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Quality of life in patients with hereditary angioedema correlates with angioedema control: Our experience at Chandigarh, India

Rajni Sharma[1,†], Suprit Basu[1,†], Reva Tyagi[1], Sangeetha Siniah[2], Prabal Barman[1], Archan Sil[1], Sanghamitra Machhua[1], Sanchi Chawla[1], Vignesh Pandiarajan[1], Rakesh Kumar Pilania[1], Saniya Sharma[1], Manpreet Dhaliwal[1], Deepti Suri[1], Amit Rawat[1], Sendhil M. Kumaran[3], Sunil Dogra[3], Surjit Singh[1], and Ankur Kumar Jindal[1,*]

ABSTRACT

Background: Hereditary angioedema (HAE) is characterized by unpredictable acute attacks that impair the patient's quality of life (QoL) not only due to the impact on functional abilities caused by edema but also due to pain and other symptoms, including fatigue, nausea, and vomiting.

Objectives: QoL studies in patients with HAE have not been carried out in the Indian subcontinent. Hence, we carried out this study to assess the QoL and to identify factors associated with impaired QoL in patients with HAE.

Methods: This was a cross-sectional observational study carried out in confirmed cases of HAE, aged >18 years, using angioedema QoL score and angioedema control test.

Results: We enrolled 135 patients with HAE (aged 18–80 years) with a mean age of 40.93 years. We observed that the QoL directly correlates with angioedema control and is also affected by other factors such as gender, duration of follow-up, and the frequency of episodes. Genitalia swelling, positive family history, and presence of mortality due to HAE in the family also significantly impact the QoL of patients with HAE. In addition, patients with type 1 HAE reported a poorer QoL as compared to patients with type 2 HAE.

Conclusion: We report the QoL of patients with HAE from settings where none of the first-line medications are available. Results of the study suggest that disease control is the most important factor that influences the QoL.

Keywords: Angioedema control; delays in diagnosis; follow-up duration; hereditary angioedema; quality of life

Key message

- We report the quality of life (QoL) of patients with hereditary angioedema (HAE) from settings where none of the first-line medications are available.
- Disease control is the most important factor that influences the QoL. In addition, gender, duration of follow-up, frequency of episodes, genitalia swelling, type of HAE, and presence of family history of HAE and death because of HAE in the family also significantly impact the QoL.
- There is an urgent need for easy availability and affordability of first-line medications in resource-limited settings like ours to have better disease control and QoL.

1. Introduction

Hereditary angioedema (HAE) is a rare disorder characterized by recurrent nonpruritic, often painful swelling episodes. Deficiency or dysfunction of the C1-inhibitor (C1-INH) protein is the most common etiology of HAE (in ~95% of cases). The episodes of angioedema are recurrent and often unpredictable (in terms of frequency, severity, duration, and location) [1–3]. Laryngeal edema is a potentially fatal manifestation and may be seen in up to 50% of all patients [4, 5]. A patient may look normal in between the episodes; however, the fear of getting an episode continues. HAE may significantly affect the quality of life (QoL) of patients. Impaired QoL in patients with HAE may be related to the severity of the disease as well as to the unpredictable nature of the condition [2]

It has been reported that approximately 50% of patients with HAE may have a major negative impact on both their capacity

[1]Pediatric Allergy Immunology Unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India, [2]Department of Pediatrics, Women and Children Hospital, Kuala Lumpur, Malaysia, [3]Department of Dermatology, Venerology and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

*Correspondence to Ankur Kumar Jindal, Pediatric Allergy Immunology Unit, Department of Pediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India.

Tel: +91-959-206-5559

Email: ankurjindal11@gmail.com

†Rajni Sharma and Suprit Basu contributed equally to this article as co-first authors.

