Hereditary Angio-Oedema for Dermatologists

Anette Bygum

Department of Dermatology and Allergy Centre, Odense University Hospital, Odense, Denmark

Keywords

Hereditary angio-oedema · Bradykinin · Mutation · Treatment

Abstract

Among angio-oedema patients, hereditary angio-oedema (HAE) should not be overlooked. Besides skin swellings, these patients might have very painful abdominal attacks and potentially life-threatening angio-oedema of the upper airway. They will not respond to traditional anti-allergic therapy with antihistamines, corticosteroids, and adrenaline, and instead need specific drugs targeting the kallikrein-kinin pathway. Classically, patients with HAE have a quantitative or qualitative deficiency of the C1 inhibitor (C1INH) due to different mutations in *SERPING1*, although a new subtype with normal C1INH has been recognised more recently. This latter variant is diagnosed based on clinical features, family history, or molecular genetic testing for mutations in *F12*, *ANGPT1*, or *PLG*. The diagnosis of HAE is often delayed due to a general unfamiliarity with this orphan disease. However, undiagnosed patients are at an increased risk of unnecessary surgical interventions or life-threatening laryngeal swellings. Within the last decade, new and effective therapies have been developed and launched for acute and prophylactic therapy. Even more drugs are under evaluation in clin-

ical trials. It is therefore of utmost importance that patients with HAE are diagnosed as soon as possible and offered relevant therapy with orphan drugs to reduce morbidity, prevent mortality, and improve quality of life.

© 2019 S. Karger AG, Basel

Introduction

Patients with angio-oedema may be referred to dermatologists for investigation and treatment. Most of these patients have associated urticaria and can be handled like this [1]. Among patients with primary angio-oedema, i.e., angio-oedema without associated urticaria, the bradykinin-mediated angio-oedema subtypes should be considered [2, 3]. Most of these patients develop angio-oedema due to medications [4, 5], especially angiotensin-converting enzyme inhibitors (ACEIs); however, others may have hereditary angio-oedema (HAE).

HAE is an ultra-rare disease with a minimum prevalence of approximately 1:65,000–95,000 inhabitants [3, 6]. The diagnosis of HAE is often delayed due to a gen-

The Department of Dermatology and Allergy Centre, Odense University Hospital, is a European Reference Network for Rare and Complex Diseases of the Skin (ERN-Skin) member.

eral unfamiliarity with this rare disease. Patients with HAE might present with one or several manifestations of the clinical triad consisting of skin swellings, abdominal pain attacks, and laryngeal oedema, described by Heinrich Quincke in 1882 [7]. The abdominal attacks can be very painful and severe mucosal swelling might potentially obstruct the upper airway causing asphyxiation [8–11]. Historically, fatality was reported in up to 40% of HAE patients without treatment [12–15]. The hereditary aspects of HAE were noticed by William Osler, who in 1888 described a family with an autosomal dominant inheritance pattern [16]. It was not until 1963, however, that the pathophysiological background was clarified, when Virginia Donaldson and Richard Evans discovered the lack of C1 inhibitor (C1INH) in patients with HAE [17]. These patients have heterozygous mutations in *SERPING1* encoding C1INH [18–20]. Almost 10 years later, an acquired form of C1INH deficiency (AAE) was identified [21]. AAE is highly associated with lymphoproliferative disorders and, less frequently, other malignancies or autoimmune or infectious diseases [22–24].

Since 2000, a new subtype of HAE has been reported as an oestrogen-dependent inherited form of angio-oedema with normal C1INH [25, 26]. HAE with normal C1INH, formerly known as HAE type III, was initially documented only in women; however, it was later also reported in males [27]. In 2006, it was revealed that some of these families had mutations in the *F12* gene encoding Hageman factor [28], and more recently mutations in the gene encoding angiopoietin-1 (*ANGPT1*) and the gene encoding plasminogen (*PLG*) have also been documented [29–34]. This means that HAE with normal C1INH does not have a single underlying cause. The majority of patients with HAE and normal C1INH have no known disease-causing variants and therefore lack specific diagnostic markers besides the clinical features. These patients have been classified as HAE of unknown origin. The prevalence of HAE with normal C1INH is hitherto unknown.

Based on current insights into genetic and pathophysiological aspects of the disease, new therapies have been developed and introduced in clinical practice for HAE with C1INH deficiency within the last decade, and additional new drugs are on the horizon [35, 36]. Several investigational drugs, such as small synthetic molecules, oligonucleotides, or antibodies, which work by inhibiting Factor XII or kallikrein, are undergoing clinical trials. Other patient groups, especially patients with HAE and normal C1INH, might also benefit from these drugs. After being diagnosed, patients should be offered relevant therapy to reduce morbidity and prevent mortality.

Fig. 1. Swelling of the upper lip in a patient with hereditary angio-oedema.

Clinical Presentation

Clinically, HAE is characterised by recurrent self-limiting episodes of localised oedema. Patients with HAE and C1INH deficiency often already develop symptoms in childhood with more severe and frequent attacks during puberty. Patients with an early symptom onset tend to have a more severe outcome [37, 38]. The majority of patients will present before the age of 20 years, while only approximately 4% of patients experience their first attack after the age of 40 years [39]. The disease is, however, life-long and there is a growing number of affected individuals aged ≥ 65 years. In the individual patient, the course of HAE can vary in severity at different stages of life. The symptoms include skin swellings (Fig. 1), abdominal pain attacks, and laryngeal oedema in a ratio of approximately 70:54:1 based on a former German study of almost 50,000 attacks [8]. Attacks are often recurrent and, in many cases, unpredictable. Swelling of the skin causes temporary disability, whereas oedema of the bowel wall can result in bowel occlusion with pain, vomiting, or diarrhoea. Historically, one-third of patients with abdominal attacks received unnecessary surgery and other patients became dependent on morphine [10, 12, 39, 40]. The most serious manifestation is laryngeal oedema, which occurs at least once in a lifetime for 50% of patients and can cause asphyxiation [12, 13, 41]. Undiagnosed patients in particular have an increased risk of asphyxiation [10]. Typically, the oedema develops gradually over several hours, peaks after 12–36 h, and subsides after 2–5 days if it is not fatal. The abdominal attacks might, however, have a sudden onset, and acute airway obstruction has also been de-

Fig. 2. Erythema marginatum in an adult (a) and new-born (b) with hereditary angio-oedema.

Table 1. Diagnostic criteria of different subtypes of bradykinin-mediated angio-oedema

	Urticaria	Family history of angio-oedema	Treatment response to high-dose anti-histamines, corticosteroids, or adrenaline	C4	C1INH antigen	C1INH function	C1q	Mutation
Hereditary angio-oedema type I	No	Yes ^a	No	↓	↓	↓	Normal	<i>SERPING1</i> ^b
Hereditary angio-oedema type II	No	Yes ^a	No	↓	Normal or ↑	↓	Normal	<i>SERPING1</i> ^b
Hereditary angio-oedema with normal C1INH ^c	No	Yes	No	Normal	Normal	Normal	Normal	<i>F12</i> <i>ANGP1</i> <i>PLG</i> Unknown
Acquired C1INH deficiency	No	No	No	↓	Normal or ↓	↓	↓	None
Drug-induced angio-oedema ^d	No	No	No	Normal	Normal	Normal	Normal	None

^a 25% may have de novo mutations and no family history. ^b In <5% of patients no mutation can be detected. ^c A positive family history of angio-oedema or mutation in *F12*, *ANGP1*, or *PLG* is required for diagnosis. ^d Especially angio-oedema induced by angiotensin-converting enzyme inhibitor.

scribed within a very short time frame, e.g., after tooth extraction [42, 43]. The frequency of attacks is highly individual and varies from virtually never to more than one attack weekly [12, 37, 44, 45]. Disease severity might vary significantly between affected family members, despite them carrying the same mutation. In general, women are more severely affected than men [37, 46, 47].

