Expert consensus on prophylactic treatment of hereditary angioedema

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Received: 25 April 2022 / Accepted: 16 May 2022 / Published online: 2 September 2022
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Summary Hereditary angioedema (HAE) is a chronic, genetic condition which severely impacts those afflicted with intermittent recurrent vascular edema in mucosal and submucosal tissue or in the dermis and subcutis. These swellings adversely impact the wellbeing of patients, both physically and emotionally. Depending on the location, patients present to doctors in a range of disciplines, and not infrequently misdiagnoses occur, such as appendicitis or an allergy, with subsequent incorrect treatment. An HAE attack can also be life-threatening if larynx is affected. However, medications for treating the more common mast cell-induced angioedema are not effective in HAE. Correct diagnosis of the condition, which often first appears in childhood or adolescence, is therefore essential for effective treatment. De novo mutations where the family history is negative are particularly challenging here. However, a range of new treatment options can help HAE patients by preventing attacks and alleviating the burden of the disease. In this review, we summarize the symptoms experienced by patients with HAE as a result of their condition, but also as a result of misdiagnoses and incorrect treatments, as well as the role of preventive treatment (long-term prophylaxis) in improving the quality of life of those affected and their families. In addition, we provide specific information about how HAE can be detected at an early stage in order to be able to refer patients to experts as soon as possible. With reference to the recommendations of the updated WAO/EAACI guidelines (2022), we argue for a stronger role for long-term prophylaxis and the promotion of modern, patient-centered management of HAE using patient-reported outcome measures (PROMs) to manage quality of life and the burden of the disease.

Keywords C1 inhibitor protein · Long-term prophylaxis · Differential diagnosis of HAE · Bradykinin · Patient-reported outcome measures

Abbreviations
AAS Angioedema Activity Score
AECT Angioedema Control Test
AE-QoL Angioedema Quality of Life
HAE Hereditary angioedema
HAE-AS Hereditary Angioedema Activity Score
PROM Patient-reported outcome measure
Introduction

As early as 1777, Franz Anton Mai (1742–1814), Professor at Heidelberg University, reported in his series of text books about the young doctor “Stolpertus”, who had a male patient with recurrent swellings that would suddenly appear with no inflammation, wheals or itching, affecting first the lips, eyelids or testes and finally the tongue, therefore becoming life-threatening [1]. About 100 years later, William Osler described the familial form of the condition, then referred to as hereditary angioneurotic edema, as localized, recurrent swellings in various regions of the body, “almost inevitably” with gastrointestinal disorders and a strongly hereditary aspect in a family (since 1762) across 5 generations [2].

Hereditary angioedema (HAE) is a chronic condition which severely impacts those afflicted and is characterized by edema in mucosal and submucosal tissue or in dermal and subcutaneous structures, caused by vasodilation [3]. Initial symptoms often manifest before the age of 20 and recur repeatedly throughout life. About half of all those affected by HAE experience their first symptoms before the age of 9 [4].

A distinction is made between several types of HAE (Table 1). Type 1—the most common form—affects approximately 85% of patients and is characterized by a deficiency of C1 inhibitor protein that controls the complement factor C1 and therefore the complement system and contact system. In the case of type 2 (approximately 15% of patients), the C1 inhibitor is dysfunctional, at a normal or elevated concentration. These two types are summarized under the category C1-INH-HAEt. In these types, there is a mutation of the SERPING1 gene, which codes the C1 inhibitor protein [3, 5]. In some cases, there is neither a deficiency nor a dysfunction of the C1 inhibitor. These types, formerly referred to as HAE type 3, are ascribed to different, previously only partially identified mutations [5] and are subsumed under the umbrella term nC1-INH-HAEt.

