

Burden of hereditary angioedema and impact on the quality of life in Portuguese patients – Real-world data

Carga do angioedema hereditário e impacto na qualidade de vida dos doentes portugueses – Dados da vida real

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ABSTRACT

Background: Hereditary angioedema (HAE) is a rare genetic disorder resulting mainly from a deficit/dysfunction of C1 esterase inhibitor. HAE is characterized by sudden, unpredictable and recurrent oedema episodes, potentially painful and/or fatal. HAE negatively affects QoL, productivity and career opportunities, leading to anxiety and depression. Being a rare disease its impact in Portuguese patients is not well-established. Our aim was to evaluate clinical characteristics and impact in a sample of Portuguese HAE patients. **Methods:** International, multi-centre, non-interventional, cross-sectional, web-based survey of adult patients (≥ 18 years old) with a self-reported physician diagnosis of HAE. Participants were asked about clinical characteristics, including patient-reported outcome measures (AECT, AE-QoL, HADS, WPAI:GH and SF-12v.2) to try to capture the patient perspective on the humanistic burden of HAE. **Results:** In this paper, we report only the data on Portuguese HAE patients. 15 patients completed the questionnaire (80% female, 86.7% type I). Mean age was 49.8 years (range: 28-81 years old). All had relatives with HAE. The most frequent co-morbidities were hypertension (26.7%) and elevated blood cholesterol (20%). Annual attack rate was ≥ 13

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in 26% of patients and ≥ 24 in 13%. The most recent reported HAE attack was abdominal (42.9%). The most recent attack had occurred in the previous 4 weeks for 60% of patients. Eleven patients were receiving long-term prophylaxis (LTP) with danazol, 1 with lanadelumab and 3 were only with on-demand therapy with icatibant. The mean $\pm$ SD score of AECT was 8.6 ± 2.6 (60% with a score < 10). The mean $\pm$ SD score of AE-QoL was 35.9 ± 31.8 . **Conclusions:** Our study showed that, even in LTP patients (mainly danazol-treated), there is still a high attack rate, low levels of disease control, and an impact on their QoL.

Key-words: Hereditary angioedema, control, AECT, quality of life, AE-QoL, PROMs.

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RESUMO

O angioedema hereditário (AEH) é uma doença genética rara que resulta principalmente de défice/disfunção do inibidor da CI-esterase, caracterizada por episódios de edema súbitos, imprevisíveis e recorrentes, potencialmente dolorosos e/ou fatais. O AEH afeta negativamente a qualidade de vida (QoL), produtividade e oportunidades de carreira, levando à ansiedade/depressão. O impacto nos doentes portugueses não está bem estabelecido. Este trabalho procurou avaliar características clínicas e impacto na QoL numa amostra de doentes portugueses com AEH. **Metodologia:** Estudo internacional, multicêntrico, não intervencional, transversal, com base num questionário anónimo online. Critérios de inclusão: adultos (≥ 18 anos) diagnosticados com AEH tipos I/II, com pelo menos um episódio de AEH no ano anterior, que tivessem recebido medicação para um episódio de AEH nos 2 anos anteriores e que consentissem no preenchimento do questionário. Os doentes foram questionados sobre aspetos clínicos, incluindo *patient-reported outcome measures* (AECT, AE-QoL, HADS, WPAI:GH, SF-12v.2) para avaliar a “carga humanística” do AEH. **Resultados:** Neste artigo analisamos apenas os resultados de doentes portugueses, provenientes de um único centro. Quinze doentes com AEH completaram o questionário (80,0% mulheres; 86,7% AEH tipo I). A média de idade foi de 49,8 anos (mínimo-máximo: 28-81 anos), todos com história familiar de AEH. As comorbilidades mais frequentes foram a hipertensão (26,7%) e colesterol elevado (20,0%). A frequência de crises/ano foi de ≥ 13 para 26% e de ≥ 24 para 13% dos doentes. A crise mais recente havia ocorrido nas últimas 4 semanas em 60% dos doentes, com 42,9% a reportarem atingimento abdominal. Três doentes não faziam profilaxia de longa duração (PLD), tendo apenas icatibant como terapêutica de crise. Dos 12 doentes sob PLD, 11 (93,3%) tomavam danazol e 1 lanadelumab. A pontuação média $\pm$ DP do AECT foi de $8,6 \pm 2,6$, (60% < 10). A pontuação média $\pm$ DP no questionário AE-QoL foi $35,9 \pm 31,8$. **Conclusões:** O nosso estudo indicou que vários doentes sob PLD, maioritariamente com danazol, reportaram uma elevada frequência de crises e doença pouco controlada e com impacto na sua QoL.