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to engage in physical activity and their psychological well-being [6–8]. HAE can affect a patient's QoL due to pain, frequent attack symptoms such as exhaustion, nausea, and vomiting, as well as effects on functional abilities caused by edema. The QoL of HAE patients is comparable to those of other chronic illnesses such as severe asthma and Crohn's disease [3, 9]. Patients with HAE have been reported to have impaired QoL as compared to patients with allergic disorders and healthy individuals [10–12].

Availability and access to the first-line treatment options in patients with HAE have resulted in better QoL of patients with HAE. The most recent international guidelines have suggested that the goal of management in HAE should be to have a near-normal QoL and no mortality. There is a lack of data regarding patients with HAE and their QoL in this part of the world [13, 14]. Lack of availability and/or access to first-line treatment options in most developing countries, such as in India, may lead to severely impaired QoL of patients with HAE. We have observed deaths because of laryngeal edema in families with HAE in India [15]. There are no data on the QoL of patients with HAE in India. Hence, this study was carried out to assess the QoL of patients with HAE and to assess various factors that may have impacted the QoL.

2. Patients and methods

This was a cross-sectional observational study carried out in the Allergy Immunology Unit, Department of Pediatrics, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India. Patients (>18 years) who had a confirmed diagnosis of C1-INH-HAE based on characteristic clinical manifestations and suggestive laboratory investigations (low C4, low C1-INH, and/or low C1-INH function) were enrolled in this study. Genetic testing for *SERPING1* (Sanger sequencing or targeted next-generations sequencing or whole exome sequencing or multiplex ligation-dependent probe assay) was carried out in all patients. Clinical and laboratory data of patients were entered in a predesigned Excel sheet.

The QoL of patients was assessed using the angioedema QoL (AEQoL) scale while disease activity was assessed using the angioedema control test (AECT) (Supplementary material 1 and 2, http://links.lww.com/PA9/A45). AEQoL uses a recall period of 4 weeks and consists of 17 items that are scored on a Likert scale of 0–4 (maximum raw score: 68). These 17 items have been divided into 4 different domains, namely, eating; fear and shame; mood and weariness; and functioning. The raw score needs to be converted into a linear score of 0–100. Higher scores signify a worse QoL. A score of less than 30 indicates no impairment; score of 30–39 indicates mild impairment; score of 40–49 indicates moderate impairment; and a score of more than 50 indicates severe impairment in QoL.

AECT uses a recall period of 12 weeks and consists of 4 items that assess the attack frequency; impact on QoL; impact of the unpredictable nature of the disease; and angioedema control on treatment. These items are scored on a Likert scale of 0–4 (maximum score: 16). AECT score of less than 10 indicates poor disease control and ≥10 indicates good disease control [16, 17].

Because the translated version of these tools has not yet been validated, the English version was used only for patients who could read and understand English. Questionnaires were printed out and filled out by a trained psychologist after interviewing each patient. The survey was carried out before the availability of plasma-derived C1-INH replacement therapy in India.

2.1. Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Department Review Board, Department of Pediatrics, Advanced Pediatrics Centre, PGIMER, Chandigarh, India (Chairperson, Prof. Surjit Singh), vide DRB No- 73/23 dated 26-9-23.

2.2. Statistical analysis

The data were analyzed using IBM SPSS version 23.0 Statistics for Windows (IBM Corp., Armonk, NY, USA). The Skewness of the data was assessed using Kolmogorov–Smirnov test. The statistical tests were used to compare the mean/median values of the variables. Spearman's correlation coefficient was used to assess the association between QoL scores and various clinical and laboratory parameters. Multiple linear regression was used to identify the predictors of impaired QoL.

3. Results

In this study, we enrolled 135 patients with HAE (aged 18–80 years) with a mean age of 40.93 years (Supplementary Table 1, http://links.lww.com/PA9/A46). There were 64 (47.4%) women and 71 (52.6%) men. Of the 135 patients, 112 (82.9%) patients were classified as type 1 HAE and 23 (17.1%) as type 2 HAE.