HAE with normal C1INH typically develops later in life, usually around 20–30 years of age. In this patient group, there might be a preponderance of facial, tongue, and upper airway swellings compared to abdominal and peripheral attacks [9]. It is important to diagnose patients based on specific criteria as shown in Table 1 [48–51]. Since this

is an oestrogen-sensitive variant of HAE, it is mostly seen in women experiencing more frequent or severe attacks when exposed to endogenous or exogenous oestrogen. However, it is important not to designate ill-defined cases of angio-oedema as HAE with normal C1INH.

Prodromal Symptoms

Many attacks are preceded by prodromal symptoms, which can be a transient reticular rash (Fig. 2a), a feeling of tightness or tingling in the area where the attack will start, or more unspecific symptoms such as nausea, anxiety, nervousness, fatigue, muscle aches, or flu-like symptoms [52–55]. The reticular rash, which is also called ery-

thema marginatum, has been reported as early as the new-born period (Fig. 2b) and could be an early marker of HAE [56, 57]. These symptoms are supposed to be due to the release of vasoactive mediators from the postcapillary venules.

Provoking Factors

Many patients experience trigger factors for swelling attacks, and published studies suggest that up to half of the attacks are due to a provoking factor [14, 58–61]. Precipitation by trauma or mental stress is quite a distinctive feature of HAE and might be a clue to the diagnosis, although mental stress can also be a trigger factor for other types of angio-oedema. One of the most characteristic traumatic events preceding a life-threatening attack of angio-oedema is dental surgery or tonsillectomy. A 14-year-old Danish boy died of asphyxiation 12 h after an uncomplicated outpatient tonsillectomy [56]. Trauma might activate the contact system producing bradykinin, and angio-oedema characteristically starts in the traumatised area. The psychoneuro-immunological connections in this disease are well known, hence the former name hereditary angioneurotic oedema [16, 62]. Mental stress can activate plasma coagulation and fibrinolysis partly related to adrenergic mechanisms or through the production of HSP-90 [63–65]. Oestrogen is clearly also a provoking factor and swelling attacks can be precipitated by oestrogens in oral contraceptives, pregnancy, or substitution therapy during menopause [66]. It is self-evident that patients with HAE should not be treated with ACEIs, which inhibit the degradation of bradykinin [67, 68]. Caution should be taken when prescribing gliptins, neprilysin, and mTOR inhibitors [2, 5, 69, 70]. Furthermore, infections, e.g., *Helicobacter pylori*, might precipitate angio-oedema attacks [56, 71]. In a multicentre study, the total number of abdominal attacks decreased significantly after *H. pylori* eradication [72].

Pathophysiology and Molecular Genetic Background

Swellings in HAE are mediated by bradykinin, and patients have an increased activity of the contact system, which is closely connected to the coagulation, fibrinolysis, and complement systems [38, 64, 73–75]. Mutations in *ANGPT1* might have a direct effect on vascular permeability [76, 77]. Under normal circumstances, these systems are clinically silent but unstable. During HAE attacks, these plasma proteolytic cascades are activated, and an excessive amount of bradykinin is produced and binds

to the bradykinin B2 receptor (BK2R) on endothelial cells, causing vasodilatation and increased vascular permeability [78, 79]. Bradykinin is generated through the activation of the contact system when plasma kallikrein cleaves high-molecular-weight kininogen [2, 64]. In HAE type I, both antigenic and functional C1INH are markedly reduced, whereas in HAE type II, patients have normal levels of C1INH but the protein is dysfunctional (Table 1). HAE type II is less common and constitutes around 10% of HAE with C1INH deficiency [6, 56]. The clinical presentation of HAE type I and II is identical. In classic HAE with C1INH deficiency, more than 95% of patients have a mutation in *SERPING1* which encodes C1INH [20, 80]. *SERPING1* is an unstable gene due to a high incidence of Alu repeat sequences and CpG sites [20]. More than 500 mutations in the *SERPING1* gene have been identified to date [81]. In patients with HAE and C1INH deficiency, a lack of mutations in *SERPING1* might be due to a lack of analytical sensitivity, mutations in genes outside the coding regions, regulatory genes, or epigenetic factors. A minority of patients with HAE and normal C1INH has mutations in *F12*, *ANGPT1*, or *PLG*; however, the molecular genetic background is unknown among the rest [28, 51, 77].

Diagnostics

Patients are diagnosed based on a personal and often also family history of angio-oedema not responding to traditional anti-allergic therapy in addition to laboratory testing (Table 1). There is a high incidence of de novo mutations seen in approximately 25% of cases, and these patients will not have a family history [56]. A diagnosis of HAE type I and II is based on the measurement of C1INH protein and function. Complement C4 is often measured as an additional test or can be used as a screening test. C4 is low in symptomatic HAE patients and in approximately 95% of patients between attacks [82–85]. In our centre, we find it rational to screen for C4, C1INH protein concentration, and C1INH function at the same time. Blood samples should be handled with care, since decay of functional C1INH can produce ambiguous results [39, 86], and low values should be repeated to confirm the diagnosis [82]. The measurement of complement C1q differentiates HAE from AAE, since C1q is typically decreased in the latter [87, 88]. In equivocal cases, especially children or older adults, to distinguish HAE from AAE, it might also be useful to perform mutational testing in the *SERPING1* gene. One has to be aware, however, that a negative

result cannot exclude a diagnosis of HAE [19, 48]. In doubtful cases it is advisable to discuss or refer patients to the local expert centre for HAE.

HAE with normal C1INH is a more challenging diagnosis and relies on the clinical phenotype and family history, a lack of response to anti-allergic medications, and eventually a treatment response to HAE medications. There is no confirmatory biochemical test; however, genetic testing of *F12*, *PLG*, and *ANGPT1* might show disease-causing variants in a minority of patients [2].

Differential Diagnoses

HAE should be differentiated from the more common idiopathic angio-oedema or angio-oedema related to foods, drugs, insect venoms, or physical factors, where angio-oedema is typically associated with urticaria [89–94]. These subtypes usually respond to treatment with antihistamines, corticosteroids, or eventually adrenaline. Aspirin and other non-steroidal anti-inflammatory drugs can induce angio-oedema through their ability to inhibit cyclooxygenase favouring leukotriene production [92]. Drug-induced angio-oedema related to ACEIs, gliptins, neprilysin, and mTOR inhibitors seems to be bradykinin mediated and is normally not accompanied by urticaria [2, 5, 68–70, 95]. Abdominal attacks are very painful and might mimic acute abdomen with a risk of surgery being performed [96]. In patients with associated urticaria, the angio-oedematous lesions can be the result of an autoimmune process [97, 98]. Angio-oedema can be mistaken for anaphylaxis and vice versa, since laryngeal angio-oedema is one of the most severe manifestations of anaphylaxis [99].

Swelling-like disorders, so called pseudoangio-oedema, can mimic some aspects of angio-oedema: acute contact dermatitis, factitious disorder, acute dystonia, orofacial granulomatosis, vena cava superior syndrome, dermatomyositis, morbus Morbihan, cellulitis, orthostatic oedema, urticarial vasculitis, autoinflammatory diseases, etc. [91, 92, 100–103].