Palavras-chave: Angioedema hereditário, controlo, AECT, qualidade de vida, AE-QoL, PROMs.

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INTRODUCTION

Hereditary angioedema (HAE) is a rare genetic disorder affecting approximately 1:50,000 individuals (1). HAE is characterized by recurrent, sudden attacks of painful swelling (oedema) events (2-4). HAE attacks can occur suddenly and tend to affect the skin of the face and/or extremities (hands, arms, feet, legs, thighs), genitourinary organs and tissues, and/or mucous membranes of the gastrointestinal tract or airways (4,5). Angioedema attacks are potentially life-threatening (6,7) with acute laryngeal oedema being historically the main cause of angioedema-related mortality (7). The frequency, severity, and course of attacks can vary widely among patients and may also vary within the same person during different stages of life (8). Patients with HAE can experience a substantial burden of illness (9) due at least in part to the unpredictable nature of HAE and potential for life-threatening attacks.

The objectives of this study were to describe demographic and clinical characteristics of Portuguese patients with HAE, including treatment history, to describe the patient perspective on the humanistic burden of HAE including delay in diagnosis, disease control, health-related quality of life (HRQoL), anxiety and depression, and the HAE burden related with work productivity and activity impairment, using several of the validated patient reported outcome measures (PROM) (10).

MATERIAL AND METHODS

This study was part of an international, multi-centre, non-interventional, cross-sectional, web-based survey of patients with self-reported physician diagnosis of HAE, which has been reported previously (11). In Portugal, participants were identified and recruited from the potentially eligible patients with HAE followed at the Immunoallergy Department of Unidade Local de Saúde de Santa Maria. In this Department, at the time of the study, the

following drugs were available for long-term prophylaxis: danazol, tranexamic acid, epsilon-aminocaproic acid, and intravenous C1-inhibitor. Additionally, lanadelumab has been available since June 2020, but with several restrictions and, in 2022, only two patients were treated with this drug. For acute attacks, subcutaneous icatibant and intravenous C1-inhibitor were available at that time. Eligibility criteria included patients with a confirmed diagnosis of type I or II HAE (at least two measurements showing low serum C4 levels and low quantitative or functional C1 inhibitor levels), age 18 years or older, experienced at least 1 HAE attack or prodromal symptom in the past year, had been treated with a prescription medication for HAE (long-term prophylaxis (LTP) or on demand) within the past 2 years, were able to understand and provide consent and had adequate fluency in Portuguese. Eligible patients were contacted by phone and were included if they provided verbal consent to receive an electronic link to the questionnaire, where they were additionally requested to confirm their consent. Participants were provided a brief overview of the survey and a survey link. The study was approved by the local Ethics Board. Participants were recruited from July 2022 to November 2022, and the survey was completed and closed by the end of December 2022. We were able to reach by phone 60 HAE patients. Of these, 24 were willing to complete the online questionnaire. Only 17 patients provided the required additional electronic consent, and only 15 completed the questionnaire successfully, which included the following PROM: Angioedema Control Test (AECT); Angioedema Quality of Life (AE-QoL); Hospital Anxiety and Depression Scale (HADS), General Health Status (SF-12 v.2), and Work Productivity and Activity Impairment General Health (WPAI:GH). WPAI:GH is a generic measure that assesses health-related loss in work productivity, which consists of 6 questions over a recall period of 7 days. It includes 4 domains: absenteeism, presenteeism, overall work productivity loss (assessing combined absenteeism and presenteeism), and activity impairment, assessing impairment in daily activities not related

to work. Each domain score is expressed as a percentage of productivity loss/impairment, where higher scores indicate a greater loss in productivity.