Mean (±SD) age of symptom onset and diagnosis was 15.7 (±8.2) years and 34.9 (±17.5) years, respectively. Swelling over the face (eyelids and/or lips) was the most common presentation in 93.7% (136/145), followed by extremities (80%) and abdominal symptoms (62.1%). Laryngeal edema was reported by 53.3% of patients while swelling of the tongue was observed in 20.7% of patients. Majority of patients (91.9%) reported having a family history of HAE, and 19.2% of patients reported the death of at least 1 family member because of HAE. The mean follow-up of the entire cohort was 88.64 months and 20% of patients were on follow-up for more than 10 years. Of all participants, 88.8% had an episode of angioedema in the preceding month, and 29.6% had one within the previous 2 weeks.

Long-term prophylaxis included a combination of attenuated androgen and tranexamic acid (30.4%), attenuated androgen alone (16.3%), and tranexamic acid alone (11.1%). For on-demand treatment, fresh frozen plasma was used as none of the first-line medications were available in India when these data were analyzed.

3.1. Assessment of QoL

QoL was assessed using the AEQoL scale. Mean (±SD) QoL score was 43.34 ± 16.15. In this study, 24.4% reported no impairment in QoL; 13.3% reported mild impairment; 23.7% reported moderate impairment; and 38.5% reported severe impairment (Fig. 1).

The most common subdomain of the AEQoL scale affected was fear and shame (mean ± SD score: 51.26 ± 28.84), followed by nutrition (mean ± SD score: 37.96 ± 28.91), and functioning (mean ± SD score: 37.40 ± 29.21). The subdomain of fatigue and mood showed the least impairment (mean ± SD score: 28.33 ± 26.89).

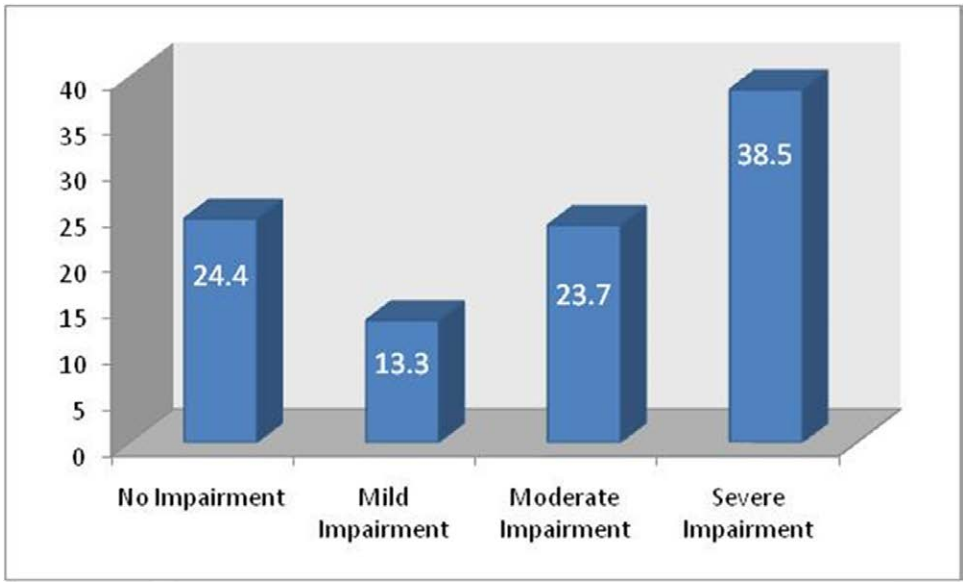

Figure 1. Severity of impairment in AEQoL. AEQoL, angioedema quality of life.

3.2. Association between AEQoL, demographic and clinical parameters

Male reported worse QoL when compared with female (P = 0.049). Patients with a higher frequency of episodes reported poorer QoL (r = –0.171; P = 0.047). Patients who were on follow-up for >2 years reported a better QoL (r = 0.288; P = 0.001) as compared to patients with follow-up duration <2 years (Supplementary Table 2, http://links.lww.com/PA9/A47).

