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REVIEW

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Understanding Quality of Life in Hereditary Angioedema: Insights from Recent Research

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ABSTRACT

Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent episodes of localized edema, significantly impairing the health-related quality of life (HRQoL) in affected individuals. The recurrent and unpredictable episodes of angioedema lead to considerable pain, discomfort, and distress, directly affecting physical functioning and daily activities. Many patients report severe emotional burdens, including anxiety and depression, stemming from both the unpredictability of attacks and the fear of potential hereditary transmission to offspring. In children, the impact of HAE is particularly pronounced, affecting social development and educational attainment. Frequent hospital visits and school absenteeism hinder their academic performance and social interactions, which are crucial for their emotional and psychological development. Psychological assessments have shown elevated anxiety levels in children with HAE, correlating this distress with decreased overall quality of life. For adults, the ramifications of HAE extend into social and economic dimensions. Adults frequently face interruptions in their employment due to the disease, leading to economic strain characterized by high medical costs and lost productivity. There is a notable relationship between the frequency of attacks and overall HRQoL, where higher attack rates correlate with lower scores in the emotional, social, and physical domains. The effectiveness of prophylactic treatments has been documented, indicating that reductions in attack frequency contribute to improved HRQoL. However, barriers such as medication access, side effects of treatments, and financial burdens remain prevalent. Despite advancements in understanding and managing HAE, the multifaceted impact of the disease necessitates comprehensive care strategies that address not only the physical symptoms but also the psychological and social dimensions of living with HAE.

Keywords: Hereditary angioedema, quality of life, anxiety and depression, disease burden

INTRODUCTION

Hereditary angioedema (HAE) is a rare genetic disorder characterized by recurrent episodes of localized edema in various body parts, including the skin, gastrointestinal tract, and respiratory system. The clinical manifestations of HAE are diverse and can be life-threatening, particularly when the larynx is involved, posing a risk of asphyxiation (1,2). Attacks can also affect the gastrointestinal tract, leading to severe abdominal pain, vomiting, and diarrhea, which are often mistaken for acute abdomen or other gastrointestinal emergencies. Moreover, cutaneous manifestations can lead to disfigurement and significant discomfort. These attacks can vary widely in frequency and severity, even within the same patient, and are often unpredictable, which adds another layer of stress and anxiety for those affected (2).

These unpredictable and potentially life-threatening attacks significantly impact the patients' quality of life (QoL) and contribute to a substantial disease burden (3). The impact of HAE on QoL is profound and multifaceted. Physically, the unpredictable and severe attacks disrupt daily activities and may necessitate frequent emergency medical care. Psychologically, the constant threat of an attack can lead to chronic anxiety and depression, severely impairing mental health. Socio-economically, HAE imposes a significant burden due to healthcare costs, lost productivity, and the overall financial strain on patients and their families (4, 5).

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In addition, there is some nuanced interplay between QoL and disease burden across different age groups. Pediatric patients with HAE face unique challenges that may differ from those encountered by adolescents and adults (6). The impact of HAE on children's social development, educational attainment, and emotional well-being is particularly pronounced, with reports of school absenteeism, social isolation, and anxiety related to the condition's unpredictable nature. As children transition into adolescence, the burden of managing HAE may intersect with the challenges of navigating peer relationships, academic responsibilities, and developing self-esteem. Similarly, adult patients with HAE confront a distinct set of issues, including disruptions in employment, financial strain associated with treatment costs, and psychological distress stemming from the chronic nature of the disease (7-9).

Identifying factors influencing the quality of life and disease burden in HAE is crucial for developing targeted interventions. Factors such as the frequency and severity of attacks, patient access to effective treatment, management of disease triggers, and availability of psychosocial support significantly influence patient outcomes (9, 10). A comprehensive approach that addresses these factors, involving personalized treatment plans and holistic care strategies, is essential for improving the quality of life for individuals with HAE. While advancements in the understanding and management of HAE have improved clinical outcomes, there remains the comprehensive burden of HAE on patients (7,11). By incorporating age groups and individual-specific considerations into disease evaluation and treatment planning, healthcare providers can optimize outcomes, improve patients' quality of life, and reduce the long-term impact of HAE on individuals' overall well-being (12,13). Many studies using standardized measurement tools provide valuable insights into the physical, psychological, and socio-economic dimensions of living with HAE. This literature review seeks to synthesize existing evidence on the quality of life and disease burden in HAE to underscore the importance of comprehensive and patient-centered care approaches.