Descriptive analyses of survey results were conducted.

RESULTS

We analysed 15 valid and completed questionnaires. The survey was completed by 12 female (80%) and 3 male HAE patients, with a mean age of 49.8 years, ranging from 28 to 81 years. Type I HAE was present in 13 and Type II in 2 patients. All patients had at least one relative with HAE.

Table I shows the characterization of the study population according to survey responses. Mean $\pm$ SD age at symptom onset was 12 ± 10 years, and mean $\pm$ SD age at diagnosis was 21 ± 10 years. Although three patients started symptoms already in adulthood, most patients developed symptoms before puberty, and one-third experienced symptoms before the age of 10. Eleven patients were on LTP with danazol for more than 3 years, one with lanadelumab for one year, and 3 patients were on demand treatment with only icatibant. Of patients treated with danazol, more than one third reported cardiovascular co-morbidities: hypertension and high blood cholesterol being the most frequently reported.

When asked to report all attacks, participants reported relatively high yearly attack rates, with a mean of approximately 10 attacks/year (Table I), but on-demand treatment was used in only 70% of the cases. More than 25% of participants reported more than 12 attacks per year (Figure 1). 60% of participants reported that their most recent attack had occurred in the past 4 weeks.

More than half of the participants (57.1%) reported having experienced prodromes before attacks. However, more than half also stated the presence of prodromal symptoms without progression to attacks.

The most reported symptoms during attacks were swelling in the extremities, abdominal pain, and abdomi-

Table I. Characterization of the study population

Parameter	Value
Total of patients, n	15
Female, n (%)	12 (80.0)
Mean age (min-max), years	49.8 (28-81)
HAE Phenotype, n (%)	
Type I	13 (86.7)
Type 2	2 (13.3)
Family history of HAE, n (%)	15 (100)
Age at symptom onset, n (%)	
<2 years	1 (6.7)
2-6 years	4 (26.7)
7-9 years	2 (13.3)
10-12 years	1 (6.7)
13-14 years	1 (6.7)
15-18 years	3 (20.0)
>18 years	3 (20.0)
Mean (SD) age at symptom onset, years	12 (10)
Age at diagnosis, n (%)	
<2 years	1 (6.7)
2-6 Years	1 (6.7)
7-10 years	1 (6.7)
11-17 years	3 (20.0)
18-20 years	3 (20.0)
21-30 years	3 (20.0)
31-40 years	2 (13.3)
41-50 years	0 (0%)
>50 years	1 (6.7%)
Mean (SD) age diagnosis, years	21 (10)
Long-term prophylaxis, n (%)	
No – Only on demand	3 (20.0)
Yes – Androgens / Lanadelumab)	11 (73.3) / 1 (6.7)
Comorbidities, n (%)	
Hypertension	4 (26.7)
High cholesterol	3 (20.0)
Sinusitis	2 (13.3)
Migraine	2 (13.3)
Cardiovascular disease, including stroke	2 (13.3)
Previous diagnosis of depression or anxiety	2 (13.3)
Attacks in the last year (self-reported)	
Patients with at least one attack, n (%)	
Mean attack number (min-max)	14 (93.3)
Treatment of attacks	10 (1-36)
Icatibant, n (%)	5 (35.7)
CI-INH, n (%)	4 (28.6)
Androgens, AF, and pain medications, n (%)	5 (35.7)
AECT <10, n (%)	9 (60.0)