Therapies

The management of HAE patients consists of primary prevention as well as the treatment of acute attacks, and in some cases, short- or long-term prophylaxis [38, 48, 104, 105]. Patients need to be informed about their disease, especially about emergency situations. It is im-

portant that they are supplied with on-demand medication and a multilingual information card with treatment guidelines. The first evidence-based recommendations for the therapeutic management of HAE were published by the Hereditary Angio-Oedema International Working Group (HAWK) in 2012, recommending a more proactive, patient-centred approach towards HAE treatment [106]. The subsequent World Allergy Organization (WAO) guideline added evidence-based grades and strength of evidence [104, 105]. Until now, drugs have been licensed only for HAE with C1INH deficiency, and use in AAE and HAE with normal C1INH is off-label.

Primary Prevention

Potentially treatable triggers of attacks should be sought out and dealt with. Patients and their general practitioners should be advised that infections should be treated promptly, including the eradication of *H. pylori*. ACEIs and oestrogen-containing drugs should not be prescribed. Trauma should be avoided and risk procedures such as dental extractions and surgical risk procedures should be undertaken only with adequate prophylactic measures [107, 108].

Treatment of Acute Attacks: On-Demand Therapy

Four different types of drugs have shown effectiveness and safety in double-blind and observational studies in HAE patients: plasma-derived C1INH concentrates (trade names Berinert® and Cinryze®), recombinant C1INH concentrate (conestat alfa with trade name Ruconest®), a kallikrein inhibitor (ecallantide with trade name Kalbitor®) launched in the USA, and a competitive BK2R inhibitor (icatibant with trade name Firazyr®) [39, 109]. These drugs have been marketed for approximately 10 years and Berinert® has been available with special permission in many countries for approximately 40 years [56]. C1INH concentrates are administered intravenously, whereas ecallantide and icatibant are given subcutaneously.

C1INH concentrates and icatibant are safe drugs with a low risk of serious adverse effects. Thromboembolic events have rarely been reported in association with plasma-derived C1INH concentrates and seem to occur in patients with underlying risk factors including indwelling catheters [110–112]. Ruconest® was associated with anaphylaxis in a single volunteer allergic to rabbit; however, no further anaphylaxis has been reported in clinical use [113]. Icatibant is associated with frequent injection site reactions.

With proper training, patients could have the option to self-administer on-demand therapy, except for ecalantide, which might cause anaphylactoid reactions [44]. For children and pregnant and lactating women, plasma-derived C1INH concentrate has the best evidence of safety [114]. Icatibant has recently become available for children from the age of 2 years.

Milder attacks, such as peripheral oedema, and less severe abdominal attacks might respond to tranexamic acid 1,000 mg every 3–4 h for 12–18 h [56]. The efficacy of this treatment is, however, sparse, and the therapy is not recommended in the international WAO/EAACI guideline [105]. In patients with AAE and HAE with normal C1INH, however, it can be a better treatment solution.

Long-Term Prophylaxis

The goal of long-term prophylaxis (LTP) is to decrease the frequency and severity of attacks. LTP is indicated in patients not sufficiently controlled with on-demand therapy. Attenuated androgens, antifibrinolytics, and C1INH concentrates have all proved their efficacy in LTP in controlled clinical trials against placebos in patients with HAE and C1INH deficiency [56, 115].

Attenuated androgens, especially danazol, are effective at preventing attacks. They have been the cornerstone of LTP in HAE for many years and can control the symptoms in more than 90% of patients [56, 116, 117]. They work by inducing the synthesis of C1INH in the liver [118]. In many countries, these drugs are used off-label. Potential adverse effects include liver dysfunction and tumours, hematuria, myopathy, hypertension, headache, mood changes, hyperlipidaemia, and virilisation of women [56, 104, 116]. Attenuated androgens must not be used in pregnancy and lactation and they are not recommended for children until growth is complete. Attenuated androgens should only be prescribed by physicians with knowledge of the side-effect profile and patients should be monitored with abdominal ultrasound, blood samples, urine analysis, and blood pressure and weight measurements. Furthermore, the dosage should be titrated down to the lowest effective dose.

Antifibrinolytics, especially tranexamic acid, have been used for many years and might be somewhat effective in up to one-third of patients [35, 56, 119, 120]. These drugs inhibit plasminogen activation and consequently reduce C1INH usage. Antifibrinolytics may be considered for patients unsuitable or intolerant of androgens and who are not candidates for LTP with C1INH concentrate.

LTP with C1INH concentrate (CSL830 or *Cinryze*®) is a very safe and effective approach [110, 111, 121, 122]. An open-label multicentre study in 146 subjects for almost 3 years documented a 93.7% reduction in attack frequency in patients treated with *Cinryze*® 1,000 units every 3–7 days [111]. Low-volume plasma-derived C1INH concentrate (CSL830 with trade name *Haegarda*®) for subcutaneous administration has been licensed in the USA and is a patient-friendly approach [35]. The dose requirements (3,000–6,000 IU twice weekly) are higher than in intravenous administration.

Lanadelumab (*Takzyhro*®), a monoclonal antibody inhibiting plasma kallikrein, was approved by the FDA (American Food and Drug Administration) and EMA (European Medicines Agency) in 2018. It should be used for LTP with an injection of 300 mg every 2 weeks in HAE patients 12 years of age and older [123, 124]. Progestins have also been used to reduce the number of HAE attacks [35, 125].

Short-Term Prophylaxis

The goal of short-term prophylaxis (STP) is to prevent attacks of angio-oedema in patients with planned invasive medical and surgical procedures or other events likely to trigger an attack [104, 107, 126]. Consensus guidelines recommend 500–1,500 units or 10–20 units/kg plasma-derived C1INH concentrate infused 1–6 h before any high-risk procedure [104, 107, 108]. Danazol can also be used for STP [56, 127]. Despite STP, all patients should have rapid access to acute treatment and airway control in the event of an attack. In addition, patients should be warned of the increased risk of an attack up to 3 days following invasive procedures.

HAE with Normal C1INH

Treatment experiences are still limited; however, case reports and studies suggest that C1INH concentrates, icatibant, and ecalantide might be beneficial for acute attacks while progestins, danazol, and tranexamic acid can be used for prophylaxis [25, 30, 32, 51, 75, 128–133].

Future Therapies

Multiple new therapies are being investigated for the treatment of HAE: oral small molecule plasma kallikrein inhibitors (BCX7353, ATN-249, and KVD818), RNA-targeted antisense against prekallikrein (IONIS-PKKRx), RNA interference drugs against Factor XII (ALN-F12 and ARC-F12), and a Factor XIIa antagonist monoclonal antibody (CSL 312) are currently being investigated [35, 36, 134]. It is possible in the future that gene therapy with

gene-editing techniques or viral vector-based gene transfer might also be an option with curative potential [135, 136].

Burden of HAE

The episodic nature of the disorder, lack of awareness among health care personnel, and limited drug availability have contributed to under-diagnosis and under-treatment of HAE. HAE patients might have immediate and long-term effects on their health-related quality of life (HR-QoL), defined as the impact a disease has on a patient's physical, mental, and social well-being. The term "burden of illness" typically refers more broadly to both the humanistic and economic impact (emergency room visits, procedures, hospitalisations, etc.) associated with a condition and its treatment. Many patients have anxiety and depression as important comorbidities [137–139]. In a web-based survey conducted in the USA before approval of the new acute treatment modalities, the economic burden of HAE was assessed based on direct treatment costs of acute attacks and routine care, as well as indirect costs, such as travel, child care, missed work, and reduced productivity. Prior to the introduction of acute treatments, US data indicated that 45% of patients presenting to health care facilities with HAE were hospitalised [140]. The average annual direct and indirect costs per patient were estimated to be USD 42,000, ranging from USD 14,000 to 96,000 [141]. The use of prophylactic C1INH concentrate was calculated to cost USD 350,000 per patient per year [142]. In addition, economic data from Europe are available, e.g., a Polish analysis of hospital-based C1INH treatment which reported the quality-adjusted life-year cost to be EUR 15,226 for recombinant C1INH and EUR 27,786 for plasma-derived C1INH concentrate [143].