MATERIALS and METHODS

The current systematic review of literature was conducted to identify studies assessing the quality of life and disease burden in patients with HAE. Databases such as PubMed, MEDLINE, and Google Scholar were searched using keywords like "hereditary angioedema," "quality of life," "disease burden," "psychological impact," and "socio-economic impact." Inclusion criteria comprised peer-reviewed articles published in English within the last two decades, focusing on pediatric, adolescent, and adult populations diagnosed with HAE. Studies were critically assessed for methodologies including patient-reported outcomes, cross-sectional surveys, and longitudinal cohort studies. Articles that did not provide explicit measurements of quality of life or disease burden were excluded from the analysis (Table I).

Physical Health Impact

Numerous studies have examined the profound physical impacts of HAE on patients, highlighting how the recurrent and unpredictable episodes of swelling significantly impair daily functioning and overall health. These physical manifestations often result in considerable discomfort and pain, ultimately limiting daily activities and adversely affecting the QoL for affected individuals.

Table I: The summaries of the studies.

Study	Study Population	Method/assessment measurements tools	Key Findings	Implications
Fijen LM et al. 2023 (6)	69 adults (Netherlands)	• Angioedema Activity Score (AAS) • Angioedema Control Test (ACT) • Angioedema Quality of Life Questionnaire (AE-QoL) • EuroQoL-5 Dimension-5 Level (EQ-5D-5L) • Treatment Satisfaction Questionnaire for Medication (TSQM) • The iMTA Medical Consumption Questionnaire (iMCQ) • The iMTA Productivity Cost Questionnaire (iPCQ)	• Disease was poorly controlled in 36% of participants. • Patients' quality of life dropped substantially during an angioedema attack. • Total costs per year per patient amount to $22,764, predominantly consisting of HAE-medication costs.	Enhanced prophylactic strategies appear necessary to achieve better disease control for a significant portion of patients with HAE.

Table I continue

Nunes FL et al. 2021 (13)	33 patients with HAE belonging to a single family (Brazil)	• Clinical assessment • Short Form Health Survey (SF-36) • Pediatric Quality of Life Inventory (PedsQL) • Health-related quality of life questionnaire for hereditary angio- edema (HAE-QoL) • Psychiatrist: clinical assessment • Hospital Anxiety and Depression Scale (HADS) • Depression Anxiety Stress Scales (DASS) • Beck Anxiety Inventory (BAI) • Beck Depression Inventory (BDI) • Children's Depression Inventory (CDI) • Child Stress Scale (SSC) • Work Productivity and Activity Impairment Questionnaire-Gen- eral Health (WPAI-GH) • Systematic management program (allergist, psychiatrist, psychologist, social worker, nurse, nurse technician)	• The mean number of angioedema attacks per month significantly decreased from 1.15 pre-intervention to 0.25 at 8 months and 0.23 at 14 months during the intervention. • Significant increases were observed in the HAE-QoL scores, with mean increases of 15.2 points at 8 months and 26 points at 14 months compared to baseline. • There was a significant decrease in anxiety, stress, and depression scores among patients by 14 months, as measured by various psychological scales (HADS, DASS, BDI). • The program improved access to effective HAE-targeted medications, with a notable increase in the use of icatibant and plasma-derived C1-INH for attacking management. • Educative initiatives improved awareness about HAE among both patients and healthcare professionals, contributing to better management and support during attacks.	The findings highlight the successful implementation of a systematic approach to managing HAE, integrating medical, psychological, and educational components to improve patient outcomes.
Lee EY et al. 2021 (14)	72 adults (Canada)	• HAE QoL questionnaire	• The total QoL scores showed a strong positive correlation with patients' levels of satisfaction and perceived control over their condition ($p < .001$ for both). • There was a negative correlation between QoL scores and the frequency of acute attacks ($p = 0.03$). • The type of treatment patients received did not influence their QoL scores. • Factors such as sex, comorbidities, and the frequency of attacks accounted for only 12% of the variation observed in total QoL scores.	• The study emphasizes that the impact on QoL is not solely determined by the frequency of HAE attacks but is also heavily influenced by patients' experiences with their care. • Physicians should take a holistic approach to managing HAE that goes beyond just medical treatment and addresses patients' overall experience and satisfaction with their care.
Liu S et al. 2019 (15)	102 adults (China)	• SF-36v2	• Patients with HAE exhibited a significant decrease in all dimensions of QoL ($p < 0.001$) when compared to the general Chinese population. • Female patients reported significantly lower scores in bodily pain ($p = 0.039$) and physical component scores ($p = 0.027$). • Patients experiencing mucosal edema tended to report lower role-physical limitations ($p = 0.031$) compared to patients who only had skin edema. • A correlation was found between decreased disease control and lower QoL scores. • Logistic regression analysis identified uncontrolled disease as a risk factor for low physical component scores (odds ratio 10.77, 95% CI 1.78–65.06; $p = 0.010$) and laryngeal edema as a risk factor for low mental component scores (odds ratio 4.75, 95% CI 1.09–20.69; $p = 0.038$).	• The study underscores the need for healthcare providers to be aware of the profound impact of HAE on patients' quality of life and to prioritize QoL assessments in clinical settings. • Importance of disease control; this emphasizes the necessity for regular monitoring and prompt management of symptoms.