Legend: n-number; SD – standard deviation; HAE – hereditary angioedema; AF – antifibrinolytics; AECT – angioedema control test

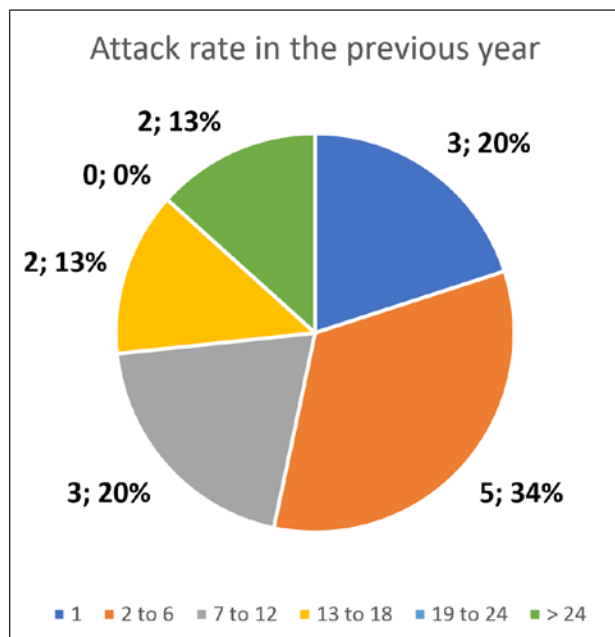


Figure 1. Attack rate in the previous year (self-reported) (n=15). Data based on participants' answers to the following question: "In the past year (12 months), how many angioedema attacks did you have? Please include any attacks in which you experienced swelling, abdominal pain, nausea, vomiting, diarrhea, or other symptoms related to your attack."

nal swelling, with 50% of participants reporting these symptoms during their most recent HAE attack; however, several other symptoms, less commonly described, were also reported (Figure 2), such as constipation or difficulty in urinating. Table 2 indicates the body locations affected in the most recent attack.

Fourteen participants reported having used some on-demand treatment in the previous year; on average, 70% of the attacks were treated. In the most recent attack, 5/14 participants received icatibant and 4/14 participants received CI-inhibitor concentrate. The remaining 5/14 participants used non-recommended on-demand treatment strategies, such as danazol, tranexamic acid, or pain-relief medications. The self-reported severity of the most recent attack in participants who received recommended on-demand treatment versus those who did not receive recommended on-demand treatment is shown in Figure 3, with the use of icatibant or CI-inhibitor being associated with a higher self-reported degree of attack severity. Additionally, participants were asked about how many doses of on-demand recommended drugs (icatibant or CI-inhibitor concentrate) they had with them, to administer in the event of an attack. No participant had more than 1 dose and 3/14 participants did not have any