Hospital costs are minimised by self-administration programmes [44, 144]. A Spanish group estimated that self-administration of icatibant in Spain could save up to EUR 2.3 million annually in direct and indirect costs compared to hospital treatment [145].

The burden of HAE was studied in a cross-sectional multicentre study in Europe: Hereditary Angio-oedema Burden of Illness Study in Europe (HAE-BOIS-Europe) [146]. Qualitative interviews were carried out to assess the real-world experiences of HAE from the patient perspective. Based on the interviews, a conceptual model (Fig. 3) was developed illustrating the hypothesised worry and work/activity interruption during attacks [147].

Patients might experience unnecessary medical procedures due to diagnostic delays and anxiety/fear about at-

tacks and passing HAE onto children. Reduced work/school productivity and limited career/educational achievement are seen. In addition, caregivers and relatives experience worry and work/activity interruption during the attacks. Health status utility weights were calculated using data from the HAE-BOIS-Europe. Utility measures quantitatively describe the net impact of a disease on the patient's life with a score of 0.0 reflecting death and a score of 1.0 reflecting full health [148]. The mean utility for an HAE attack and the period between attacks was 0.44 and 0.72, respectively. For comparison, the mean utility of an acute HAE attack is comparable to that of ischemic heart disease or renal failure on haemodialysis. The mean utility between attacks is comparable to ankylosing spondylitis.

An angio-oedema-specific, validated QoL questionnaire has been developed in Germany to be used in patients with recurrent angio-oedema [149]. The AE-QoL has a 4-dimensional structure (functioning, fatigue/mood, fears/shame, and food) and a total score. The HAE-QoL is a disease-specific QoL questionnaire recently introduced to specifically assess HR-QoL in HAE patients [150, 151].

The availability of the new therapies and the concept of home therapy for acute attacks have greatly improved patients' QoL [44, 152, 153]. Using new HAE-specific drugs prophylactically, or at the earliest symptoms, might nearly normalise the lives of HAE patients.

The high costs of these drugs might be counterbalanced by lower rates of health service use, reduced HAE-associated morbidity and mortality, and improved QoL. National and international patient networks (www.haei.org) have been established and could support patients and collaborate with health care professionals.

Discussion and Future Considerations

Among patients with primary angio-oedema without explanation, HAE with and without C1INH deficiency should be considered and further investigations performed in collaboration with HAE specialists. It is of utmost importance for HAE patients to receive the correct diagnosis and have access to effective therapy in due time. Inequities, however, exist among countries, and many patients still might not have access to appropriate therapies [142]. The disease-related mortality can be reduced or at best eliminated, if adequate treatment and information are given to the patient after diagnosis. It is recommended that patients are followed by an expert centre and that

Fig. 3. Burden of illness in hereditary angio-oedema: conceptual model. Reproduced with permission from Bygum et al. [152]. ADL, activities of daily living; HAE, hereditary angio-oedema.

new and expensive therapies are tailored to the individual patient. In the near future, more therapies with novel mechanisms and simplified dosing regimens will be available for HAE patients, and physicians can optimise the treatment even more to improve the disease burden.

Key Message

Physicians treating angio-oedema should be familiar with bradykinin-mediated angio-oedema and be able to recognise hereditary angio-oedema.

References

- Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, et al.; Endorsed by the following societies: AAAAI, AAD, AAIITO, ACAAI, AEDV, APAAACI, ASBAI, ASCIA, BAD, BSACI, CDA, CMICA, CSACI, DDG, DDS, DGAKI, DSA, DST, EAACI, EIAS, EDF, EMBRN, ESCD, GA²LEN, IAACI, IADVL, JDA, NVvA, MSAI, ÖGDV, PSA, RAACI, SBD, SFD, SGAI, SGDv, SIAAIC, SDeMaST, SPDV, TSD, UNBB, UNEV and WAO. The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018 Jul;73(7):1393–414.
- Cicardi M, Zuraw BL. Angioedema due to bradykinin dysregulation. *J Allergy Clin Immunol Pract*. 2018 Jul - Aug;6(4):1132–41.
- Aygören-Pürsün E, Magerl M, Maetzel A, Maurer M. Epidemiology of Bradykinin-mediated angioedema: a systematic investigation of epidemiological studies. *Orphanet J Rare Dis*. 2018 May;13(1):73.
- Stone C Jr, Brown NJ. Angiotensin-converting enzyme inhibitor and other drug-associated angioedema. *Immunol Allergy Clin North Am*. 2017 Aug;37(3):483–95.
- Hudey SN, Westermann-Clark E, Lockey RF. Cardiovascular and diabetic medications that cause bradykinin-mediated angioedema. *J Allergy Clin Immunol Pract*. 2017 May - Jun;5(3):610–5.
- Bygum A. Hereditary angio-oedema in Denmark: a nationwide survey. *Br J Dermatol*. 2009 Nov;161(5):1153–8.
- Quincke H. Über akutes umschriebenes hautödem. *Monatsh Prakt Dermatol*. 1882;1:129–31.
- Bork K, Ressel N. Sudden upper airway obstruction in patients with hereditary angioedema. *Transfus Apheresis Sci*. 2003 Dec;29(3):235–8.
- Bork K, Gül D, Hardt J, Dewald G. Hereditary angioedema with normal C1 inhibitor: clinical symptoms and course. *Am J Med*. 2007 Nov;120(11):987–92.
- Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol*. 2012 Sep;130(3):692–7.
- Honda D, Ohsawa I, Shimizu Y, Maiguma M, Hidaka T, Suzuki H, et al. Suffocation due to acute airway edema in a patient with hereditary angioedema highlighted the need for urgent improvements in treatment availability in Japan. *Intern Med*. 2018 Nov;57(21):3193–7.
- Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)*. 1992 Jul;71(4):206–15.
- Bork K, Siedlecki K, Bosch S, Schopf RE, Kreuz W. Asphyxiation by laryngeal edema in patients with hereditary angioedema. *Mayo Clin Proc*. 2000 Apr;75(4):349–54.
- Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med*. 1976 May;84(5):580–93.
- Landerman NS. Hereditary angioneurotic edema. I. Case reports and review of the literature. *J Allergy*. 1962 Jul-Aug;33(4):316–29.
- Osler W. Landmark publication from The American Journal of the Medical Sciences: Hereditary angio-neurotic oedema. 1888. *Am J Med Sci*. 2010 Feb;339(2):175–8.
- Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C1-esterase. *Am J Med*. 1963 Jul;35:37–44.
- Bock SC, Skriver K, Nielsen E, Thøgersen HC, Wiman B, Donaldson VH, et al. Human C1 inhibitor: primary structure, cDNA cloning, and chromosomal localization. *Biochemistry*. 1986 Jul;25(15):4292–301.
- Bygum A, Fagerberg CR, Ponard D, Monnier N, Lunardi J, Drouet C. Mutational spectrum and phenotypes in Danish families with hereditary angioedema because of C1 inhibitor deficiency. *Allergy*. 2011 Jan;66(1):76–84.
- Loules G, Zamanakou M, Parsopoulou F, Vatsiou S, Psarros F, Csuka D, et al. Targeted next-generation sequencing for the molecular diagnosis of hereditary angioedema due to C1-inhibitor deficiency. *Gene*. 2018 Aug;667:76–82.
- Caldwell JR, Ruddy S, Schur PH, Austen KF. Acquired C1 inhibitor deficiency in lymphosarcoma. *Clin Immunol Immunopathol*. 1972;1(1):39–52.
- Zingale LC, Castelli R, Zanichelli A, Cicardi M. Acquired deficiency of the inhibitor of the first complement component: presentation, diagnosis, course, and conventional management. *Immunol Allergy Clin North Am*. 2006 Nov;26(4):669–90.
- Bygum A, Vestergaard H. Acquired angioedema—occurrence, clinical features and associated disorders in a Danish nationwide patient cohort. *Int Arch Allergy Immunol*. 2013;162(2):149–55.
- Zanichelli A, Azin GM, Wu MA, Suffritti C, Maggioni L, Caccia S, et al. Diagnosis, course, and management of angioedema in patients with acquired C1-inhibitor deficiency. *J Allergy Clin Immunol Pract*. 2017 Sep - Oct;5(5):1307–13.
- Bork K, Barnstedt SE, Koch P, Traupe H. Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet*. 2000 Jul;356(9225):213–7.
- Binkley KE, Davis A 3rd. Clinical, biochemical, and genetic characterization of a novel estrogen-dependent inherited form of angioedema. *J Allergy Clin Immunol*. 2000 Sep;106(3):546–50.
- Bork K, Gül D, Dewald G. Hereditary angioedema with normal C1 inhibitor in a family with affected women and men. *Br J Dermatol*. 2006 Mar;154(3):542–5.
- Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun*. 2006 May;343(4):1286–9.