Table I continue

Aabom A et al. 2017 (16)	14 children (Denmark)	• PedsQL (Child Self-Report and Parent Proxy-Report forms) • The Children's Dermatology Life Quality Index	• Children who experienced recent attacks had lower HRQoL scores, indicating that acute episodes have a detrimental effect on the quality of life. • The HRQoL scores were not significantly correlated with overall disease severity or the age of the children, suggesting that other factors may influence quality of life beyond the clinical condition. • Home therapy was associated with lower HRQoL scores, which may indicate that those requiring more intensive management at home could have higher overall severity scores and experience more frequent attacks. • There was a strong agreement between child and parent responses on PedsQL forms, indicating consistency in reporting quality of life.	• Based on the findings, healthcare providers should pay particular attention to HRQoL when children with C1-INH-HAE experience symptoms.
Kuman Tunçel Ö et al. 2019 (26)	33 adults (Turkey)	• SF-36 • Revised Form of the Multidimensional Scale of Perceived Social Support • Anxiety Sensitivity Index-3 • Adult Separation Anxiety Questionnaire	• Subscales of SF-36 showed significantly lower scores in all areas except for physical functioning, vitality, and mental health compared to population norms. • Quality of life scores correlated with several psychological and social factors, including depression, anxiety, anxiety sensitivity, separation anxiety, perceived social support, perceived discrimination, perceived limitations, treatment-naive C1-inhibitor function, and C1q levels. • Patients using attenuated androgens had better scores for physical role functioning ($p = 0.006$). • HE negatively influenced patients' marital issues and decisions regarding childbearing.	• Hereditary angioedema significantly affects the quality of life of patients and influences their family dynamics and lifestyle. • Patients displaying symptoms of depression and/or anxiety should be referred to psychiatrists to improve their quality of life. • Higher levels of C1-inhibitor function and C1q appear to be associated with a better quality of life, which warrants further investigation.
Banerji A et al. 2020 (27)	445 patients (USA)	• HAE-QoL • HADS	• Based on the Hospital Anxiety and Depression Scale, 49.9% of respondents had anxiety and 24.0% reported depression. • Mean HAE-QoL scores were lower with higher attack frequency, and 24.8% of patients rated their general health as "poor" or "fair." • Most patients (68.5%) had received or were currently undergoing long-term prophylaxis. • Mean percentage impairments included 5.9% (SD 14.1%) for absenteeism, 23.0% (SD 25.8%) for presenteeism, 25.4% (SD 28.1%) for work productivity loss, and 31.8% (SD 29.7%) for activity impairment.	• Despite the availability of multiple HAE-specific therapies, there remain significant unmet needs and gaps in the management of HAE in patients and they need to be addressed.
Kessel A. et al. 2017 (28)	33 children with HAE and 52 healthy controls (Israel and Hungary)	• State Trait Anxiety Inventory for Children (STAIC) • Peds-QL	• Children with HAE exhibited significantly higher state and trait anxiety compared to controls ($p<0.001$). • A higher trait anxiety score was positively correlated with the number of angioedema-affected sites ($r=0.52$, $p=0.003$). • The presence of HAE attacks and higher trait anxiety scores predicted lower HRQoL in children with C1-INH-HAE.	• The study suggests that addressing anxiety, and its implications for quality of life, should be an integral part of the clinical management of pediatric patients with HAE.