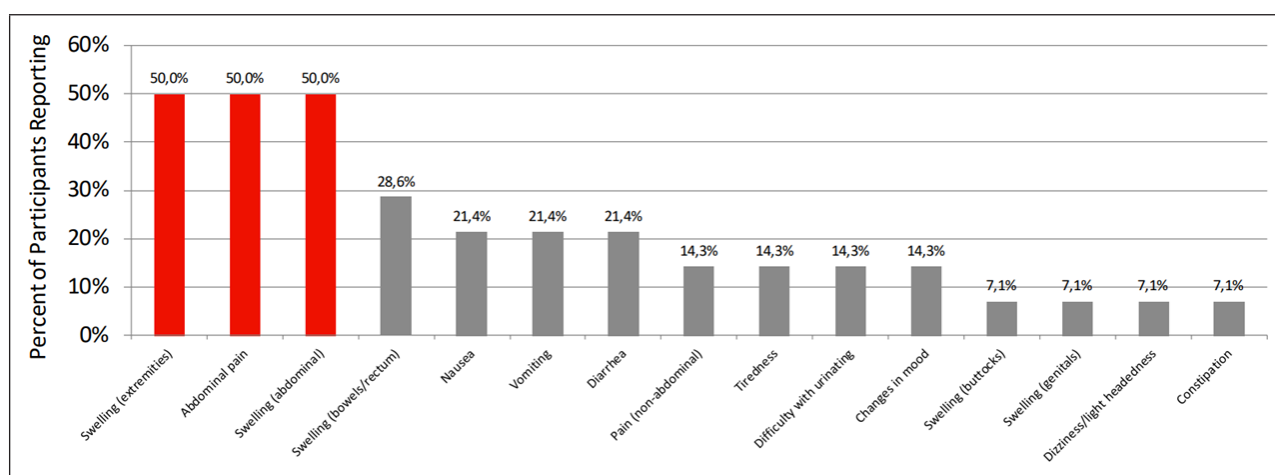


Figure 2. Most commonly reported symptoms during the most recent hereditary angioedema attack (n=14). Data based on participants' answers to the following question: "Considering your most recent HAE attack in the past year, which symptoms did you have?"

Table 2. Body areas affected during the most recent HAE attack (n=14) (patients could report more than one area). Data based on participants' answers to the following question: "Considering your most recent HAE attack in the past year, which body sites were affected?"

Body sites affected	n	%
Abdomen	6	43
Feet	5	36
Intestines	5	36
Bladder	4	29
Legs	3	21
Hands	3	21
Arms	2	14
Buttocks	1	7
Genitals	1	7

recommended on-demand medications at home at the time of the survey.

Regarding disease control, 9 participants (60%) had an AECT score below 10, indicating uncontrolled disease. Mean $\pm$ SD values for AECT scores in the 15 participants were 8.6 ± 2.6 . Other PROM scores are shown in Table 3. In AE-QoL, the greatest impairment was in the domain of fears/shame (46.9) with mean $\pm$ SD total AE-QoL sco-

re of 35.8 ± 31.0 . Regarding anxiety and depression, 2 participants had mild anxiety, 3 had moderate anxiety, and 2 mild depression, according to HADS scores. The remaining participants had normal scores, and if we consider all 15 participants together, then the mean total values of each subscale fall within the normal range (< 7). Regarding the WPAI-GH questionnaire, participants reported having missed a mean $\pm$ SD of $1.6\% \pm 3.3$ of work hours specifically due to HAE (absenteeism) and being impaired while working a mean $\pm$ SD of $8.0\% \pm 11.3$ of the time (presenteeism). Work productivity loss was reported as a mean $\pm$ SD of $9.3\% \pm 13.0$ of the overall working hours. The greatest impact on HAE patients' employment was activity impairment ($20.0\% \pm 29.0$ of the time). In the SF-12 v.2 questionnaire the ratings on each domain were rated similarly, with scores ranging, on average, between 40 and 50, with the highest score on vitality (50.60) and the lowest on mental health (Table 3).

DISCUSSION

We analysed 15 valid and completely filled questionnaires from 12 female (80%) and 3 male HAE patients. Although they represent a small sample of Portuguese