Patients with type 1 HAE showed poorer QoL (P = 0.006), worse functioning (P = 0.007), low feeling and mood (P = 0.021), and more fear and shame compared to patients with type 2 HAE (P = 0.03).

3.3. Disease control

Results of the AECT are mentioned in Supplementary Table 3, http://links.lww.com/PA9/A48. The study population was divided into two groups (well-controlled and poorly controlled disease). Patients with poorly controlled disease also reported poorer QoL as compared to patients with well-controlled diseases (Fig. 2). Mean AEQoL score in patients with poorly controlled disease was 37.77 ± 15.92 while the mean AEQoL score in patients with well-controlled disease was 53.10 ± 11.24. This difference was statistically significant (P = 0.000). The scores of subdomains of AEQoL also showed a significant difference between patients with poorly controlled disease and well-controlled disease (Table 1).

3.4. Impact of patient demographics and clinical parameters on QoL

There was no significant impact on QoL in patients with diagnostic delays (delay in diagnosis >10 years) when compared to those who were diagnosed within 10 years of the onset of symptoms. The presence of HAE in the family and the history of death due to HAE in the family led to significantly poorer QoL. The presence of laryngeal edema, abdominal pain, facial swelling, and extremity swelling was not associated with significantly impaired QoL whereas the presence of genital swelling was associated with significantly poorer QoL (Table 2).

3.5. Association between AEQoL and AECT

The QoL appeared to positively correlate with the angioedema control (the higher the scores in AECT, the better the QoL [r = –0.361; P = 0.000]).

3.6. Potential factors of a poorer quality of life

A linear regression method was used to investigate the linear connection between overall QoL and demographic and clinical characteristics. Based on the duration of follow-up, disease control, and gender, a multiple linear regression was generated to predict QoL. A significant regression equation was found (F = 18.045; P = 0.000), with an R^2 of 0.531. The predicted QoL of participants is equal to 33.399 (disease control) + 1.468 (duration of follow-up) + 13.479 (gender), where the duration of follow-up is 0–2 years and ≥2 years. QoL was found to be significantly predicted by male gender, disease control, and length of follow-up.

4. Discussion

We report the QoL of patients with HAE in settings where none of the first-line treatment options are available. We observed that the QoL directly correlates with angioedema control and is also affected by other factors such as gender, duration of follow-up, and the frequency of episodes. Genitalia swelling, positive family history, and presence of mortality due to HAE in the family also significantly impact the QoL of patients with HAE. In addition, patients with type 1 HAE reported a poorer QoL than those with type 2 HAE.

HAE is a chronic disease characterized by unpredictable episodes of often painful, disfiguring, and potentially life-threatening episodes. Patients with HAE face a significant physical and psychological burden that affects their QoL. It may even affect patient's relationships, education, and employment [4, 18–21]. It has been observed that the disease's unpredictable nature significantly impacts QoL even in the absence of angioedema episodes at that particular moment [7, 19, 22–25]. Patient's overall disease experience may not be effectively reflected by the severity and number of attacks. Several other factors may also affect the QoL in patients with HAE [16, 18, 19, 23, 26, 27].