Statement of Ethics

The author has no ethical conflicts to disclose.

Disclosure Statement

Anette Bygum has been involved in clinical research and educational events involving CSL-Behring, Dyax, BioCryst, and Shire/Takeda. No funding was given for this study.

- 29 Bafunno V, Firinu D, D'Apolito M, Cordisco G, Loffredo S, Leccese A, et al. Mutation of the angiotensin-converting enzyme 1 gene (ANGPT1) associates with a new type of hereditary angioedema. *J Allergy Clin Immunol*. 2018 Mar;141(3):1009–17.
- 30 Bork K, Wulff K, Steinmüller-Magin L, Braenne I, Staubach-Renz P, Witzke G, et al. Hereditary angioedema with a mutation in the plasminogen gene. *Allergy*. 2018 Feb;73(2):442–50.
- 31 Dewald G. A missense mutation in the plasminogen gene, within the plasminogen kringle 3 domain, in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun*. 2018 Mar;498(1):193–8.
- 32 Belbézier A, Hardy G, Marlu R, Defendi F, Dumestre Perard C, Boccon-Gibod I, et al. Plasminogen gene mutation with normal C1 inhibitor hereditary angioedema: three additional French families. *Allergy*. 2018 Nov;73(11):2237–9.
- 33 Yakushiji H, Hashimura C, Fukuoka K, Kaji A, Miyahara H, Kaname S, et al. A missense mutation of the plasminogen gene in hereditary angioedema with normal C1 inhibitor in Japan. *Allergy*. 2018 Nov;73(11):2244–7.
- 34 Firinu D, Loffredo S, Bova M, Cicardi M, Margaglione M, Del Giacco S. The role of genetics in the current diagnostic workup of idiopathic non-histaminergic angioedema. *Allergy*. 2019 Apr;74(4):810–2.
- 35 Farkas H, Debrezeni ML, Kóhalmi KV. Investigational drugs in phase I and phase II clinical trials for hereditary angioedema. *Expert Opin Investig Drugs*. 2018 Jan;27(1):87–103.
- 36 Chen M, Riedl MA. Emerging therapies in hereditary angioedema. *Immunol Allergy Clin North Am*. 2017 Aug;37(3):585–95.
- 37 Bork K, Meng G, Staubach P, Hardt J. Hereditary angioedema: new findings concerning symptoms, affected organs, and course. *Am J Med*. 2006 Mar;119(3):267–74.
- 38 Zuraw BL. Clinical practice. Hereditary angioedema. *N Engl J Med*. 2008 Sep;359(10):1027–36.
- 39 Henao MP, Kraschnewski JL, Kelbel T, Craig TJ. Diagnosis and screening of patients with hereditary angioedema in primary care. *Ther Clin Risk Manag*. 2016 May;12:701–11.
- 40 Craig T, Riedl M, Dykewicz MS, Gower RG, Baker J, Edelman FJ, et al. When is prophylaxis for hereditary angioedema necessary? *Ann Allergy Asthma Immunol*. 2009 May;102(5):366–72.
- 41 Zanichelli A, Arcoleo F, Barca MP, Borrelli P, Bova M, Cancian M, et al. A nationwide survey of hereditary angioedema due to C1 inhibitor deficiency in Italy. *Orphanet J Rare Dis*. 2015 Feb;10(1):11.
- 42 Bork K, Hardt J. Hereditary angioedema: long-term treatment with one or more injections of C1 inhibitor concentrate per week. *Int Arch Allergy Immunol*. 2011;154(1):81–8.
- 43 Degroote DF, Smith GL, Huttula GS. Acute airway obstruction following tooth extraction in hereditary angioedema. *J Oral Maxillofac Surg*. 1985 Jan;43(1):52–4.
- 44 Bygum A. Hereditary angioedema - consequences of a new treatment paradigm in Denmark. *Acta Derm Venereol*. 2014 Jul;94(4):436–41.
- 45 Zanichelli A, Vacchini R, Badini M, Penna V, Cicardi M. Standard care impact on angioedema because of hereditary C1 inhibitor deficiency: a 21-month prospective study in a cohort of 103 patients. *Allergy*. 2011 Feb;66(2):192–6.
- 46 Kreiberg KB, Bygum A. Reporting through smartphone application results in detailed data on acquired and hereditary angioedema attacks. *Allergy*. 2019 Mar;all.13792.
- 47 Steiner UC, Weber-Chrysochoou C, Helbling A, Scherer K, Grendelmeier PS, Wuillemin WA. Hereditary angioedema due to C1 - inhibitor deficiency in Switzerland: clinical characteristics and therapeutic modalities within a cohort study. *Orphanet J Rare Dis*. 2016 Apr;11(1):43.
- 48 Cicardi M, Aberer W, Banerji A, Bas M, Bernstein JA, Bork K, et al.; HAWK under the patronage of EAACI (European Academy of Allergy and Clinical Immunology). Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014 May;69(5):602–16.
- 49 Fernando SL. The nebulous diagnosis of type III hereditary angioedema. *Ann Allergy Asthma Immunol*. 2013 Jul;111(1):65–6.
- 50 Kaplan A. Type III hereditary angioedema: defined, but not understood. *Ann Allergy Asthma Immunol*. 2012 Sep;109(3):153–4.
- 51 Zuraw BL, Bork K, Binkley KE, Banerji A, Christiansen SC, Castaldo A, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. *Allergy Asthma Proc*. 2012 Nov-Dec;33(6 Suppl 1):S145–56.
- 52 Caballero T, Maurer M, Longhurst HJ, Aberer W, Bouillet L, Fabien V; IOS Study Group. Triggers and prodromal symptoms of angioedema attacks in patients with hereditary angioedema. *J Investig Allergol Clin Immunol*. 2016;26(6):383–6.
- 53 Magerl M, Doumoulakis G, Kalkounou I, Weller K, Church MK, Kreuz W, et al. Characterization of prodromal symptoms in a large population of patients with hereditary angio-oedema. *Clin Exp Dermatol*. 2014 Apr;39(3):298–303.
- 54 Reshef A, Prematta MJ, Craig TJ. Signs and symptoms preceding acute attacks of hereditary angioedema: results of three recent surveys. *Allergy Asthma Proc*. 2013 May-Jun;34(3):261–6.
- 55 Prematta MJ, Bewtra AK, Levy RJ, Wasserman RL, Jacobson KW, Machnig T, et al. Per-attack reporting of prodromal symptoms concurrent with C1-inhibitor treatment of hereditary angioedema attacks. *Adv Ther*. 2012 Oct;29(10):913–22.
- 56 Bygum A. Hereditary and acquired angioedema in Denmark. *Forum Nord Derm Venereol*. 2014; Suppl 17:1–73.
- 57 Martinez-Saguer I, Farkas H. Erythema marginatum as an early symptom of hereditary angioedema: case report of 2 newborns. *Pediatrics*. 2016 Feb;137(2):e20152411.
- 58 Winnewisser J, Rossi M, Späth P, Bürgi H. Type I hereditary angio-oedema. Variability of clinical presentation and course within two large kindreds. *J Intern Med*. 1997 Jan;241(1):39–46.
- 59 Agostoni A, Aygören-Pürsün E, Binkley KE, Blanch A, Bork K, Bouillet L, et al. Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol*. 2004 Sep;114(3 Suppl):S51–131.
- 60 Donaldson VH, Rosen FS. Hereditary angio-neurotic edema: a clinical survey. *Pediatrics*. 1966 Jun;37(6):1017–27.
- 61 Cicardi M, Bergamaschini L, Marasini B, Boc-cassini G, Tucci A, Agostoni A. Hereditary angioedema: an appraisal of 104 cases. *Am J Med Sci*. 1982 Jul-Aug;284(1):2–9.
- 62 Berger M. Why HAE? *Clin Immunol*. 2005 Jan;114(1):2.
- 63 Evers AW, Verhoeven EW, Kraaijaat FW, de Jong EM, de Brouwer SJ, Schalkwijk J, et al. How stress gets under the skin: cortisol and stress reactivity in psoriasis. *Br J Dermatol*. 2010 Nov;163(5):986–91.
- 64 Kaplan AP, Joseph K. The bradykinin-forming cascade and its role in hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010 Mar;104(3):193–204.
- 65 Jern C, Eriksson E, Tengborn L, Risberg B, Wadenvik H, Jern S. Changes of plasma coagulation and fibrinolysis in response to mental stress. *Thromb Haemost*. 1989 Sep;62(2):767–71.
- 66 Caballero T, Farkas H, Bouillet L, Bowen T, Gompel A, Fagerberg C, et al.; C-1-INH Deficiency Working Group. International consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency. *J Allergy Clin Immunol*. 2012 Feb;129(2):308–20.
- 67 Ricketti AJ, Cleri DJ, Ramos-Bonner LS, Vernaleo JR. Hereditary angioedema presenting in late middle age after angiotensin-converting enzyme inhibitor treatment. *Ann Allergy Asthma Immunol*. 2007 Apr;98(4):397–401.
- 68 Rasmussen ER, Mey K, Bygum A. Angiotensin-converting enzyme inhibitor-induced angioedema—a dangerous new epidemic. *Acta Derm Venereol*. 2014 May;94(3):260–4.