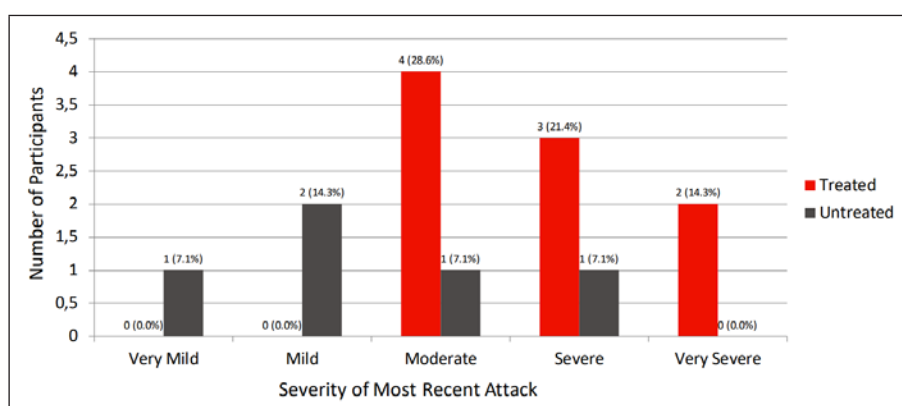


Figure 3. Severity of most recent attack by rescue treatment (n=14). Data based on participants' answers to the following question: "Thinking of your most recent angioedema attack, please rate its overall severity."

Table 3. Hereditary angioedema patient-reported outcome measures (PROM) (n=15)

AE-QoL	Mean	(± SD)
Functioning	29.6	(34.5)
Fatigue / Mood	29.3	(28.9)
Fears / Shame	46.9	(37.8)
Nutrition	31.7	(31.7)
Total AE-QoL score (%)	35.9	(31.8)
WPAI	Mean	(± SD)
Absenteeism	1.6	(3.3)
Presenteeism	8.0	(11.3)
Work productivity loss	9.3	(13.0)
Activity impairment	20.0	(29.0)
HADS	Mean	(± SD)
Anxiety	5.9	(4.2)
Depression	3.3	(2.9)
Total HADS	9.2	(6.8)
SF-12 v.2	Mean	(± SD)
Physical function	49.2	(11.4)
Role physical	48.3	(11.6)
Bodily pain	45.9	(12.6)
General health	41.1	(11.1)
Vitality	50.6	(11.3)
Social functioning	47.5	(14.0)
Role emotional	44.1	(15.0)
Mental health	40.8	(10.8)
Physical composite	46.8	(9.8)
Mental composite	47.5	(11.5)

Legend: AE-QoL – Angioedema Quality of Life questionnaire. AE-QoL score (%) ranges from 0 to 100. Higher scores indicate greater impairment (lower QoL). The AE-QoL assesses HR-QoL in those with angioedema over the past 4 weeks; WPAI – Work Productivity and Activity Impairment questionnaire. Higher values indicate greater percentage impairment and less work productivity. The WPAI assesses work productivity over the past week; SD – standard deviation; HADS – Hospital Anxiety and Depression Scale. Each subscale ranges from 0 to 21 (reference values: 0-7 normal; 8-10 mild; 11-14 moderate; 15-21 severe). The HADS assesses how the participant has been feeling in the past week; SF-12 v.2 – Short Form Health Survey 12-item, version 2.0. Each subscale ranges from 0 to 100, with higher scores indicating greater health. The SF-12 version 2.0 assesses general HR-QoL questionnaire over the past week.

HAE patients, our results demonstrate that these patients carry a heavy burden in several aspects of their lives. The first burden is that many patients have symptoms yet remain without a diagnosis for a long time. Similar to other studies (12, 13), the mean $\pm$ SD age at which symptoms started was, in our population, 12 ± 10 years, while the mean $\pm$ SD age at diagnosis was 21 ± 10 years, indicating a diagnostic delay of approximately 9 years. This long diagnostic delay is an important finding that should be emphasized, also in line with data from a recent systematic review (14).

