HAE-AS: A Specific Disease Activity Scale for Hereditary Angioedema With C1-Inhibitor Deficiency

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Abstract

Background: The activity of hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE) varies between patients and within individual patients.

Objective: This study aims to develop a disease activity scale for C1-INH-HAE (HAE-AS) with sound measurement properties.

Methods: Eleven countries participated in a prospective multicenter cohort study. A clinical questionnaire was self-completed by 290 adult patients with C1-INH-HAE. Patients also completed 2 quality of life scales, the SF-36v2 and the HAE-QoL. Rasch analysis and classic psychometric methods were used to preselect a series of clinical items: number of attacks by location and number of treated attacks, emergency room visits, psychological/psychiatric treatment, missed school/workdays in the previous 6 months; general health; and impairment in everyday work/activities due to pain.

Results: The mean (SD) age was 41.5 (14.7; range, 18-84) years, and 69% were females. The final 12-item Rasch model showed that the HAE-AS had satisfactory reliability (person separation index, 0.748), local item independence, unidimensionality, and no item bias by age or sex. The HAE-AS provided scores in a linear measure, with a mean of 10.66 (3.92; range, 0-30). Further analysis with classic psychometric methods indicated that the HAE-AS linear measure presented moderate-to-high convergent validity with quality of life scales (SF-36v2: physical component, r=−0.33; mental component, 0.555; HAE-QoL, −0.61), and good discriminative validity by age, sex, and disease severity (P<.05).

Conclusions: The HAE-AS is a short, valid, reliable, and psychometrically sound measure of the activity of C1-INH-HAE that could prove useful for research studies.

Key words: C1-INH-HAE. Clinical activity. Hereditary angioedema. Psychometric properties. Rasch analysis.
Introduction

Hereditary angioedema due to C1-inhibitor deficiency (C1-INH-HAE) is a genetic disease in which C1-inhibitor (C1-INH) function or level is reduced [1,2]. It is considered a rare disease that is difficult to diagnose and has an estimated prevalence of approximately 1 in 50 000 inhabitants [2] and a minimal prevalence that varies from 1.09 to 1.75 per 100 000 inhabitants [3,4].

C1-INH-HAE is characterized by unpredictable and recurrent episodes of nonerythematous, nonpruritic submucosal or subcutaneous edema affecting different areas of the body (extremities, face, upper airways, genitals, and gastrointestinal tract), which last between 2 and 5 days if left untreated [1,5,6]. Angioedema attacks can produce significant morbidity and may require patients to be admitted to hospital [7]. Upper airway edema can lead to airway compromise and fatal asphyxiation [8]. The impact of C1-INH-HAE on patient health-related quality of life (HRQOL) has been documented [9-11].

The severity of C1-INH-HAE was recently defined by Bygum et al [12] as the overall disease experience of the patient and includes the previous problems that the disease has imposed on the patient since its onset, the current burden of disease, and the long-term risks and prognosis, including the patient’s fears of potential problems. It is important to emphasize that the severity of C1-INH-HAE can vary during a patient’s lifetime, although not always progressively [1,6]. Several instruments have been proposed for measuring the severity of C1-INH-HAE [12], yet none have been validated, and no comprehensive psychometric studies have been performed to describe their measurement properties. In addition, the activity of C1-INH-HAE is considered to be “the sum of current problems (over a specified period of time) that a patient has experienced with his or her disease” [12]. The activity of C1-INH-HAE often fluctuates throughout a patient’s life, mainly due to different levels of exposure to triggers and in response to treatment [13,14]. Both activity and severity can differ between family members and patients with the same mutation in the C1NH gene, and, as previously mentioned, can change in individual patients during their lifetime [1,12].

The activity of C1-INH-HAE has been proposed as an important parameter on which to select long-term prophylaxis [16]. A specific disease activity instrument, validated for application in C1-INH-HAE, could be useful for designing studies on this condition. The present study aims to develop a disease activity scale for C1-INH-HAE, the Hereditary Angioedema Activity Score (HAE-AS), with sound psychometric properties evaluated through psychometric analysis following the Rasch model and the classical test theory.