Table I continue

Engel-Yeger B et al. 2017 (35)	34 children, 64 healthy controls (Israel and Hungary)	• PedsQL	• The number of attacks was negatively correlated with overall HRQoL (r = -0.48, p = 0.008), school-related HRQoL (r = -0.39, p = 0.02), and psychosocial HRQoL (r = -0.43, p = 0.01). • Patients experiencing multi-site attacks, including laryngeal, abdominal, and peripheral attacks, had lower HRQoL compared to those with only peripheral attacks across total scores (p = 0.04), physical domain (p = 0.04), and school domain (p = 0.02).	• Children with symptomatic C1-INH HAE exhibit reduced HRQoL. The impairment in HRQoL is influenced by both the frequency and location of C1-INH-HAE attacks, with notable effects observed primarily in the school and physical domains.
Nordenfelt P. et al. 2017 (36)	133 adults (Sweden)	• EQ-5D-5L • RAND Corporation Short Form 36 (RAND-36) • AE-QoL • AAS	• The most affected dimensions of health-related quality of life (HR-QoL) were: • EQ-5D-5L: Pain/discomfort and anxiety/depression. • RAND-36: Energy/fatigue, general health, and pain. • AE-QoL: Fears/shame and fatigue/mood. • There were significant associations (p < 0.05) between AAS and: • EQ-5D-5L • All RAND-36 dimensions except physical function • All AE-QoL dimensions	• The integration of various HR-QoL instruments provides a more comprehensive understanding of patient experiences. • Increased disease activity was correlated with diminished HR-QoL, highlighting the need for more proactive management of the • condition.
Baptist AP. et al. 2024 (37)	17 patients aged 60 years and older (USA)	• Thematic saturation approach	Seven core themes emerged from the focus groups: • Medication and Insurance Challenges: Difficulties in securing medications and concerns regarding insurance. • Historical Experience of HAE: Participants reflected on their experiences living with HAE before the availability of newer and more effective treatments. • Increased Attack Frequency and Severity with Age: Notable worsening of HAE attacks in terms of frequency and severity as patients aged. • Comorbid Conditions: The impact of additional health issues such as arthritis, memory loss, and irritable bowel syndrome on managing HAE. • Menopausal Changes: Changes in HAE symptoms associated with menopause. • Shifting Perspectives with Age: Evolving views on HAE with aging, including effects on relationships, decisions about parenthood, and future healthcare goals. • Desire for Inclusion in Research: Interest in support groups and participation in clinical trials to improve care.	• Older adults with HAE face specific challenges that may differ from those of younger patients. Healthcare providers should recognize and address these unique concerns to optimize care for this population.

In a study that investigated the quality of life of patients with HAE across multiple healthcare facilities in Canada, the researchers employed a quantitative research approach and utilized standardized HAE QoL questionnaire consisting of 7 domains (physical functioning and health, disease-related stigma, emotional role and social functioning, concern about offspring, perceived control over illness, mental health and treatment difficulties) to evaluate the impact of HAE on patients' well-being. The results of the study revealed a significant impairment in