If there is qualitative or quantitative deficiency in functional C1 inhibitor, this results in increased production of bradykinin. If the contact system is activated, bradykinin is separated from kininogen synthesized in the liver. This strong trigger of vasodilation increases capillary permeability. The acute, strong rise in the bradykinin level as a result of increased synthesis results in high vascular permeability. As a result, fluid escapes into adjoining tissue, and angioedema occurs [6].
Undiagnosed HAE patients: Risk of asphyxiation as a result of laryngeal angioedema

HAE attacks typically affect extremities, the face, tongue, and larynx, but the abdomen and genitalia are also often affected [3]. The swellings are usually painful and have a significant physical and emotional impact [7, 8]. The attacks can range from mild to severe and, if the upper respiratory tract, particularly the larynx is affected, also acutely life-threatening. Although they are not the most common form of HAE attacks, approximately half of patients experience them at least once in their lifetime. Immediate effective treatment is essential to prevent death as a result of asphyxiation or permanent brain damage as a result of a lack of oxygen. The risk is particularly high if HAE has not yet been diagnosed, as a cohort study of 728 patients from 182 families showed: 214 of the patients died; 70 of these as a direct consequence of a laryngeal attack (63 of 70 had no HAE diagnosis). Mortality as a result of asphyxiation was therefore considerably higher in patients without an HAE diagnosis than in patients with a known HAE diagnosis (63 vs. 7 cases). This increased mortality corresponded to an average loss of 31 years of life compared to patients who died as a result of other causes [7].

HAE is a genetic condition with generally autosomal dominant inheritance [5]. However, a negative family history does not preclude an HAE diagnosis, as 25% of HAE patients have a spontaneous mutation [5]. Cases of de novo mutations were found in a recent analysis in Belarus of 11 out of 64 C1-INH-HAE patients from 26 families [8].

Due to the severity of impact of symptoms and the risks of an undetected or untreated HAE attack, early detection, diagnosis, and effective prevention or treatment of all attacks are particularly important. In this review, we will discuss the need to treat HAE, focusing on the role of preventive treatment and the impact of new treatment options on modern management of HAE. We will also summarize the current knowledge on symptoms caused by HAE, offer specific tips for early detection in everyday practice, and highlight the key role of long-term prophylaxis and patient-reported outcome measures (PROMs) as part of optimum management of HAE in line with the updated WAO/EAAIC guidelines [9].

Recurrent angioedema: Could it be HAE?

HAE is a group of rare diseases. In 2018, Aygören-Pürrün et al. performed a systematic search and analysis of the epidemiological evidence on the prevalence of bradykinin-induced angioedema such as HAE. The prevalence of HAE was estimated to be between 1.1 and 1.6 cases per 100,000 people based on North American and European data [10]. Mansi et al. analyzed the data for 1058 patients with recurrent angioedema without wheals in an angioedema center, where 377 patients (35.6%) were diagnosed with hereditary angioedema and 353 patients (33% of the total patient group) with a C1 inhibitor deficiency (C1-INH-HAE). In all, 24 patients had normal C1-INH values (nC1-INH-HAE), with a known mutation having been identified in 6 patients. In the population with normal C1-INH values, HAE was therefore a more common cause of angioedema than previously assumed [11].

Medications to treat the essentially more common mast cell-induced angioedema are ineffective against HAE: The swellings do not respond to antihistamines or corticosteroids, which are typically used for allergic angioedema [12]. Even omalizumab, which is commonly effectively used to treat mast cell-induced angioedema as part of chronic urticaria, does not have any effect on HAE [11, 13]. This and the prevalence of HAE in patients with recurrent angioedema highlight the importance of a specific diagnosis in patients who present in the dermatology, allergy, gastroenterology, internal medicine, or ENT department, depending on the location and suspected cause, or even in the emergency department with signs of an angioedema attack.

Misdiagnoses and delays in diagnosis are common with HAE

Delays in getting a specific diagnosis and effective treatment present a massive problem for HAE patients. In a patient survey, Banerji et al. established that nearly half of patients with C1-INH–HAE (47.1%) and 56.7% of patients with nC1-INH-HAE did not receive a correct diagnosis until more than 10 years after their first HAE symptoms [14].

In an observational study conducted between 2009 and 2012 including 150 European patients, the mean time before receiving a diagnosis was 8–21 years after the start of symptoms, depending on the HAE type [15]. A Japanese study found that the delay between the first attack and diagnosis of HAE can be even longer. According to this study with 121 patients, it took an average of 15.6 years to receive a diagnosis of HAE, although in some cases a diagnosis was given within the first year, and in some cases not until 53 years after the initial manifestation of the HAE. Patients attended an average of 4.6 different departments or clinics before receiving a diagnosis [16].

