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Hereditary Angio-Oedema for Dermatologists

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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 clinical 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.

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-

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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, lifelong 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-

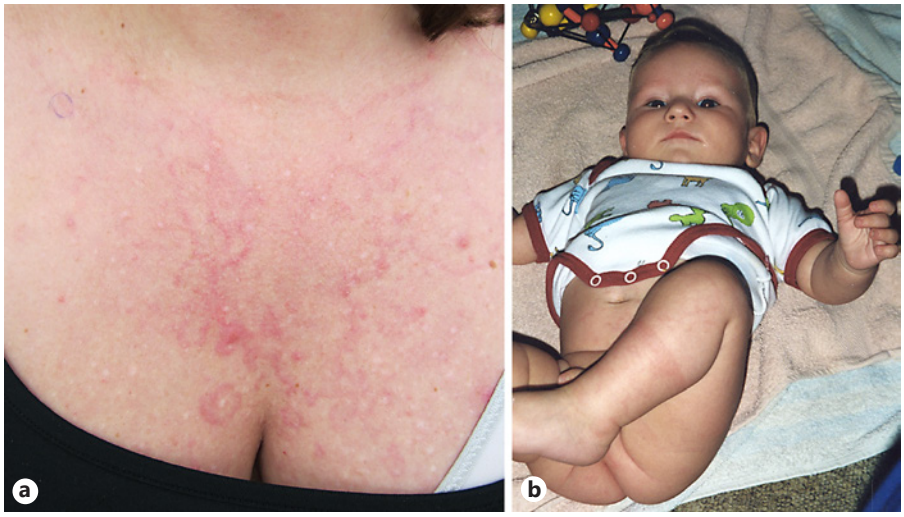

Fig. 2. Erythema marginatum in an adult (**a**) and new-born (**b**) with hereditary angio-oedema.

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

	Urticaria	Family history of angio-oedema	Treatment response to high-dose antihistamines, corticosteroids, or adrenaline	C4	C1INH antigen	C1INH function	C1q	Mutation
Hereditary angio-oedema type I	No	Yes[a]	No	↓	↓	↓	Normal	*SERPING1*[b]
Hereditary angio-oedema type II	No	Yes[a]	No	↓	Normal or ↑	↓	Normal	*SERPING1*[b]
Hereditary angio-oedema with normal C1INH[c]	No	Yes	No	Normal	Normal	Normal	Normal	*F12* *ANGP1* *PLG* 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 important 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 ecallantide, 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 ecallantide 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 attacks 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

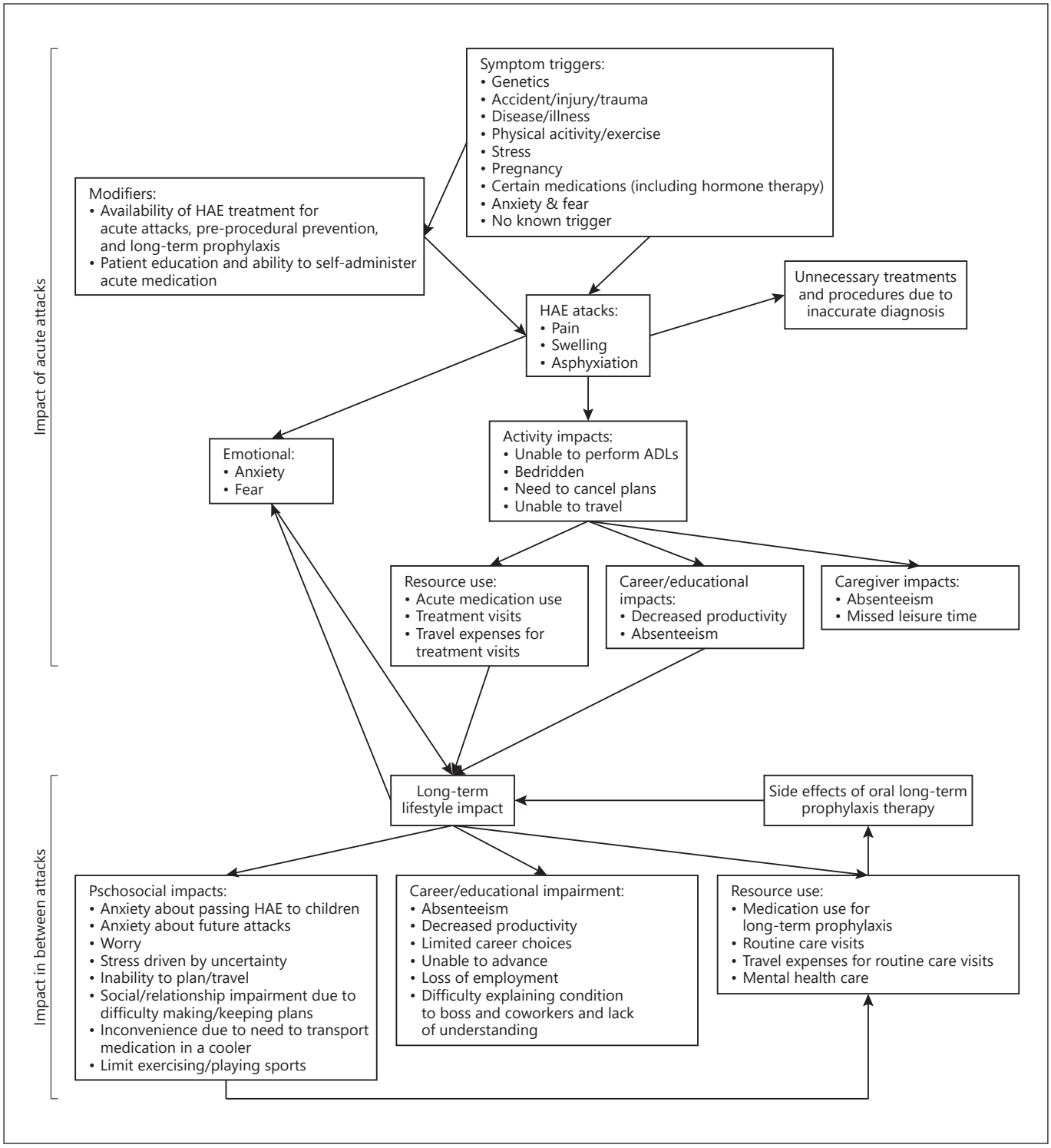

Fig. 3. Burden of illness in hereditary angio-oedema: conceptual model. Reproduced with permission from Bygum et al. [152]. ADL, activities of daily living; HAE, hereditary angio-oedema.

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.

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.

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