After the diagnosis is established, the second burden relates to the number of attacks, which can be unpredictable, highly disfiguring, painful, and even life-threatening. Several participants on LTP with danazol still experienced attacks, and 60% presented AECT scores that show uncontrolled disease. Furthermore, frequent attacks impose a constant feeling of fear and shame. This was clearly captured in our study, where the main impact on the AE-QoL questionnaire was on the fears/shame domain. Even when patients have a number of attacks that justify starting LTP, as was the case in 80% of participants, LTP with second-line drugs such as danazol does not automatically mean a low number of attacks or no impact on quality of life. In fact, our data showed a mean of 10 attacks (0-36) in the preceding year. If we stratify attack rates as shown in Figure 1, we can see that only 20% had one attack in the previous year, 34% had between 2 and 6 attacks, and 46% of patients had more than one attack every two months, 26% with more than one attack/month. Although there are some differences, our results are in line with previous studies (12, 13) that have also shown a high attack rate even in HAE patients receiving LTP, especially in those receiving second-line LTP drugs, such as androgens or anti-fibrinolytics. The number of danazol-treated patients was higher than in other countries participating in this multi-national study (11), but it reflects the severity of our patients and the unavailability of other convenient long-term prophylactic options at the time of the survey in our country.

Although frequent, most of the attacks were reported by our patients as moderate or mild. This is also in line with data from other studies on LTP, with androgens showing a positive effect in reducing the frequency and severity of attacks in danazol-treated HAE patients, especially if higher danazol doses are used (15).

Although information on drug doses was not collected, in our hospital, HAE LTP danazol is usually used at low doses ($\leq 200\text{mg}$) for safety reasons, which often do not allow optimal levels of control in most patients. But even low androgen doses may constitute risk factors for aggravating important diseases that have been shown to be more frequent among HAE patients, such as hypertension, dyslipidaemia, thromboembolic phenomena, and ultimately cardiovascular diseases, as already acknowledged in recent studies (16) and also suggested in our data, as 26,7% reported hypertension and 20% high cholesterol levels. Nevertheless, in our study we did not have a comparative control arm. In HAE patients who show insufficient responses to usual danazol doses or who show evidence of adverse events of danazol, it is mandatory to reassess long-term therapeutic options, also acknowledging recent guideline changes (17).

Probably related to the high attack rate, corresponding to uncontrolled disease, our population showed elevated AE-QoL scores, with a mean total value of 35.9 ± 31.8 . HAE imposes a significant burden on quality of life for several reasons, and our AE-QoL mean scores represent, as defined in 2019 by Kulthanan K *et al* (18), small albeit unequivocal impact in the quality of life of this HAE population. Regarding the SF-12 questionnaire, a generic QoL questionnaire, three previous studies in HAE populations (12, 13, 19) have reported mean physical composite scores between 43.7 and 49.2% and mean mental composite scores varying between 42.6 and 44.9%. In our study these two composite scores had similarly reduced mean values: 46.8 and 47.5%, respectively, reflecting a lower health status than the norm (50%).

Most of our population sample had low AECT scores, with a mean $\pm$ SD of 8.6 ± 2.6 , and 60% having a score

<10 , indicating perceived uncontrolled disease (20). In the overall cohort of the multinational survey, mean AECT scores were slightly lower, with 75% having an AECT score < 10 (11). Although specific for angioedema and not specifically for HAE, AECT is an excellent tool for evaluating HAE control in daily practice and has been extensively used in clinical studies and in real-world studies in HAE patients. In an international study, in which 62.5% of patients were on LTP with CI inhibitor or danazol, Mendivil *et al* (12) reported mean $\pm$ SD AECT scores of 8.0 ± 4.0 , varying between 6.2 in Austria and 9.7 in France. These numbers, along with our data, show that there is a wide margin for improvement in the long-term management of HAE patients and that control evaluation should be sought in every visit to discuss with each patient if changes in the current LTP regimen are needed.

Despite the data showing a reduced quality of life and a sizable percentage of patients with uncontrolled disease, when the psychological impact was measured with the HADS scale, normal mean levels of anxiety and depression were reported. Similar values were noted in 2021 by Zarnowski *et al*, in a population of 37 HAE patients, showing mean anxiety and depression scores below 7, which represent normal values (21). In this study, these values were lower in patients receiving LTP than in those with on-demand therapy only. The fact that 80% of patients in our study were also on LTP may help to explain why there was no evidence of a significant impact on anxiety or depression.