A current investigation in Germany found a similar average delay of 18.1 years (median: 15.0 years) until a diagnosis was reached, with greater delays in older patients and index patients, in other words de novo mutations [17]. In 2021, Zarnowski et al. established an average time to correct diagnosis of 14.2 years (±14.5 years), with longer delays to diagnosis in patients over the age of 50 [18].

However, this period is very tough for those affected: with numerous doctors’ appointments in various specialist clinics and emergency admissions they
can over time lose trust in the medical system and its ability to provide them with a correct diagnosis or effective treatment. The everyday life, school, work, and social life of patients are not only interrupted during times of attacks, the patients are also affected by the unpredictability of attacks during attack-free periods [19]. The chronic complement consumption between times of attacks, the patients are also affected by the social life of patients are not only interrupted during effective treatment. The everyday life, school, work, and social life of patients are not only interrupted during times of attacks, the patients are also affected by the unpredictability of attacks during attack-free periods.

Typical misdiagnoses made in 50.6% of HAE patients were appendicitis and an allergy [17]. Patients with a misdiagnosis mostly (80%) also received the wrong treatment, often resulting in treatment with medication (65.6%), but in 56.3% of cases also unnecessary surgical interventions. However, even where a diagnosis exists—documented by the HAE emergency health card issued by a doctor and carried by the patient—patients generally do not receive effective emergency treatment with a C1 inhibitor preparation or bradykinin antagonist in the event of angioedema attacks.

Angioedema can come with wheals or without them. Common forms of angioedema, from allergic reactions or a chronic urtica, are histamine- and mast cell-induced and are typically associated with itchy wheals. However, this is not the case with HAE angioedema, i.e., these present as localized subcutaneous or submucosal swellings and never feature wheals or itching [6, 25].

Better awareness of this rare and intermittent condition and information about de novo cases are important for early detection of HAE. Patients should also be advised to inform accident and emergency departments and emergency services about their condition.

Detecting HAE in practice

In 2016, Banerji et al. described the “classic” HAE patient journey as follows: On experiencing their first signs and symptoms, patients first attempt to determine if any triggers are at play, and if so, which ones. As a result, patients assess the need to see a doctor, depending on the frequency and severity of their attacks. In the case of children, the pediatrician is usually the first port of call, while with adults it may be the family doctor, gastroenterologist, dermatologist, allergologist or ENT doctor or even the accident and emergency department. It the visit to the doctor raises a suspicion of HAE rather than a misdiagnosis and unnecessary, ineffective treatment, a referral to an HAE expert and ultimately individual management of the condition can follow [26].

A key step in the clinical evaluation of angioedema is a thorough examination of the patient's personal and family medical history [25], including the frequency, location, any past treatment attempts and familial events (Table 2). The possibility of a de novo mutation must also not be disregarded [10, 27].

The triggers and progression of attacks can also be instructive. Most attacks occur spontaneously and without warning. However, there are triggers that increase the risk of an attack, for example, physical trauma such as medical or dental procedures, but also infection, exercise, and stress. Fluctuations in estrogen levels during menstruation, ovulation, use of hormonal contraceptives, pregnancy, breastfeeding, and menopause can affect the frequency and severity of HAE attacks [29].

Prior to HAE attacks, prodromal symptoms such as fatigue, a general feeling of being unwell, malaise, debility (asthenia) can occur, but also inner unease,

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### Table 2: Distinction between different angioedema. (Adapted in accordance with [28])

| Recurrent | Laryngeal angioedema | Wheals | Painful abdominal attacks | Prodomal symptoms | Attacks triggered by NSAIDs | Decade of first symptoms | Abnormal family history (angioedema/abdominal attacks/death as a result of asphyxiation) | Estrogen sensitivity |
|-----------|----------------------|--------|--------------------------|------------------|---------------------------|------------------------|--------------------------------------------------------------------------------------------|------------------|
| HAE       | ++                   | –      | ++                       | ++               | –                         | 0–2                    | +                                                                            | +                |
| nC1-INH-HAE | ++                   | –      | –                        | –                | –                         | 0–4                    | ++                                                                         | ++               |
| C1-INH-AAE | –                    | –      | –                        | –                | –                         | >6                     | +                                                                          | +                |
| ACEi/RAAS | –                    | –      | –                        | –                | –                         | >5                     | –                                                                          | –                |
| AsU/CsU   | –                    | –      | –                        | –                | –                         | >0                     | –                                                                          | –                |