the quality of life of patients with HAE. Factors such as disease severity, frequency of attacks, and the emotional burden associated with the condition were found to contribute to a diminished quality of life in these individuals. The study underscores the importance of comprehensive care strategies that address both the physical and psychological aspects of HAE to enhance patient well-being and quality of life (14). Another study assessed the health-related quality of life (HRQoL) of Chinese patients with HAE using the 36-item Short Form Health Survey (SF-36v2) and explored potential risk factors for low HRQoL. The results indicated a significant reduction in all dimensions of HRQoL in HAE patients compared to the general Chinese population. Patients with mucosal edema tended to report lower limitations in role-physical than those with only skin edema. Interestingly, there were no differences in HRQoL scores based on disease subtype, age, or disease severity. The study also found a correlation between decreased disease control and decreased HRQoL scores, with uncontrolled disease being a risk factor for low physical component scores and laryngeal edema being a risk factor for low mental component scores. The study highlighted unsatisfactory disease control as a risk factor for decreased physical component scores and laryngeal edema as a risk factor for decreased mental component scores. These findings stress the importance of addressing disease control and specific symptoms to improve the quality of life for individuals with HAE (15). In the study in which researchers utilized the Pediatric Quality of Life Inventory (PedsQL) and other measurements including the Children's Dermatology Life Quality Index and visual analog scales to evaluate the HRQoL of the Danish children with HAE, the results indicated that HAE had a significant negative impact on the quality of life, affecting various aspects such as physical health, emotional well-being, social functioning, and school performance. The frequency of angioedema attacks and the challenges associated with treatment regimens were key factors contributing to the decreased HRQoL scores in this population. The children who had experienced recent angioedema attacks exhibited lower HRQoL scores. HRQoL scores did not show significant correlations with overall disease severity or age. Their finding that home treatment was associated with a reduction in HRQoL was unexpected, although this association was also noted with higher overall severity scores and increased attack frequency. The study highlights the importance of addressing the holistic needs of Danish children with HAE to improve their overall well-being and quality of life. Additionally, it emphasizes the significance of tailored support and interventions for children facing the challenges imposed by this condition (16).

Given the physical effects of HAE on patients' quality of life, there are also several studies that highlight the effects of various long-term prophylactic treatments on physical effects and quality of life. However, as discussed below, it is not possible to separate the physical effects of HAE from other effects such as psychological, social, and economic effects, and therefore the effects of long-term prophylactic treatments on these effects. The studies which aimed to demonstrate the effects of long-term prophylactic treatments with C1 inhibitor therapies showed significantly reductions in the frequency of HAE attacks. In addition, patients experienced improved quality of life as measured by the AE-QoL. The reduction in attack frequency leads to less physical pain and discomfort, enabling patients to engage more in daily activities and improve their overall well-being (17-20). The randomized clinical trial which assessed the efficacy of lanadelumab in preventing HAE attacks included a total of 125 patients and demonstrated both the therapeutic effectiveness and the impact on QoL. In addition to substantial reductions in the mean number of attacks and attack severity, there was a notable improvement in quality of life scores. Also, the significant reduction in attack frequency and severity translated into improved emotional well-being and confidence among patients. The study indicated that the expectation of reduced unpredictability in attacks allowed patients to engage more fully in daily activities without the constant worry of an impending attack (21). The HELP open-label extension (OLE) Study investigated the impact of long-term lanadelumab treatment on patient-reported outcomes (PROs) for HAE patients including the AE-QoL, Short Form Health Survey 12-item version 2, Hospital Anxiety and Depression Scale (HADS), and Work Productivity and Activity Impairment measures. Results showed that rollover patients demonstrated a mean improvement of -10.2 (SD 17.9) in AE-QoL total score indicating a further enhancement in HRQoL and reported controlled disease (Angioedema Control Test total score ≥10) at high rates by the end of the study. Other PROs indicated a slight improvement in anxiety, high treatment satisfaction, increased work productivity or activity, and overall positive treatment responses to lanadelumab therapy (22). Recent trials have shown that Berotralstat, an oral kallikrein inhibitor, effectively reduces the frequency of attacks in HAE patients. The studies

emphasized significant improvements in quality of life, with patients reporting enhanced physical function and reduced anxiety related to the unpredictability of attacks. Berotralstat was associated with favorable AE-QoL scores, indicating substantial improvements in physical and emotional well-being (23). The situation is a bit more complicated with danazol. A review highlighted that while androgens can effectively prevent HAE attacks, they are associated with significant side effects that may impact quality of life negatively. Patients often reported concerns regarding weight gain, mood changes, and androgenic side effects, which can detract from the perceived benefits of the treatment (24). Tranexamic acid has shown some efficacy in preventing HAE attacks, but studies indicated limited effectiveness compared to C1 inhibitors. Patients using this treatment often experienced fewer attacks, but overall improvements in quality of life were less pronounced than with other prophylactic treatments (25).

Overall, these studies demonstrate that long-term prophylactic treatments for HAE can effectively improve quality of life and emotional well-being while also highlighting the importance of managing side effects and considering individual patient needs in treatment options. When considering the initiation of long-term prophylaxis, it is important to take into account not only the frequency and severity of attacks but also the assessment of quality of life.

