). Plasma-derived C1-inh concentrates have been widely used for many years and carry the potential risk of contamination of pathogens as in the case with other plasma-derived products [37]. The recombinant human C1-inh was produced as an alternative and has been used to treat angioedema attacks for a few years in some countries. The studies evaluating the efficacy of this drug in acute attacks of HAE showed that it rapidly improves the episodes and it is well tolerated with headache and nausea as the most common adverse effects [38–41].

In a recently published review, it was observed that weight-adjusted doses of 20-U/kg plasma-derived C1-inh concentrates lead to more rapid improvement in symptoms within 15 min than the standard 500-U dose of the drug that works in 30–45 min. Moreover, approximately 30% of the laryngeal attacks treated with 500-U plasma-derived C1-inh need a second dose while patients with laryngeal edema treated with a 20-U/kg dose do not require an additional dose. Therefore, a 20-U/kg-dosing regimen induces a quicker and more effective response [42].

### 5.3. Icatibant

Icatibant is a potent bradykinin B2 receptor antagonist. After application, symptoms begin to resolve within 30–45 min, an improvement of symptoms occurs in an average of 1.16 h, and 7–14% of patients with laryngeal edema need a second dose of the drug [42, 43]. It has some advantages including its subcutaneous application, its ready form, and preservation in room temperature. Therefore, it can be easily carried and taken by the patient. Disadvantages include side effects like pain at the injection site and a short half-life, which can lead to rebound attacks [9].

### 5.4. Ecallantide

Ecallantide is a recombinant protein and a potent kallikrein inhibitor [44]. It effectively improves acute angioedema attacks and is used subcutaneously like icatibant, but it is a frozen product and has a short half-life. Ecallantide was licensed for patients 16 years old and older at first but recently was approved for those 12 years and older [45]. It leads to an improvement in symptoms within approximately 93 min and 10% of the patients treated with laryngeal edema need a second dose [46]. Although ecallantide is generally well tolerated, anaphylaxis was observed in 4% of the patients, so it is not approved for self-administration and has a warning sign on its box [47].

### 5.5. Long-term prophylaxis

Determining if patients are in need of long-term prophylaxis can be a compelling problem for physicians. The decision depends on the frequency, severity, and location of the episodes, the

presence of comorbidity, access to emergency medical attention, and the patient's preference. According to a previous consensus report, patients who have attacks more than once a month, who have attacks more than 5 days in a month, and those with a history of obstruction of the respiratory airways should take a long-term prophylaxis [20]. In the years that followed with the approval for self-administration of icatibant, the human C1-inhibitors in some countries provided appropriate control of attacks and less need for long-term prophylaxis [48].

Anabolic steroids (17$\alpha$-alkylated androgens), antifibrinolytics, and C1-inh concentrates can be utilized for this purpose (**Table 3**).

17$\alpha$-alkylated androgens leading to an increase in the serum level of C1-inh decrease the severity and frequency of episodes in most patients, but they have adverse effects [49, 50]. Both adverse effects and the efficacy of 17$\alpha$-alkylated androgens are dose-dependent; therefore, adjustment of the minimum dose, which is both protective against severe attacks and

| Drug | Recommended dosage for adults (usual, range) | Recommended dosage for children (usual, range) | FDA approved/HAE indication | Adverse effects |
|---|---|---|---|---|
| 17-$\alpha$ alkylated androgens | | | | Common: weight gain, virilization, acne, altered libido, muscle pains, and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities, and increase in liver enzymes, hypertension, alterations in lipid profile Unusual: decreased growth rate in children, masculinization of the female fetus, cholestatic jaundice, peliosis hepatis, and hepatocellular adenoma |
| Danazol | Minimal effective dose does not exceed 200 mg/day | Not recommended; if absolutely necessary do not exceed 2.5 mg/kg/day (50 mg/week to 200 mg/day) | Yes/yes | |
| Stanozolol | Minimal effective dose does not exceed 2 mg/day | 0.5 mg/day (0.5 mg/week to 2 mg/day) | Yes/yes | |
| Oxandrolone | Minimal effective dose does not exceed 10 mg/day | 0.1 mg/kg/day (2.5 mg/week to 7.5 mg/day) | Yes/no | |
| Antifibrinolytics | | | | |
| ε-Aminocaproic acid | 2 g three times daily (1 g twice daily to 4 g three times daily) | 0.05 g/kg twice daily (0.02 g/kg twice daily to 0.1 g/kg twice daily) | Yes/no | Common: nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps with increased muscle enzymes Unusual: enhanced thrombosis |
| Tranexamic acid | 1 g twice daily (0.25 g twice daily to 1.5 g twice daily) | 20 mg/kg twice daily (10 mg/kg twice daily to 25 mg/kg three times daily) | Yes/no | |