HAE: hereditary angioedema, nC1-INH-HAE: HAE with normal C1-INH values, C1-INH-AAE: angioedema with acquired C1-INH deficiency, ACE inhibitor- and renin angiotensin aldosterone system-induced angioedema, AsU/CsU: acute/chronic spontaneous urticaria, NSAIDs: nonsteroidal anti-inflammatory drugs + common/typical; ++: very common/typical; –: rare/atypical; N/A: not available, unknown

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### Table 3: Checklist of features of possible HAE. (Adapted in accordance with [11])

| Checklist: Could it be HAE? |
|-----------------------------|
| Recurrent angioedema         |
| Recurrent, extremely painful abdominal complaints |
| Swelling attacks congesting the upper respiratory tract |
| Positive family history      |
| Start of symptoms in childhood or adolescence |
| No response to standard emergency anti-allergic medications |
| Occurrence of prodromal symptoms |
| Absence of wheals            |
restlessness, and reddening of the skin (erythema marginatum) or localized unpleasant sensations such as wheals [30]. Attacks usually begin slowly, peaking after 12–24 h, and if untreated can generally last 48–72 h [31]. Table 2 shows typical patterns of various angioedema, on the basis of which distinctions can be drawn between different angioedema attacks (in accordance with [32]).

There is therefore a series of significant indications that would point to HAE (see checklist in Table 3).

An exact diagnosis of the subtype should be made by HAE experts based on specific characteristics and laboratory parameters [25].

**Disease burden, early detection and correct diagnosis**

The burden of the disease is essentially determined by the unpredictability of individual attacks or their severity. In the Icatibant Outcome Survey, an international HAE treatment register, the frequency and severity of attacks were analyzed over 7 years. Between July 2009 and July 2019, the analysis included 315 patients without and 292 with long-term prophylaxis. Across the population as a whole, the frequency of attacks remained stable over the 7 years. However, 28.8–34.5% of patients reported a change in frequency between the first and second year of occurrence of at least 5 attacks a year. In almost half of patients, the activity of the disease also varied to a similar extent in the subsequent years. High individual variability occurred more commonly without long-term prophylaxis [33]. Without preventive treatment, the average patient in some cases suffers an attack every 10–20 days [27].

The number of untreated attacks can be very high in individual cases, as a current report from Japan shows: Here 121 patients reported an average of 15.7 (between 0 and 100) attacks per year, but only half of these (53.1%) were treated [16]. The existence or otherwise of an HAE diagnosis made a material difference to the progression of the disease: The number of hospitalizations per year due to serious attacks was 14.3 prior to diagnosis and fell to just 4.3 after diagnosis [16]. This again confirms the importance of early detection and correct diagnosis [18].

If those affected seek medical help, but do not receive treatment, or receive ineffective treatment, and do not receive a diagnosis that allows a proactive approach to the condition, this can result in them looking for alternatives that make living with HAE easier. The longer it takes to reach a correct diagnosis and start adequate treatment tailored to HAE, the more resigned they become, to the point of denying the disease. In a minority of cases, chronic pain also develops, with regular visits to emergency departments or prolonged use of opiates to treat the pain [34].

In open qualitative interviews with 30 patients from Spain, Germany, and Denmark, the recurring theme that came across was that not only the attacks themselves, but also unnecessary treatments and procedures had a lasting impact on the health-related quality of life of patients [35]. The type of HAE seems to be immaterial in this respect: In approximately three quarters of those affected, the condition has a significant impact on quality of life [14]. As many of those affected experience their first attacks in childhood, the impact on them is already significant even in their early years [36].