- 69 Andersen LK, Jensen JE, Bygum A. Second episode of near-fatal angioedema in a patient treated with everolimus. *Ann Allergy Asthma Immunol*. 2015 Aug;115(2):152–3.
- 70 Hermannrud T, Bygum A, Rasmussen ER. Recurrent angioedema associated with pharmacological inhibition of dipeptidyl peptidase IV. *BMJ Case Rep*. 2017 Jan;10:2017. <https://doi.org/10.1136/bcr-2016-217802>.
- 71 Farkas H, Füst G, Fekete B, Karádi I, Varga L. Eradication of *Helicobacter pylori* and improvement of hereditary angioneurotic oedema. *Lancet*. 2001 Nov;358(9294):1695–6.
- 72 Visy B, Füst G, Bygum A, Bork K, Longhurst H, Bucher C, et al. *Helicobacter pylori* infection as a triggering factor of attacks in patients with hereditary angioedema. *Helicobacter*. 2007 Jun;12(3):251–7.
- 73 Kaplan AP. Enzymatic pathways in the pathogenesis of hereditary angioedema: the role of C1 inhibitor therapy. *J Allergy Clin Immunol*. 2010 Nov;126(5):918–25.
- 74 Björkqvist J, de Maat S, Lewandrowski U, Di Gennaro A, Oschatz C, Schönig K, et al. Defective glycosylation of coagulation factor XII underlies hereditary angioedema type III. *J Clin Invest*. 2015 Aug;125(8):3132–46.
- 75 De Maat S, Hofman ZL, Maas C. Hereditary angioedema: the plasma contact system out of control. *J Thromb Haemost*. 2018 Sep;16(9):1674–85.
- 76 d'Apolito M, Santacroce R, Colia AL, Cordisio G, Maffione AB, Margaglione M. Angiotensin-converting enzyme deficiency affects the endothelial barrier and causes hereditary angioedema. *Clin Exp Allergy*. 2019 Jan; Epub ahead of print. <https://doi.org/10.1111/cea.13349>.
- 77 Zuraw BL. Hereditary angioedema with normal C1 inhibitor: four types and counting. *J Allergy Clin Immunol*. 2018 Mar;141(3):884–5.
- 78 Nussberger J, Cugno M, Cicardi M, Agostoni A. Local bradykinin generation in hereditary angioedema. *J Allergy Clin Immunol*. 1999 Dec;104(6):1321–2.
- 79 Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE 3rd. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest*. 2002 Apr;109(8):1057–63.
- 80 Speletas M, Szilagyi A, Psarros F, Moldovan D, Magerl M, Kompoti M, et al. Hereditary angioedema: molecular and clinical differences among European populations. *J Allergy Clin Immunol*. 2015 Feb;135(2):570–3.
- 81 Mete Gökmen N, Gülbahar O, Onay H, Peker Koc Z, Özgül S, Köse T, et al. Deletions in SERPING1 lead to lower C1 inhibitor function: lower C1 inhibitor function can predict disease severity. *Int Arch Allergy Immunol*. 2019;178(1):50–9.
- 82 Gompels MM, Lock RJ, Morgan JE, Osborne J, Brown A, Virgo PF. A multicentre evaluation of the diagnostic efficiency of serological investigations for C1 inhibitor deficiency. *J Clin Pathol*. 2002 Feb;55(2):145–7.
- 83 Karim Y, Griffiths H, Deacock S. Normal complement C4 values do not exclude hereditary angioedema. *J Clin Pathol*. 2004 Feb;57(2):213–4.
- 84 Tarzi MD, Hickey A, Förster T, Mohammadi M, Longhurst HJ. An evaluation of tests used for the diagnosis and monitoring of C1 inhibitor deficiency: normal serum C4 does not exclude hereditary angio-oedema. *Clin Exp Immunol*. 2007 Sep;149(3):513–6.
- 85 Aabom A, Bygum A, Koch C. Complement factor C4 activation in patients with hereditary angioedema. *Clin Biochem*. 2017 Oct;50(15):816–21.
- 86 Wagenaar-Bos IG, Drouet C, Aygören-Pürsun E, Bork K, Bucher C, Bygum A, et al. Functional C1-inhibitor diagnostics in hereditary angioedema: assay evaluation and recommendations. *J Immunol Methods*. 2008 Sep;338(1-2):14–20.
- 87 Grünewald T. Acquired C1 esterase inhibitor deficiency. *Ann Intern Med*. 2000 Nov;133(10):837.
- 88 Markovic SN, Inwards DJ, Frigas EA, Phyllyk RP. Acquired C1 esterase inhibitor deficiency. *Ann Intern Med*. 2000 Jan;132(2):144–50.
- 89 Cicardi M, Bergamaschini L, Zingale LC, Gioffré D, Agostoni A. Idiopathic nonhistaminergic angioedema. *Am J Med*. 1999 Jun;106(6):650–4.
- 90 Frigas E, Nzeako UC. Angioedema. Pathogenesis, differential diagnosis, and treatment. *Clin Rev Allergy Immunol*. 2002 Oct;23(2):217–31.
- 91 Grigoriadou S, Longhurst HJ. Clinical Immunology Review Series: an approach to the patient with angio-oedema. *Clin Exp Immunol*. 2009 Mar;155(3):367–77.
- 92 Kaplan AP, Greaves MW. Angioedema. *J Am Acad Dermatol*. 2005 Sep;53(3):373–88.
- 93 Rye Rasmussen EH, Bindslev-Jensen C, Bygum A. Angioedema—assessment and treatment. *Tidsskr Nor Lægeforen*. 2012 Nov;132(21):2391–5.
- 94 Zingale LC, Beltrami L, Zanichelli A, Maggioni L, Pappalardo E, Cicardi B, et al. Angioedema without urticaria: a large clinical survey. *CMAJ*. 2006 Oct;175(9):1065–70.
- 95 Sánchez-Borges M, González-Aveledo LA. Angiotensin-converting enzyme inhibitors and angioedema. *Allergy Asthma Immunol Res*. 2010 Jul;2(3):195–8.
- 96 Nzeako UC, Longhurst HJ. Many faces of angioedema: focus on the diagnosis and management of abdominal manifestations of hereditary angioedema. *Eur J Gastroenterol Hepatol*. 2012 Apr;24(4):353–61.
- 97 Radonjic-Hoesli S, Hofmeier KS, Micaletto S, Schmid-Grendelmeier P, Bircher A, Simon D. Urticaria and angioedema: an update on classification and pathogenesis. *Clin Rev Allergy Immunol*. 2018 Feb;54(1):88–101.
- 98 Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immunol*. 2017 Jun;139(6):1772–1781.e1.
- 99 Greenberger PA. Anaphylactic and anaphylactoid causes of angioedema. *Immunol Allergy Clin North Am*. 2006 Nov;26(4):753–67.
- 100 Andersen MF, Longhurst HJ, Rasmussen ER, Bygum A. How not to be misled by disorders mimicking angioedema: a review of pseudoangioedema. *Int Arch Allergy Immunol*. 2016;169(3):163–70.
- 101 Krause K, Grattan CE, Bindslev-Jensen C, Gattorno M, Kallinich T, de Koning HD, et al. How not to miss autoinflammatory diseases masquerading as urticaria. *Allergy*. 2012 Dec;67(12):1465–74.
- 102 Maurer M, Magerl M, Metz M, Siebenhaar F, Weller K, Krause K. Practical algorithm for diagnosing patients with recurrent wheals or angioedema. *Allergy*. 2013 Jun;68(6):816–9.
- 103 Rasmussen ER, Pallesen KA, Bygum A. Acute dystonia mimicking angioedema of the tongue: a video-illustrated case. *BMJ Case Rep*. 2013 Jul;8:2013. <https://doi.org/10.1136/bcr-2013-010205>.
- 104 Craig T, Aygören-Pürsün E, Bork K, Bowen T, Boysen H, Farkas H, et al. WAO guideline for the management of hereditary angioedema. *World Allergy Organ J*. 2012 Dec;5(12):182–99.
- 105 Maurer M, Magerl M, Ansotegui I, Aygören-Pürsün E, Betschel S, Bork K, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—The 2017 revision and update. *Allergy*. 2018 Aug;73(8):1575–96.
- 106 Cicardi M, Bork K, Caballero T, Craig T, Li HH, Longhurst H, et al.; HAWK (Hereditary Angioedema International Working Group). Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy*. 2012 Feb;67(2):147–57.
- 107 Farkas H, Zotter Z, Csuka D, Szabó E, Nébenführer Z, Temesszentandrás G, et al. Short-term prophylaxis in hereditary angioedema due to deficiency of the C1-inhibitor—a long-term survey. *Allergy*. 2012 Dec;67(12):1586–93.
- 108 Grant JA, White MV, Li HH, Fitts D, Kalfus IN, Uknis ME, et al. Preprocedural administration of nanofiltered C1 esterase inhibitor to prevent hereditary angioedema attacks. *Allergy Asthma Proc*. 2012 Jul-Aug;33(4):348–53.
- 109 Longhurst H. Optimum use of acute treatments for hereditary angioedema: evidence-based expert consensus. *Front Med (Lausanne)*. 2018 Mar;4:245.