[a]Registration and availability of these drugs differ from country to country. FDA, Food and Drug Administration; HAE, hereditary angioedema [34]. http://dx.doi.org/10.1016/j.anai.2012.10.008



**Table 3.** Drugs used for long-term prophylaxis in HAE[a] [34].

cause fewer side effects, is crucial and varies from patient to patient [21]. Treatment with 17$\alpha$-alkylated androgens can be started with a high dose that can be reduced to reach the most effective but least harmful dose. The most frequent adverse effects of the 17$\alpha$-alkylated androgens are menstrual irregularities, changes in libido, hirsutism, acne, changes in mood, weight gain, myalgia, erythrocytosis, increased blood pressure, and abnormalities in lipid profiles [51, 52]. Less commonly, these drugs can lead to hepatotoxicity involving hepatic adenomas and hepatic carcinoma [53, 54]. Because of these adverse effects, patients should be periodically monitored by blood count, liver enzyme, lipid profiles, and liver ultrasound [14]. Moreover, the attenuated androgens lead to the closure of epiphyseal cartilage prematurely [55]. Stanozolol is used more commonly in some European countries since it was observed to cause fewer side effects and is more effective as well as it is approved for children's use in the US [10, 56]. 17$\alpha$-alkylated androgens are relatively contraindicated in patients with prostate or breast cancer, known hepatic dysfunction, children, and pregnant women [57, 58]. Because of these side effects, they are no longer authorized in German-speaking European countries [48].

Antifibrinolytics including ε-aminocaproic acid and tranexamic acid are helpful in treating HAE by inhibiting the production of plasmin from plasminogen [55]. Although they have few side effects involving most commonly nausea, vomiting, and diarrhea, which are dose-dependent, they are not as effective as androgens. In some earlier studies, antifibrinolytics were observed to decrease the frequency of attacks; however, in a recently published study, no differences were detected between groups with and without antifibrinolytics [59–61]. As a consequence, they suggested antifibrinolytics for long-term prophylaxis where plasma-derived C1-inh is not accessible and androgens are not suitable for use [55].

In recent guidelines, the importance of quality-of-life scores of the patients is more emphasized than the number of attack days for making the decision of long-term prophylaxis [48]. Cinryze® was approved in 2011 in Europe and in 2008 in the US for the use of long-term prophylaxis and its recommended dose for adolescents and adults is 1000 U every 3–4 days [48]. Recombinant human C1-inh, which is used in the treatment of attacks, was shown to be effective for long-term prophylaxis in preliminary data [62]. A possible side effect of long-term and high dose of C1-inh therapy is the undesirable immunization with this protein [48].

### 5.6. Short-term prophylaxis

Short-term prophylactic therapy protects patients with HAE from acute attacks caused by a known triggering factor such as dental, minor, or major surgical interventions [21]. For this purpose, various prophylactic regimens are used. C1-inh concentrates between 1000 and 2000 U for adults and 20 U/kg for children or two units of fresh-frozen plasma for adults and 10 ml/kg for children can be administered before procedures [10]. Another regimen includes a high dose of 17$\alpha$-alkylated androgens starting with 6–10 mg/kg/day in divided doses, such as danazol 200 mg three times a day for 5–10 days before and 2 days after the procedure. No studies comparing the efficacy of these prophylactic modalities have been published. Therefore, it must be individualized according to the cost, benefit-harm ratio, and the patient's preferences. In pregnant patients, C1-inh administration is preferred [21]. In children, if plasma-derived C1-inh is not available, danazol can be used for a short duration [55].

## 6. HAE in pregnancy

The influence of pregnancy on the course of the HAE is variable. Some patients can experience fewer attacks while others experience them more frequently [9]. There are a few case series about pregnancy and delivery in HAE, which include few patients. Therefore, the approach and management of pregnancies is debated. In a recently published study, 125 pregnancies in 61 patients were analyzed and 59.2% of the patients reported a mild increase in HAE symptoms, 14% reported no symptoms, and the symptoms of 40% of the patients were sustained in a similar severity and frequency throughout the pregnancy. A HAE diagnosis was known before gestation in 30.7% of the pregnancies. Long-term prophylaxis was used in nine pregnancies including one with epsilon-amino-caproic acid, two with tranexamic acid, two with anabolic steroids (temporary usage for 8 and 12 weeks in two male-confirmed fetuses), and four with plasma-derived C1-inh concentrates. None of the babies experienced side effects from these drugs. Most of the deliveries were vaginal (88%) with cesarean sections required in 15 patients. Ten patients did not receive prophylaxis and one of them experienced mild symptoms during delivery and was treated with a plasma-derived C1-inh concentrate. After vaginal delivery without prophylaxis, a few patients developed mild local edema [63]. Similar observations were also reported by other authors [64, 65]. In another study, none of the patients who received prophylactic treatment before cesarean sections experienced any symptoms [66].