In addition to the consequences of a lack of treatment or of receiving the wrong treatment, adverse impacts on quality of life include restrictions on everyday activities such as school, education, work, and social or family life, regardless of the location and severity of the HAE attacks. Estimating the individual impact based on the location of the HAE attacks could therefore significantly underestimate the effect of the disease on the lives of patients [37]. However, the frequency of attacks was more critical [38, 39]: A higher frequency was associated with reduced productivity and increased absences, made education and a career path more difficult, and was a significant constraint on the options open to those affected and their families [38, 40].

In addition, there are fears of future attacks, the risks when travelling, for example, or passing the condition on to children. Based on the Hospital Anxiety and Depression Scale, 38% of patients have clinically relevant anxiety symptoms [41], and more recent data revealed that between 25% and 43.2% of those affected experience anxiety [18]. Concern about a choking attack was often a particular cause of anxiety and restricted quality of life [40]. These fears do not come from nowhere, as approximately half of German patients (43.8%) had at least one family member who had died as a result of HAE [18].

Patients are therefore affected not only on a purely physical level, but also emotionally and psychologically, both when they experience acute attacks and in the periods in between attacks [41]. Psychological stress is also a common trigger and can further increase the frequency of attacks and the consequences of the disease [18].

Compared to patients with allergic conditions, 193 French HAE patients scored significantly lower values in all areas of health-related quality of life, apart from purely physical aspects [38]. Both specific fears and depression play a role here [40, 42, 43], and the latter may possibly have a pathophysiological connection with HAE through inflammation [44].

**Normalization of quality of life in HAE patients with long-term prophylaxis**

A series of studies have demonstrated the difference made by early detection, diagnosis and treatment of HAE. The aim of treatment is to fully manage the condition and normalize the life of patients. The key
theme of modern HAE management is to improve the health-related quality of life of those affected and their families. The most important innovation in the range of HAE treatments, by expert consensus and in accordance with the latest international guidelines on HAE management, is the emphasis on long-term prophylaxis [11, 45]. This treatment recommendation is based on the now well-established long-term prophylaxis treatment options, such as C1 inhibitors obtained from plasma (intravenously [IV] or subcutaneously [SC]), lanadelumab (SC) and berotralstat (orally), which significantly reduce the frequency and severity of attacks [41, 46–51].

Compared to the placebo and therefore to merely acute treatment of HAE (on-demand treatment), long-term prophylaxis (for example with twice-weekly administration of C1-INH SC) is associated with improved values in general health, anxiety, performance or loss of work and restrictions on activities [50]. Zarnowski et al. reported that out of 37 patients in Germany, those with long-term prophylaxis (n = 17, 45.9%) had significantly better control of their disease and quality of life than patients receiving only on-demand treatment [18]. With prophylaxis, those affected therefore suffered less from anxiety and depression than patients who did not receive such preventive treatment [41, 52, 53].

**Recommendation from updated WAO/EAACI guidelines:** Patients should be re-evaluated at every appointment from a perspective of long-term prophylaxis. This should factor in the activity of the disease, the burden and management of the disease, as well as patient preferences [9].

Thanks to progress in treatment, patients are therefore now able to live a largely normal life [53, 54]. However, this requires implementation of the diagnostic and therapeutic knowledge gained over the past few years.

The recurring central themes that became evident from patient surveys were the severe impact HAE has on life, the need for access to expert knowledge, and the importance of simple treatments, where possible manageable by the patient or a caregiver, in order to gain control of the disease [37, 55]. Improved access to effective HAE treatment, whether from a perspective of acute treatment or with a focus on long-term prophylaxis, is one of the key factors that can improve the quality of life of those affected [55–58]. However, this includes not only the basic possibility of a treatment, but also patient-centered management that allows individualized treatment approaches [43, 59–62]. As part of ongoing observation of the activity and management of the disease, but also of the patient's quality of life, it is possible to assess if and when a current treatment regime should be adjusted. New tools for assessing HAE-related quality of life and the activity of the HAE in the patient play a particularly important role here [11, 52, 60, 61]. A validated patient-reported outcome measures (PROMs) tool for assessing the activity of the disease, the HAE AS (Hereditary Angioedema Activity Score), allows a symptom-specific record of the activity of the disease to be created [61, 63].