- 110 Craig T, Shapiro R, Vegh A, Baker JW, Bernstein JA, Busse P, et al. Efficacy and safety of an intravenous C1-inhibitor concentrate for long-term prophylaxis in hereditary angioedema. *Allergy Rhinol (Providence)*. 2017 Mar;8(1):13–9.
- 111 Zuraw BL, Kalfus I. Safety and efficacy of prophylactic nanofiltered C1-inhibitor in hereditary angioedema. *Am J Med*. 2012 Sep;125(9):938.e1–7.
- 112 Crowther M, Bauer KA, Kaplan AP. The thrombogenicity of C1 esterase inhibitor (human): review of the evidence. *Allergy Asthma Proc*. 2014 Nov-Dec;35(6):444–53.
- 113 Hack CE, Relan A, Baboeram A, Oortwijn B, Versteeg S, van Ree R, et al. Immunosafety of recombinant human C1-inhibitor in hereditary angioedema: evaluation of ige antibodies. *Clin Drug Investig*. 2013 Apr;33(4):275–81.
- 114 Baker JW, Craig TJ, Riedl MA, Banerji A, Fitts D, Kalfus IN, et al. Nanofiltered C1 esterase inhibitor (human) for hereditary angioedema attacks in pregnant women. *Allergy Asthma Proc*. 2013 Mar-Apr;34(2):162–9.
- 115 Riedl MA, Grivcheva-Panovska V, Moldovan D, Baker J, Yang WH, Giannetti BM, et al. Recombinant human C1 esterase inhibitor for prophylaxis of hereditary angio-oedema: a phase 2, multicentre, randomised, double-blind, placebo-controlled crossover trial. *Lancet*. 2017 Sep;390(10102):1595–602.
- 116 Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. *Ann Allergy Asthma Immunol*. 2008 Feb;100(2):153–61.
- 117 Füst G, Farkas H, Csuka D, Varga L, Bork K. Long-term efficacy of danazol treatment in hereditary angioedema. *Eur J Clin Invest*. 2011 Mar;41(3):256–62.
- 118 Pappalardo E, Zingale LC, Cicardi M. Increased expression of C1-inhibitor mRNA in patients with hereditary angioedema treated with Danazol. *Immunol Lett*. 2003 May;86(3):271–6.
- 119 Cicardi M, Zingale L. How do we treat patients with hereditary angioedema. *Transfus Apheresis Sci*. 2003 Dec;29(3):221–7.
- 120 Farkas H. Pediatric hereditary angioedema due to C1-inhibitor deficiency. *Allergy Asthma Clin Immunol*. 2010 Jul;6(1):18.
- 121 Longhurst H, Cicardi M, Craig T, Bork K, Grattan C, Baker J, et al.; COMPACT Investigators. Prevention of hereditary angioedema attacks with a subcutaneous C1 inhibitor. *N Engl J Med*. 2017 Mar;376(12):1131–40.
- 122 Zuraw BL, Busse PJ, White M, Jacobs J, Lumry W, Baker J, et al. Nanofiltered C1 inhibitor concentrate for treatment of hereditary angioedema. *N Engl J Med*. 2010 Aug;363(6):513–22.
- 123 Banerji A, Riedl MA, Bernstein JA, Cicardi M, Longhurst HJ, Zuraw BL, et al.; HELP Investigators. Effect of lanadelumab compared with placebo on prevention of hereditary angioedema attacks: a randomized clinical trial. *JAMA*. 2018 Nov;320(20):2108–21.
- 124 Kaplon H, Reichert JM. Antibodies to watch in 2019. *MAbs*. 2019 Feb/Mar;11(2):219–38.
- 125 Saule C, Boccon-Gibod I, Fain O, Kanny G, Plu-Bureau G, Martin L, et al. Benefits of progestin contraception in non-allergic angioedema. *Clin Exp Allergy*. 2013 Apr;43(4):475–82.
- 126 Zuraw BL, Banerji A, Bernstein JA, Busse PJ, Christiansen SC, Davis-Lorton M, et al.; US Hereditary Angioedema Association Medical Advisory Board. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol Pract*. 2013 Sep-Oct;1(5):458–67.
- 127 Jurado-Palomo J, Muñoz-Caro JM, López-Serrano MC, Prior N, Cabañas R, Pedrosa M, et al. Management of dental-oral procedures in patients with hereditary angioedema due to C1 inhibitor deficiency. *J Invest Allergol Clin Immunol*. 2013;23(1):1–6.
- 128 Binkley KE. Factor XII mutations, estrogen-dependent inherited angioedema, and related conditions. *Allergy Asthma Clin Immunol*. 2010 Jul;6(1):16.
- 129 Bork K, Wulff K, Witzke G, Hardt J. Treatment for hereditary angioedema with normal C1-INH and specific mutations in the F12 gene (HAE-FXII). *Allergy*. 2017 Feb;72(2):320–4.
- 130 Bork K. Diagnosis and treatment of hereditary angioedema with normal C1 inhibitor. *Allergy Asthma Clin Immunol*. 2010 Jul;6(1):15.
- 131 Bork K, Wulff K, Hardt J, Witzke G, Staubach P. Hereditary angioedema caused by missense mutations in the factor XII gene: clinical features, trigger factors, and therapy. *J Allergy Clin Immunol*. 2009 Jul;124(1):129–34.
- 132 Piñero-Saavedra M, González-Quevedo T, Saenz de San Pedro B, Alcaraz C, Bobadilla-González P, Fernández-Vieira L, et al. Hereditary angioedema with F12 mutation: clinical features and enzyme polymorphisms in 9 Southwestern Spanish families. *Ann Allergy Asthma Immunol*. 2016 Nov;117(5):520–6.
- 133 Vitrat-Hincky V, Gompel A, Dumestre-Perrard C, Boccon-Gibod I, Drouet C, Cesbron JY, et al. Type III hereditary angio-oedema: clinical and biological features in a French cohort. *Allergy*. 2010 Oct;65(10):1331–6.
- 134 Bhattacharjee G, Revenko AS, Crosby JR, May C, Gao D, Zhao C, et al. Inhibition of vascular permeability by antisense-mediated inhibition of plasma kallikrein and coagulation factor 12. *Nucleic Acid Ther*. 2013 Jun;23(3):175–87.
- 135 Haslund D, Ryø LB, Seidelin Majidi S, Rose I, Skipper KA, Fryland T, et al. Dominant-negative SERPING1 variants cause intracellular retention of C1 inhibitor in hereditary angioedema. *J Clin Invest*. 2019 Jan;129(1):388–405.
- 136 Qiu T, Chiuchiolo MJ, Whaley AS, Russo AR, Sondhi D, Kaminsky SM, et al. Gene therapy for C1 esterase inhibitor deficiency in a Murine Model of Hereditary angioedema. *Allergy*. 2018 Jul; [Epub ahead of print].
- 137 Caballero T, Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, et al. The humanistic burden of hereditary angioedema: results from the Burden of Illness Study in Europe. *Allergy Asthma Proc*. 2014 Jan-Feb;35(1):47–53.
- 138 Fouche AS, Saunders EF, Craig T. Depression and anxiety in patients with hereditary angioedema. *Ann Allergy Asthma Immunol*. 2014 Apr;112(4):371–5.
- 139 Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc*. 2010 Sep-Oct;31(5):407–14.
- 140 Zilberberg MD, Jacobsen T, Tillotson G. The burden of hospitalizations and emergency department visits with hereditary angioedema and angioedema in the United States, 2007. *Allergy Asthma Proc*. 2010 Nov-Dec;31(6):511–9.
- 141 Wilson DA, Bork K, Shea EP, Rentz AM, Blaustein MB, Pullman WE. Economic costs associated with acute attacks and long-term management of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010 Apr;104(4):314–20.
- 142 Longhurst H, Bygum A. The humanistic, societal, and pharmaco-economic burden of angioedema. *Clin Rev Allergy Immunol*. 2016 Oct;51(2):230–9.
- 143 Kawalec P, Holko P, Paszulewicz A. Cost-utility analysis of Ruconest[®] (conestat alfa) compared to Berinert[®] P (human C1 esterase inhibitor) in the treatment of acute, life-threatening angioedema attacks in patients with hereditary angioedema. *Postepy Dermatol Allergol*. 2013 Jun;30(3):152–8.
- 144 Manson AL, Price A, Dempster J, Clinton-Tarestad P, Greening C, Enti R, et al. In pursuit of excellence: an integrated care pathway for C1 inhibitor deficiency. *Clin Exp Immunol*. 2013 Jul;173(1):1–7.
- 145 Blasco AJ, Lázaro P, Caballero T, Guilarte M. Social costs of icatibant self-administration vs. health professional-administration in the treatment of hereditary angioedema in Spain. *Health Econ Rev*. 2013 Feb;3(1):2.