Psychological Impact

The psychological impacts of HAE represent a critical aspect of the disease that extends beyond its physical manifestations. Many patients experience significant emotional distress due to the unpredictability and discomfort associated with recurrent angioedema attacks. This chronic condition can lead to increased levels of anxiety, depression, and social isolation, thereby complicating not only their mental health but also their overall quality of life. A particularly pervasive concern among individuals with HAE is the fear of transmitting the disorder to future generations, which adds an additional layer of anxiety regarding family planning and the potential burden on offspring. Understanding these psychological effects is essential for developing comprehensive treatment strategies that address both the physical and emotional needs of individuals living with HAE. Numerous studies have explored these facets, shedding light on the psychological burden patients face and the importance of integrated care approaches. A study from our country aimed to evaluate the quality of life of patients with HAE and analyze the relationship between quality of life and various demographic, clinical, laboratory, and psychiatric parameters. A comprehensive assessment was conducted through face-to-face interviews, psychiatric evaluations using the Hamilton depression and anxiety rating scales, and completion of multiple questionnaires. Results from 33 HAE patients revealed that quality of life scores were notably lower in several domains compared to population norms, with correlations found between quality of life and factors such as depression, anxiety, anxiety sensitivity, perceived social support, and complement levels. Patients using attenuated androgens showed better physical role functioning scores. The study highlighted the impact of HAE on marital relationships and reproductive decisions of patients. Recommendations included psychiatric referral for patients with depressive or anxious symptoms to enhance quality of life. Additionally, higher levels of C1-inhibitor function and C1q were associated with improved quality of life, warranting further investigation in future studies (26). Another study focused on evaluating the burden of HAE from the patients' perspective in the United States. A total of 445 patients participated, with most being aged 18 to 64 years and predominantly diagnosed with HAE type I. Key findings included the fact that the majority of the patients had experienced an attack within the past month, with commonly affected sites being the abdomen and extremities. Symptoms such as pain and swelling were frequently reported. Most patients had received or were on long-term prophylaxis. A significant portion reported anxiety and depression, with lower quality of life scores linked to higher attack frequency. The study highlighted issues such as absenteeism, presenteeism, work productivity loss, and activity impairment, indicating a substantial burden of illness despite treatment advances for patients with HAE in the United States (27). In another study conducted in the pediatric population, results showed that children with C1-INH-HAE had significantly higher levels of state and trait anxiety compared to healthy controls. Differences in anxiety levels were observed among C1-INH-HAE patients with attacks, asymptomatic patients, and controls. Higher levels of trait anxiety were correlated with the number of angioedema-affected sites. Presence of HAE attacks and higher trait anxiety predicted lower HRQoL in children with C1-INH-HAE. Overall, the study concluded that children with C1-INH-HAE experience elevated anxiety levels, which are associated with decreased HRQoL across various domains (28). In a study focus-

ing on patients with HAE due to C1-inhibitor deficiency, who were administered subcutaneous C1-inhibitor with recombinant hyaluronidase for attack prevention, significant improvements in health-related quality of life were observed despite the study's premature termination. Results showed a notable decrease (indicating improvement) in average AE-QoL total scores from the baseline to the end of the study. Significant improvements were noticed in the Functioning, Fear/Shame, and Nutrition domains. Patients receiving the higher C1-INH dose reported greater declines in Functioning and Nutrition domains compared to those on the lower dose. Remarkably, a considerable proportion of patients experienced a substantial reduction in AE-QoL total score, highlighting the positive impact of subcutaneous C1-INH prophylaxis on quality of life within a relatively short treatment duration of up to 16 weeks. Despite the study challenges and initial use of intravenous C1-INH by a significant portion of participants, the findings suggest an overall enhancement in health-related quality of life following the subcutaneous prophylactic treatment regimen (29).