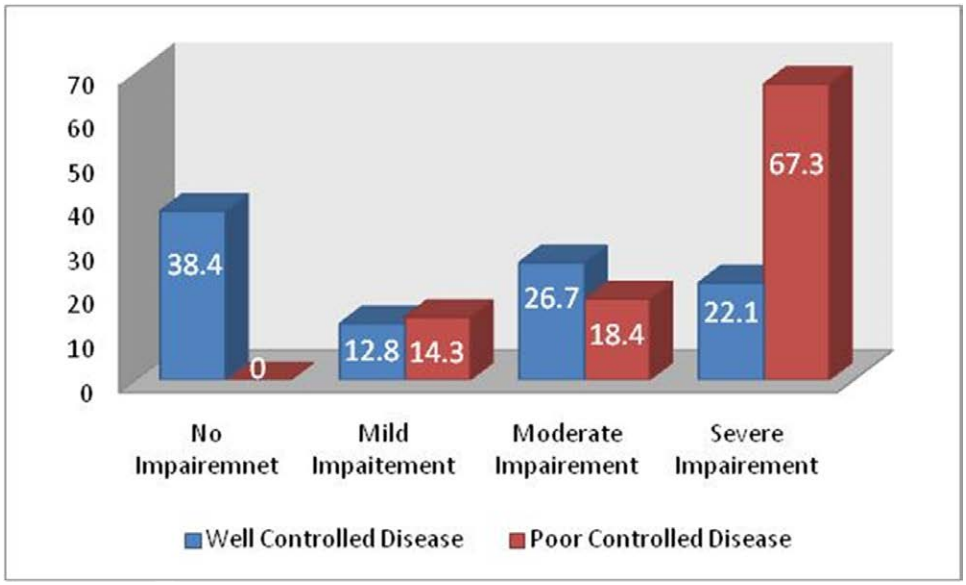

Figure 2. Impact of disease control in AEQoL. AEQoL, angioedema quality of life.

Table 1.

Association between various domains of Angioedema quality of life (AEQoL) Scores and the disease control

Variables	Poorly controlled disease Mean (±SD) n = 86	Well control disease Mean (±SD) n = 49	*P* value	r (with ACET)*
Functioning	30.34 (±27.81)	51.52 (±26.98)	<0.001	0.303
Fatigue and mood	19.83 (±23.44)	45.33 (±25.435)	<0.001	0.369
Fear and shame	44.12 (±30.29)	65.55 (±19.06)	<0.001	0.253
Nutrition	30.55 (±28.97)	52.77 (±24.98)	<0.001	0.346
Total score	38.35 (±15.83)	53.31 (±11.60)	<0.001	0.361

'r' represents correlation.

*Significance with a *P* value less than 0.001.

Availability and access to first-line treatment options for patients with HAE have led to significant improvement in the QoL of patients [28].

However, there is no data on the QoL of patients with HAE in developing countries where none of the first-line medications are available. Nonavailability of the first-line medications is likely to significantly affect the QoL of patients with HAE.

AEQoL, HAE-QoL, and the United States HAE Association QoL (HAEA-QoL) assessments are some of the tools that have been designed and validated for the assessment of QoL of patients with HAE. Other tools include the 36-item Short-Form Health Survey (SF-36) and the Euro QoL 5-dimensions survey [19, 26–28]. Most of the reported randomized clinical trials and cohorts on HAE have used the AEQoL scale to evaluate QoL. We also used AEQoL in our study. However, HAE-QoL scores are now increasingly being used in developed countries [23, 26]. In the present study, the mean QoL score was 43.34 ± 16.15, which is like the baseline scores observed in a study by Lumry et al [28] (mean AEQoL score 47.50 ± 21.94), the scores improved significantly with the use of the first-line therapy.

Most patients in the present study (75.6%) reported that HAE has a negative influence on their QoL. Of these, 13.3% reported mild impairment, 23.7% reported moderate impairment, and 38.5% reported significantly impaired QoL. The fears/shame domain of the AEQoL was affected the most. This is consistent with the observation that patients with HAE experience anxiety and sadness more frequently than the general population [10, 11, 19, 23–26].

We found that males had poorer QoL than females with HAE. This is in contrast to the findings from previous studies [12, 20]. It is possible that as more males are employed and work outdoors in India, the disease affects their QoL more than that of females. Patients on prolonged follow-up reported a better QoL. It may be because patients adjust to their medical condition more if they gain a better understanding of their disease. People with type 1 HAE reported poorer QoL, worse functioning, low mood, and more fear compared to patients with type 2 HAE. A similar comparison has not been done previously, however, Liu et al. [12] observed that low CI-INH is a risk factor for poorer QoL.