Methods

Patients and Measures

A prospective multicenter cohort study of 290 adult patients was performed in 11 countries: Spain (n=44), Hungary (n=38), Austria (n=18), Germany (n=42), Argentina (n=16), Brazil (n=34), Canada (n=21), Denmark (n=27), Israel (n=9), Poland (n=22), and Romania (n=19).

A convenience sample was selected and proved to be heterogeneous regarding sex, age, age at onset of clinical symptoms, educational level, geographical origin, and disease severity. Patients were selected by their HAE physicians to complete the questionnaires. All the participating patients signed an informed consent form. The inclusion criteria were age ≥18 years with a confirmed laboratory diagnosis of C1-INH-HAE (type I or type II). The exclusion criteria were cognitive impairment that prevented the patient from understanding the questions and lack of fluency in the target language. Ethical approval for the study was provided by the Research Ethics Committee of Hospital Universitario La Paz (approval number PI-281) and local ethics committees as required. An ad hoc self-administered demographic and clinical questionnaire to assess the characteristics of disease (CQ-HAE) was completed by patients during hospital visits or at home. CQ-HAE was culturally adapted a priori to a chosen common language (American English) using the standard method for linguistic validation. The resultant CQ-HAE in American English was subsequently adapted following the same forward-backward methodology for each of the target languages spoken in the participating countries [17].

Patients also completed 2 HRQOL scales: a generic one, the Short Form 36-item Health Survey (SF36v2), and a C1-INH-HAE–specific one, the Hereditary Angioedema Quality of Life questionnaire (HAE-QoL). Validated versions of the SF36v2 and the HAE-QoL in the language of each participating country were used.
The SF-36v2 is a generic patient-reported measure of health status [18]. It yields a health-profile measure that has been extensively used in clinical and population studies. The SF-36v2 is divided into 2 components, the physical and the mental summary. Raw data from SF-36v2 were used, with no missing data imputation. The HAE-QoL is a specific measure of QOL in patients with C1-INH-HAE [17,19]. It contains 25 items on 7 dimensions (total score range, 25-135). On both HRQOL scales, higher values indicate higher QOL.

A descriptive, qualitative ad hoc score for disease severity in the last 6 months was used [17]. The 4 categories were as follows: (1) asymptomatic (no angioedema episodes, no long-term prophylactic treatment); (2) mild (no life-threatening angioedema episodes, no long-term prophylactic treatment and ≤3 episodes in the last 6 months); (3) moderate (no life-threatening angioedema episodes and ≤6 episodes in the last 6 months with long-term prophylactic treatment [excluding maintenance treatment with plasma-derived human C1-inhibitor concentrate, pdhC1INH] or 4-12 episodes in the last 6 months without long-term prophylactic treatment); and (4) severe (at least 1 life-threatening angioedema episode and/or long-term prophylactic treatment with pdhC1INH and/or >6 episodes in the last 6 months despite long-term prophylactic treatment and/or >12 episodes in the last 6 months without long-term prophylactic treatment).

The HAE-AS was initially designed using a set of 14 clinical items from the CQ-HAE clinical questionnaire: number of attacks by location; treated attacks; emergency room visits; psychological/psychiatric treatment; missed school/workdays in the previous 6 months; general health; and impairment in everyday work/activities due to pain. These clinical items were chosen based on a literature review, patient interviews, and discussion with physicians who have extensive experience in the management of C1-INH-HAE. The time frame was 6 months for all but 2 items ("11-general health" and "12-impairment in everyday work and activities due to pain"), which were limited to the previous month. The 6-month time interval is similarly used in other studies on HRQOL in hereditary angioedema [17] and as a follow-up interval in longitudinal studies [1,14].