Economic Effects

Hereditary angioedema imposes a significant economic burden on both patients and healthcare systems, as highlighted by various studies documenting the extensive financial implications of the disease (30). A study conducted in the Netherlands aimed to assess the comprehensive burden of HAE on patients, including disease control, quality of life, treatment satisfaction, and societal costs. According to the results, average annual costs per patient were €22,764, mainly attributed to HAE-medication expenses, with significant cost discrepancies among patients. The findings highlight the multifaceted impact of HAE on patients in the Netherlands, providing valuable insights for cost-effectiveness analyses and reimbursement decisions for HAE treatments (6). A landmark study utilized an internet-based survey to evaluate the economic impact of HAE on 457 adult patients, revealing an average annual direct medical cost of $25,884 per patient. Notably, 83% of this cost is attributed to treating acute attacks, which necessitate emergency department (ED) visits that alone account for nearly 50% of direct costs. Patients with severe attacks incur higher costs, with average annual expenses reaching up to $96,460, compared to $14,379 for mild attacks (31). In terms of indirect costs, participants reported missing an average of 3.3 workdays per recent attack, leading to significant productivity losses. The findings illustrate that, despite the development of new therapies, the high costs associated with HAE, both in direct treatment and lost productivity, present substantial challenges to effective healthcare delivery (31). Overall, at the individual level, patients with HAE often incur significant medical costs. These may include ongoing treatments, medications, emergency interventions, and potential hospitalizations. The financial burden can be substantial, particularly for those without comprehensive health insurance (32, 33). Another issue is loss of productivity; attacks of HAE can lead to significant work absenteeism, resulting in income loss and reduced job security. For some individuals, chronic health issues may necessitate either early retirement or job transitions, further exacerbating economic instability. Access to adequate health insurance can be a significant issue for individuals with HAE. Limited coverage can lead to increased out-of-pocket expenses, which heightens financial strain and may result in significant debt for those requiring long-term treatment (32, 33). In addition, the incidence of HAE places considerable demand on healthcare resources. Increased utilization of emergency services, hospital admissions, and chronic care results in higher costs for the healthcare system and, by extension, taxpayers. Furthermore, long-term economic consequences are possible; if HAE is not effectively managed, long-term complications may arise, imposing even greater economic burdens on individuals and healthcare systems. Increased demand for extensive medical care can overwhelm social security systems and healthcare resources (32, 33).

Social Effects

Hereditary angioedema significantly affects various dimensions of patients' social functioning, leading to profound implications for their overall quality of life. The unpredictable nature of angioedema episodes often culminates in considerable emotional distress, hindering patients' ability to engage in social interactions and maintain productive relationships. Notably, individuals with HAE frequently report feelings of embarrassment and isolation, largely stemming from the visibility of symptoms during acute episodes. This phenomenon can result in avoidance of social settings and reluctance to pursue vocational opportunities, thereby straining interpersonal relationships with family, friends, and colleagues (6, 34). The results of a study examining HRQoL among children with HAE provide significant insights into the social impacts of the condition in children population. The study indicated

that children with C1-inhibitor deficiency HAE exhibited lower HRQoL scores in social functioning dimensions compared to healthy controls. This impairment reflects the challenges these children face in engaging with peers, participating in group activities, and maintaining social relationships, which are vital for their emotional and psychological development. Children experiencing more frequent attacks were found to have a more pronounced negative impact on their ability to attend school and engage socially. The results suggest that children with HAE are likely to miss school days due to acute episodes, which not only impacts their academic performance but also their social interactions within the school environment. The findings also suggest that mothers of children with HAE perceive similar challenges regarding their children's social difficulties. The correlation between child-reported HRQoL and maternal assessments underscores the importance of involving both perspectives in managing HAE. Mothers' insights into their children's experiences can enhance the development of comprehensive care strategies. The study states that the holistic needs of children with HAE is crucial for improving their overall well-being. Interventions that provide emotional support, promote social interactions, and educate both patients and families about managing the condition can mitigate the negative social impacts associated with HAE (35). Another study aimed to assess HRQoL among adults with HAE by utilizing a combination of generic and disease-specific quality of life instruments alongside evaluations of disease activity including the EuroQol 5 Dimensions 5 Level (EQ-5D-5L), the RAND Corporation Short Form 36 (RAND-36), and the Angioedema Quality of Life instrument (AE-QoL) and the Angioedema Activity Score (AAS). Sixty-four adults responded, revealing that dimensions such as pain, anxiety, and mood disturbances were major contributors to impaired HRQoL. Women reported significantly lower HRQoL in domains related to general health and energy/fatigue. The study highlighted a direct correlation between increased disease activity and reduced HRQoL, emphasizing the influence of recurrent attacks on patients' social interactions and ability to participate in community and familial activities. Patients with higher disease activity scores exhibited notably impaired emotional and social functioning, further illustrating the social burden of HAE (36). As patients with HAE advance in age, the social ramifications of the disease evolve, presenting distinct and complex challenges that differ significantly from those experienced by younger individuals. A study aimed at assessing the impact of HAE on older adults utilized qualitative methodology, involving focus groups with seventeen patients aged 60 years and above. The findings from thematic analysis revealed seven core themes, including challenges related to medication access and insurance, as well as the management of HAE prior to the availability of modern treatment options. Participants noted an increase in both the frequency and severity of HAE attacks with aging, alongside the influence of comorbid conditions such as arthritis and memory loss. Additionally, the dynamics of HAE during menopause significantly affected their experiences, highlighting evolving perspectives on care, relationships, and decision-making processes. These insights underline the unique challenges faced by older adults with HAE, emphasizing the need for healthcare providers to acknowledge and address these issues to optimize care and improve patient outcomes (37).