Regarding the WPAI:GH questionnaire, participants reported having missed a mean $\pm$ SD of $1.6\% \pm 3.3$ of work hours specifically due to HAE (absenteeism). Presenteeism was reported as a mean $\pm$ SD of $8\% \pm 11.3$ of the time, and work productivity loss was reported as a mean $\pm$ SD of $9.3\% \pm 13.0$ of the overall work hours. These values are lower than reported in previous papers (11,12,22) but these data could be influenced by the participants' employment status, which was not assessed in the survey. Participants' age (mean 50 years, with the oldest participant being 81 years old) is also a factor that may influence employment status and, therefore, work productivity measurements.

By contrast, the mean $\pm$ SD values of $20.0\% \pm 29.0$ reported for activity impairment are more in line with other studies in HAE patients (11,12,22) and also assess the impact of the disease irrespective of employment status. WPAI:GH is a generic PROM that measures work productivity and activity impairment over a short period (the previous week) and, for that reason, may miss patients who did not experience attacks in that period. This potential limitation has also been noted in a recent paper on the validation of PROM in patients with angioedema (23).

One additional aspect of note is the patients' autonomous use of on-demand therapeutic strategies that are not recommended in the guidelines, such as danazol (purely on-demand use only or on-demand dose increase), or tranexamic acid, or even just analgesic drugs. In a previous paper, our group already reported this fact (24), which was also observed in other real-world studies (21,25,26) in a small percentage of patients. Despite a physician's recommendation to treat every attack with first-line effective therapy whenever available, we can speculate that this patient's decision probably happens in milder attacks where patients would avoid injectable and sometimes painful therapy. Despite guideline recommendations, three patients in our study did not have any effective rescue medication with them at the time of the survey, and no patient had more than one dose of effective on-demand therapy. Hence, another explanation for not using effective first-line medications could be an attempt to spare effective treatment for worsening or to treat moderate-severe attacks. Additionally, there are sometimes barriers that patients must overcome to get a new dose of the effective therapies, for instance, the need for a prescription from their HAE physician or some constraints related to the exclusive hospital-based drug dispensing in Portugal.

The importance of our paper is that it reports the results of a survey of a sample of Portuguese HAE patients with an extensive assessment of the real-world illness burden for HAE, without any doctor-induced bias. These results are also included in the global results of a multinational survey, conducted in several different countries

worldwide (11), something that could allow some future regional comparisons.

However, this study also has some limitations. Portuguese participants surveyed were recruited through a single clinical centre, and a low participation rate (25%) led to a small number of recruited patients, which could add bias, since patients with more severe or active disease are more likely to respond. These aspects may affect generalizability and comparability and, therefore, should be interpreted cautiously. The fact that all surveys were based solely on self-reported data, and no third-party confirmation was engaged to confirm any participant responses, may be associated with some recall bias.

CONCLUSIONS

This exploratory study allowed us to gather real-world data showing that there are Portuguese HAE patients who have an important disease burden and still face several unmet needs. Despite a small sample size, most of our adult participants receiving long-term danazol prophylaxis still had a high attack rate, insufficient disease control, and a clear impact on their QoL, as assessed by the various patient-reported outcome measures applied in this study. It is possible that this information may sometimes go unnoticed by their attending physicians, and, therefore, we believe that our study helps to underline the stringent need to routinely apply these PROMs in the real world of daily clinical practice. Only with this type of comprehensive information will it be possible to truly assess and discuss with patients if a modification of their long-term treatment plan is needed.

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Conflicts of interest

AS has received speaker fees from Takeda, Biocryst and CSL Behring; EP has no conflict of interest; MW is an employee of Takeda Development Center Americas, Inc. and holds stock/options in Takeda Pharmaceutical Company Limited; RM is an employee of ICON, which was contracted by Takeda to perform this study; MBF has received speaker fees and honoraria for advisory boards from Takeda, Biocryst and CSL Behring.

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