### Data Analysis

Data management was centralized at Hospital Universitario La Paz, Madrid, Spain. Data were entered twice using a program designed to detect inconsistencies in order to guarantee accuracy. Three researchers evaluated discrepancies.

The Rasch model was analyzed using RUMM2030 [20]. A series of properties were iteratively examined in this analysis, as follows: fit to the Rasch model; category response ordering (ordered thresholds); reliability; local independence of items; unidimensionality; and differential item functioning (DIF) by sex, age (split by median, 40 years), family C1-INH-HAE history, and type. Rasch analysis for polytomous items requires a sample size of 250 or higher to ensure accurate estimates [21]. A detailed explanation of Rasch data analysis may be found in the Supplemental Material.

After obtaining the interval linear measure through Rasch analysis, further analyses were performed using SPSS: acceptability (scores distribution), known-groups

### Table 1. Disease Activity Scale for Hereditary Angioedema (Hereditary Angioedema Activity Score: HAE-AS)

| Item                                                                 | Option 1 | Option 2 | Option 3 | Option 4 |
|----------------------------------------------------------------------|----------|----------|----------|----------|
| 1. Peripheral attacks in the last 6 months                           | 0. No attacks | 1. 1 to 5 attacks | 2. 6 to 20 attacks | 3. >20 attacks |
| 2. Abdominal attacks in the last 6 months                            | 0. No attacks | 1. 1 to 5 attacks | 2. 6 to 20 attacks | 3. >20 attacks |
| 3. Facial attacks in the last 6 months                               | 0. No attacks | 1. 1 to 20 attacks | 2. >20 attacks |
| 4. Genital attacks in the last 6 months                              | 0. No attacks | 1. 1 to 5 attacks | 2. 6 to 20 attacks | 3. >20 attacks |
| 5. Upper airway attacks in the last 6 months                         | 0. No attacks | 1. 1 to 20 attacks | 2. >20 attacks |
| 6. Attacks at other locations in the last 6 months                   | 0. No attacks | 1. 1 to 20 attacks | 2. >20 attacks |
| 7. Number of treated attacks in the last 6 months                    | 0. No attacks | 1. 1 to 20 attacks | 2. >20 attacks |
| 8. Emergency visits in the last 6 months                             | 0. No | 1. 1 to 10 visits | 2. >10 visits |
| 9. Psychological and/or psychiatric treatment due to C1INHHAE in the last 6 months | 0. No | 1. Yes |
| 10. Days not attending school/work due to C1INHHAE in the last 6 months | 0. 0 day | 1. 1 to 5 days | 2. 6 to 15 days | 3. >15 days |
| 11. General health in the last month                                 | 0. Excellent | 1. Good | 2. Regular | 3. Poor |
| 12. Impairment in everyday work and activities due to pain in the last month | 0. Not at all | 1. A little bit | 2. Quite a bit | 3. Extremely |
validity, and convergent validity of the linear scale with related measures. The known-groups validity was evaluated with independent \( t \) tests by sex and age at onset of clinical symptoms, with significantly higher scores expected for women and patients with early onset of clinical symptoms [22]. Convergent validity was assessed with Pearson correlations, hypothesising moderate correlations (\( r=0.30-0.59 \)) to high correlations (\( >0.59 \)) with the 2 components of SF-36 and HAE-QoL [23]. In addition, an analysis of variance of the linear measure by severity of C1-INH-HAE score was performed. The standard error of measurement (SEM), calculated as SD \( \sqrt{(1-r)} \), where SD=standard deviation and \( r=\)reliability, was taken as a precision indicator [24]. Values equal to or less than half of the SD were considered satisfactory.

Lastly, a receiver operating characteristic (ROC) curve was constructed to establish a cut-off for classifying severe disease according to the HAE-AS linear measure. The HAE severity score was used as a gold standard (asymptomatic/mild/moderate vs severe). The optimal cut-off was assessed using the Youden index (highest sum of sensitivity and specificity) [25].