We observed that the majority of patients in the present study had positive family history and 19.2% had a history of loss of at least 1 family member because of HAE. The diagnostic delay in the present study (19.2 years) was more than the delays reported in previous cohorts (8–12.6 years) [18–24]. Despite a positive family history, there were significant delays in diagnosis.

The impact of different clinical variables on QoL was evaluated in the present study. It was observed that the presence of affected members and deaths due to HAE in the family significantly affected the QoL. However, the delay in diagnosis did not impact the QoL. We also observed significantly reduced QoL in patients with genitalia swelling. This has also been reported in other cohorts [19, 25, 26]. Studies have shown significantly poorer QoL in patients with HAE who have experienced swelling in the face and tongue, and abdominal pain [26]. We did not observe a similar result in the present study.

Male gender, disease control, and duration of follow-up were found to significantly predict QoL using a multivariate linear regression. The correlation between overall QoL and illness control was also found to be significantly positive. Better disease control had a favorable impact on patient's QoL. This study is limited by its cross-sectional nature, recall bias, and lack of a control group. A multicentric longitudinal study with the inclusion of a control population is the way forward.

Table 2.

Impact of patient demographics and clinical parameters on quality of life

Variables	QoL mean ±SD (number of HAE patients with the clinical parameter)	QoL mean ±SD (number of HAE patients without the clinical parameter)	*P* value
Delay in diagnosis (>10 years)	42.02 ± 16.5 (51)	39.8 ± 15.6 (84)	0.5
Family member affected	48.40 ± 14.83 (123)	38.64 ± 15.99 (12)	**<0.05**
Deaths in family (due to HAE)	46.98 ± 17.38 (26)	40.59 ± 14.67 (109)	**0.02**
Laryngeal edema (reported at least once)	43.88 ± 16.2 (72)	42.71 ± 16.09 (63)	0.67
Abdominal pain (reported at least once)	44.5 ± 15.4 (83)	41.02 ± 17.32 (52)	0.23
Facial swelling	43.4 ± 15.5 (126)	43.12 ± 17.2 (9)	0.9
Extremity swelling	44.55 ± 15.74 (108)	46.8 ± 16.5 (27)	0.34
Tongue swelling	43.82 ± 17.3 (28)	43.2 ± 15.9 (107)	0.86
Genitalia swelling	50.57 ± 13.04 (28)	40.41 ± 16.3 (107)	**<0.05**

Bold figures indicate significant values.
HAE, hereditary angioedema; QoL, quality of life.

5. Conclusions

We report the QoL of patients with HAE from settings where none of the first-line medications are available. Results of the study suggest that disease control is the most important factor that influences the QoL. In addition, gender, duration of follow-up, frequency of episodes, genitalia swelling, type of HAE, and presence of family history of HAE and death because of HAE in the family also significantly impact the QoL.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contributions

Ankur Kumar Jindal and Rajni Sharma: conceptualization, writing of the initial draft, critical revision of the manuscript and final approval, patient management. Suprit Basu: writing of the initial draft, revision of the manuscript, and patient management. Reva Tyagi, Prabal Barman, and Archan Sil: Writing and editing of the manuscript. Sanchi Chawla, Saniya Sharma, and Sanghamitra Machhua: Laboratory investigations, writing and editing of the manuscript. Sendhil M. Kumaran, Sunil Dogra, Deepti Suri, Vignesh Pandiarajan, and Rakesh Kumar Pilania: revision of the manuscript and patient management. Manpreet Dhaliwal, Surjit Singh, and Amit Rawat: laboratory investigations, writing and editing of the manuscript. Surjit Singh: conceptualization, critical revision of the manuscript, patient management.

SUPPLEMENTARY MATERIAL

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