The frequency of attacks and their severity (HAE-AS) do not on their own provide sufficient information. The impact of the disease on the patient's quality of life should be taken into account on an individual basis. Doctors can underestimate the impact if quality of life is assessed solely on the basis of the patient's qualitative history. The HAE-related quality of life is recorded with the AE QoL (Angioedema Quality of Life Questionnaire) [64] and management of the disease can be determined and observed with the AECT (Angioedema Control Test) [67]. There is therefore also a focus on the impact of HAE on work, school, family life and social and physical activities [59]. In some patients receiving ongoing long-term prophylactic treatment, this can also result in a change in treatment and allow improvements in disease management and quality of life that can be measured with AECTs and AE QoL Questionnaires [18].

**Recommendation from the updated WAO/EAACI guidelines:** Monitoring of activity, impact, and management of the disease should take place as part of long-term prophylaxis for all patients and thus allow treatment, dosages, and the success of treatment to be optimized [9].

More recent surveys of HAE patients on their practical experiences of treatment options show that while patients are undoubtedly benefiting from modern medications, they often also find the treatment itself difficult [54], even if they learn to deal with the specific restrictions. It is assumed that the first main difference that can make access to treatment easier for patients is the forms in which long-term prophylactic treatments are administered (IV, SC, or orally). In the latest patient survey in Germany, three quarters of patients whose ongoing long-term prophylactic treatment was in non-oral form were very interested or extremely interested in moving over to a tablet form of long-term prophylactic treatment (74%, n = 48). Half of patients who were not yet receiving any preventive treatment (53%, n = 38) were also interested in the oral form of long-term prophylaxis [66]. Individual effectiveness, possible side effects or the practicality of the treatment and how it fits into the patient's everyday life are further factors that should be recorded as part of HAE management and may result in an adjustment of treatment in consultation with the expert treating the patient [60, 68].

The use of PROMs such as AAS, HAE AS, AECT, and AE QoL is therefore useful at all stages of HAE management, even where long-term prophylaxis is already in place, in order to support individualized treatment to ensure optimal treatment of HAE [68]. In addition, patients can also benefit from receiving information
about new treatment options, as making treatment easier can still be a relevant issue even when an established long-term prophylactic treatment regime is in place [66]. Ongoing follow-up by experts therefore ensures that management of HAE is tailored to the patient and his or her respective current life situation (Table 4).

**Table 4** Towns and cities with HAE experts and treatment centers in Germany and Austria

| Germany   | Austria          |
|-----------|------------------|
| 04103 Leipzig | 1090 Vienna      |
| 04129 Leipzig | 2700 Wiener Neustadt |
| 23538 Lübeck    | 3020 St. Pölten  |
| 24105 Kiel      | 4020 Linz        |
| 30625 Hanover    | 5020 Salzburg    |
| 38118 Brunswick | 6020 Innsbruck   |
| 40225 Düsseldorf | 6780 Schwaz    |
| 47805 Krefeld    | 6807 Feldkirch-Tisis |
| 48149 Munich     | 8036 Graz        |
| 55131 Mainz      | 8054 Seiersberg  |
| 60596 Frankfurt am Main | 9020 Klagenfurt |
| 64546 Mörfelden-Walldorf |          |
| 80337 Munich     |                  |
| 81454 Munich     |                  |
| 85521 Ottobrunn  |                  |
| 89075 Ulm        |                  |
| 10117 Berlin     |                  |

Contact information at [http://www.hae-austria.at/hae-aerzte-in-oesterreich/](http://www.hae-austria.at/hae-aerzte-in-oesterreich/); [https://hae-online.de/behandlungszentren/weitere-neue-behandlungszentren.php](https://hae-online.de/behandlungszentren/weitere-neue-behandlungszentren.php); [https://hae-online.de/behandlungszentren.php](https://hae-online.de/behandlungszentren.php)

**Correct diagnosis**

Diagnosis should take place as soon as possible after the first symptoms appear. Misdiagnoses and incorrect treatment are much rarer now than they were. However, de novo cases still present a challenge to doctors from across a wide range of disciplines due to the often seemingly nonspecific and intermittent way that they manifest themselves. Specialized laboratory diagnostics allow a specific diagnosis of HAE to allow effective treatment to be started.