- 146 Bygum A, Aygören-Pürsün E, Caballero T, Beusterien K, Gholizadeh S, Musingarimi P, et al. The hereditary angioedema burden of illness study in Europe (HAE-BOIS-Europe): background and methodology. *BMC Dermatol*. 2012 Apr;12(1):4.
- 147 Bygum A, Aygören-Pürsün E, Beusterien K, Hautamaki E, Sisic Z, Wait S, et al. Burden of illness in hereditary angioedema: a conceptual model. *Acta Derm Venereol*. 2015 Jul;95(6):706–10.
- 148 Aygören-Pürsün E, Bygum A, Beusterien K, Hautamaki E, Sisic Z, Boysen HB, et al. Estimation of EuroQol 5-Dimensions health status utility values in hereditary angioedema. *Patient Prefer Adherence*. 2016 Sep;10:1699–707.
- 149 Weller K, Groffik A, Magerl M, Tohme N, Martus P, Krause K, et al. Development and construct validation of the angioedema quality of life questionnaire. *Allergy*. 2012 Oct;67(10):1289–98.
- 150 Prior N, Remor E, Gómez-Traseira C, López-Serrano C, Cabañas R, Contreras J, et al. Development of a disease-specific quality of life questionnaire for adult patients with hereditary angioedema due to C1 inhibitor deficiency (HAE-QoL): spanish multi-centre research project. *Health Qual Life Outcomes*. 2012 Jul;10(1):82.
- 151 Prior N, Remor E, Pérez-Fernández E, Caminoa M, Gómez-Traseira C, Gayá F, et al. Psychometric field study of hereditary angioedema quality of life questionnaire for adults: HAE-QoL. *J Allergy Clin Immunol Pract*. 2016 May-Jun;4(3):464–473.e4.
- 152 Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. *Eur J Dermatol*. 2009 Mar-Apr;19(2):147–51.
- 153 Christiansen SC, Bygum A, Banerji A, Busse P, Li H, Lumry W, et al. Before and after, the impact of available on-demand treatment for HAE. *Allergy Asthma Proc*. 2015 Mar-Apr;36(2):145–50.