CONCLUSION

In summary, HAE exerts a multifaceted impact on patients' quality of life, encompassing significant physical, psychological, economic, and social dimensions. Physically, recurrent and unpredictable episodes of edema not only lead to severe discomfort and potential life-threatening complications but also significantly impair daily functioning. Psychologically, the fear associated with these unpredictable attacks contributes to heightened levels of anxiety and depression, further complicating the patients' emotional well-being. Economically, the substantial costs associated with acute management and long-term treatment create a financial burden that can strain both patients and healthcare systems. Furthermore, the social repercussions of HAE, including isolation and disruptions in interpersonal relationships, underscore the importance of comprehensive care strategies that integrate social support mechanisms. Acknowledging these interconnected dimensions is crucial for developing holistic management approaches that enhance treatment adherence and ultimately improve the overall quality of life for individuals with HAE (Figure 1). Future investigations should focus on the interplay between these factors to optimize patient outcomes and inform tailored therapeutic interventions.

Conflict of Interest

Authors declare that they have no conflict of interest.

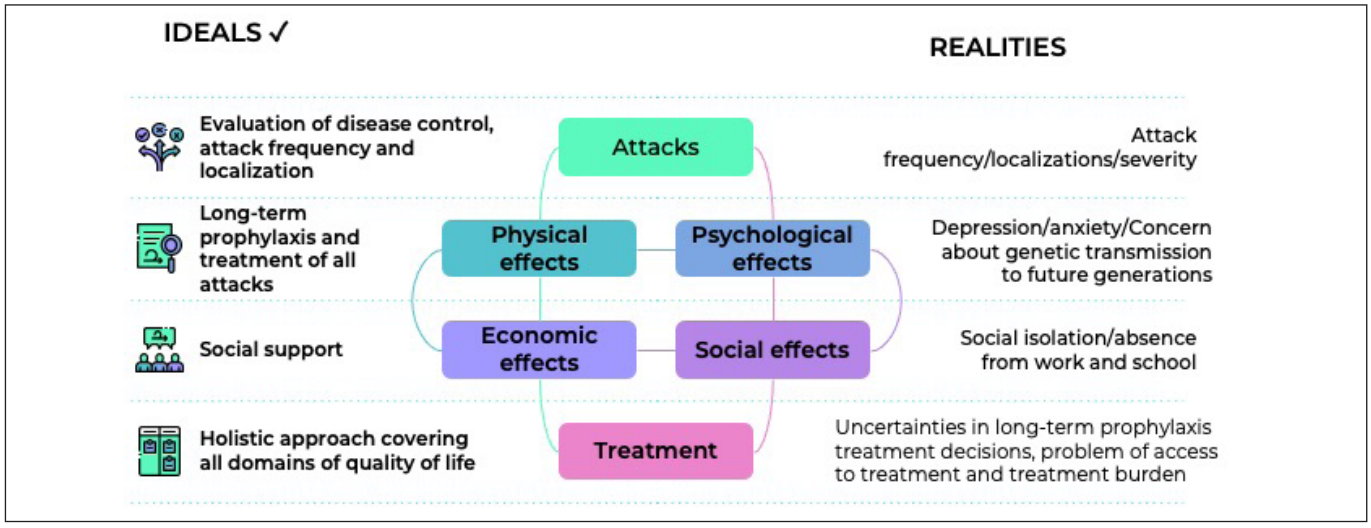

Figure 1. Bridging the Gap- ideals vs. realities in hereditary angioedema management.

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Authorship Contributions

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