**Access to expert knowledge**

If HAE is suspected, not only a correct diagnosis is required, but it must also be fully explained to the patient. Those affected should be informed of all the possibilities and treatment options, as ultimately each patient has the right to be free from attacks. The comprehensive care in HAE treatment centers offers individual, modern management of the disease after diagnosis.

**Management of HAE with PROM tools and modern medication**

Important tools in the current management of HAE include AECT and AE-QoL as a reflection of how well the disease is being managed (AECT) and what quality of life (AE-QoL) is being achieved. These are an essential part of monitoring the disease and managing treatment, as patients may tend to modify their behavior to avoid attacks, in other words they may restrict the way they live their lives. In addition, how the patients assess that the disease is being managed can differ significantly from the AECT measurement. Asking questions about quality of life is the starting point of the AECT/AEQoL-led discussion with the patient.

**Overarching goal: living free from attacks**

Does every patient have to have long-term prophylaxis? Of course, no treatment will be started against the patient's will, and the relevant decision will always as a shared decision-making process. That said, the impact of HAE as a restrictive, difficult, and dangerous condition must not be underestimated. The unpredictability of the frequency and severity of attacks and, depending on the location, the acute risk to life are arguments in favor of long-term prophylaxis for HAE. In addition, there are adverse impacts that are reflected in the AECT and AE-QoL questionnaires. Preventive treatment allows better management of the disease and can help to get some normality back.

However, patients have a right to be accepted, to live (and also to suffer in) their lives as they wish.

**Practical tips: Providing HAE patients with optimal care**

Thanks to progress in the treatment of HAE, HAE can be managed individually, and patients can live to a great extent a normal life. Five issues are key to ensuring that this goal is met even more often than before: early detection, correct diagnosis, access to expert knowledge, HAE management using PROM tools and modern medication, and the overarching goal of a life free from attacks for patients.

**Early detection**

Patients are being diagnosed more quickly than before, particularly if there are family cases of HAE. It is therefore all the more important to focus on de novo mutations without a relevant family history. In the case of recurrent angioedema without urticaria and possibly with earlier unsuccessful treatment attempts, a hereditary angioedema must be ruled out.
Prophylaxis and freedom from attacks bring huge changes to the lives of patients, affect secondary gains from the disease, and shape relationships with partners and family. However, the possibility and purpose of a treatment should be explained to the patients. In the doctor/patient discussion, setting the bar low at an offer to try a treatment often helps. The different types of prophylaxis facilitate access here by offering a form of administration that suits individual preferences. The stories of other patients can often be more convincing than scientific medical facts. It should always be borne in mind that patients generally need time to adjust to new treatments. The same applies to building confidence in prophylaxis and the associated establishment of a more normal quality of life.

Conclusion

Hereditary angioedema is a huge burden for patients and their families. Early detection of de novo mutations is still a particular challenge for doctors across a range of disciplines. Following a correct diagnosis, an individualized treatment decision should be taken in specialized HAE centers as part of a discussion between the patient and doctor that is led as far as possible by PROM tools and by taking into account the wishes of the patient. Long-term prophylaxis should be a key component of treatment here. Recent progress in HAE treatment has therefore opened up the chance of comprehensive, individualized treatment and leading a normal life, despite HAE.

Funding

Open access funding provided by Medical University of Vienna.

Conflict of interest

The contribution of the authors to this article and the editorial support from MWI GmbH were financed by BioCryst Pharma Deutschland GmbH. J. Greve received financial support for research support from Shirley/Takeda and financial allowances for travel expenses and the conference fees for attending a scientific conference from Shirley/Takeda and CSL Behring GmbH. T. Kinaciyan received fees for lectures and/or consultancy and/or research funds and support for research, outside of this work, from the following companies: Shirley/Takeda, CSL Behring, BioCryst Pharmaceuticals, KalVista and Novartis. M. Maurer is or was until recently a lecturer and/or consultant and/or has received research funds from Ahylum, Astra, BioCryst, Centogene, CSL Behring, KalVista, Moxie, Pharming, Pharvaris and Shirley/Takeda. C. Schöffl received fees and nonfinancial support from Shirley/Takeda and CSL Behring and fees from BioCryst and Novartis, outside of this work. B. Dillenburger and A. Recke declare that they have no competing interests.

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