In conclusion, the course of HAE varies from patient to patient in pregnancy. Although the frequency and severity of episodes can increase in some patients, others may not have any symptoms. Patients who have had severe or more frequent episodes during this pregnancy or a previous pregnancy or have additional risk factors are recommended to have a vaginal delivery with a prophylactic plasma-derived C1-inh concentrate before delivery [63]. In addition, plasma-derived C1-inh should be accessible during delivery and hospitalization [63].

## 7. HAE in childhood

Episodes of angioedema and abdominal pain can begin in childhood; however, an accurate diagnosis is often delayed leading to the administration of inadequate or incorrect therapies and even to death [55, 67]. Moreover, life-threatening laryngeal edema can be the first clinical presentation [67, 68]. Therefore, it is crucial to scan the entire family, including children, in a newly diagnosed patient. In this way, the disease can be detected and serious angioedema attacks can be prevented through prophylactic or therapeutic modalities [55].

A consensus of treatment strategies in pediatric patients with HAE was reported in 2007 [69]. Afterwards, a German group covered the treatment options in pediatric patients and addressed the problem that previous consensus reports could not meet the needs of individual countries because of different approved drugs. Therefore, they suggested treatment strategies for German-speaking countries and pointed out that in every country physicians should consider the approved treatment options in their country before choosing an off-label drug approved in other countries [55].

For long-term prophylaxis, the only choice is plasma-derived C1-inh. Androgens should be avoided for long-term usage. If plasma-derived C1-inh is not available, danazol can be substituted for short-term prophylaxis [55]. Although the effectiveness of tranexamic acid is lower than the androgens, in children tranexamic acid can be used for long-term prophylaxis [55].

The drugs used in the management of HAE in children are shown in **Tables 2** and **3** [34].

## 8. Future promising interventions

Preventing angioedema episodes in HAE patients is still an important problem since there are limited options comprising oral-attenuated androgens, which have various side effects leading to dose limitations and plasma-derived C1-inh, which is administered intravenously and therefore not practical [70, 71]. Additionally, on-demand treatment of acute episodes has the risk of laryngeal angioedema and leads to a reduction in the quality of life since the angioedema attacks continue to occur [72–74]. Given these problems, new practical safe and effective treatment options to prevent acute episodes are necessary.

Avoralstat is a newly developed oral plasma kallikrein inhibitor for which studies are ongoing. In the recently published first in-human study, the authors observed that the amount of the drug sufficient to inhibit the plasma kallikrein (400 mg every 8 h) was well tolerated [75].

There is no curative treatment for HAE. Amerantunga et al. argued that HAE can be considered a metabolic liver disease and as in other metabolic liver disorders liver transplantation and hepatocyte transformation can be curative options [76, 77]. However, these treatments have surgical risks and need long-term immunosuppression [77]. They also asserted that although liver-based gene therapies are not practical, they can be the alternative curative options where a recombinant virus as a vector can infect the hepatocytes leading to the production of the targeted protein [77].

Another future concern is to prevent the development of HAE with prenatal genetic diagnosis before implantation occurs [78]. Although it seems to be reasonable, the strategy has some limitations. First of all, in some parents, the mutations causing the disease cannot be determined, and in one quarter of the patients, the disease is caused by de novo mutations. Furthermore, because of the hormonal stimulation during in vitro fertilization, it can possibly lead to angioedema attacks. Lastly, there is a risk of having mild influenced offspring [78]. Therefore, patients need intensive genetic counseling before such a therapy.

## 9. Conclusion

In summary, HAE is a rare life-threatening disease with highly variable clinical presentations. Physicians and the public are not familiar with the disease. There are still unknown features of the disease and delay in diagnosis or misdiagnosis leading to inaccurate treatment. It is, however, crucial to recognize the disease to prevent mortality and morbidity. Therefore, more

comprehensive studies are needed to describe the disease, and social work is essential to increase the awareness.

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