Results

The mean age of the sample was 41.5 (14.7; range, 18-84) years, and 69.0% were females. Most patients had a family history of C1-INH-HAE (69.7%) and had been diagnosed with C1-INH-HAE type I (80.0%). The mean score for the SF-36 physical and mental components was 49.7 (8.8) and 46.2 (10.4), respectively. The mean HAE-QoL score was 95.5 (25.5). In accordance with the severity scores, 38.6% of patients had severe disease. Information about the initial HAE-AS items is shown in Supplemental Table S1.

The results of Rasch analysis are presented in Supplemental material, Tables S2 and S3, and Figure S1. In summary, the final analysis based on 12 items provided a good fit to the Rasch model, with good reliability (PSI=0.748), absence of local dependency, unidimensionality, and no relevant DIF. The final HAE-AS questionnaire is provided in Table 1.

Table 2 displays the transformation of the ordinal ratings into an interval linear measure of the HAE-AS scale. The mean score for the linear measure on a scale of 0 to 30 was 10.66 (3.92), with a normal distribution and a skewness and kurtosis coefficient of –0.469 and –0.230, respectively. The SEM was 1.984.

The linear measure of the HAE-AS presented higher scores in women (mean difference=–1.597; \( P=0.001 \)) and in patients with early onset of clinical symptoms (mean difference=1.182; \( P=0.009 \)). The linear measure showed a negative, moderate correlation with the physical and mental components of SF-36 (\( r=–0.330 \) and \( r=–0.555 \), respectively, \( p<0.001 \)) and a high correlation with HAE-QoL (\( r=–0.641 \)). A higher linear measure score was associated with greater severity according to the C1-INH-HAE score (linear trend \( F=182.938, P<0.001 \); Figure).

The area under the ROC curve was large (0.859; 95%CI, 0.813-0.906). According to the Youden index, a value greater than 12 on the linear scale was considered the best cut-off for severe C1-INH-HAE (sensitivity, 73.2%; specificity, 88.3%; predictive positive and negative values, 81.2% and 82.7%, respectively).

Table 2. Table for Conversion of Ordinal Scores Into an Interval Linear Measure (Cut-off for Severe Activity: 12-13).

| Raw score | Linear Measure | Raw score | Linear Measure |
|-----------|----------------|-----------|----------------|
|           | Logit scale    | 0-30 scale| Logit scale    | 0-30 scale    |
| 0         | –5.504         | 0.000     | 15             | –0.081        | 16.148       |
| 1         | –4.214         | 3.841     | 16             | 0.097         | 16.678       |
| 2         | –3.388         | 6.301     | 17             | 0.277         | 17.214       |
| 3         | –2.86          | 7.873     | 18             | 0.462         | 17.765       |
| 4         | –2.466         | 9.046     | 19             | 0.653         | 18.333       |
| 5         | –2.145         | 10.002    | 20             | 0.854         | 18.932       |
| 6         | –1.869         | 10.824    | 21             | 1.067         | 19.566       |
| 7         | –1.623         | 11.556    | 22             | 1.298         | 20.254       |
| 8         | –1.399         | 12.223    | 23             | 1.551         | 21.007       |
| 9         | –1.189         | 12.849    | 24             | 1.834         | 21.850       |
| 10        | –0.991         | 13.438    | 25             | 2.158         | 22.815       |
| 11        | –0.801         | 14.004    | 26             | 2.539         | 23.949       |
| 12        | –0.616         | 14.555    | 27             | 3.013         | 25.361       |
| 13        | –0.436         | 15.091    | 28             | 3.667         | 27.308       |
| 14        | –0.258         | 15.621    | 29-30          | 4.571         | 30.000       |

Note: This table is not valid for cases with missing data. To use this table, sum the item scores according to Table 1. For instance, a total score of 9 corresponds to –1.189 logits or to a score of 12.8 on a 0-30 scale (mild disease). Dotted line: cut-off score (12-13).
Activity Scale for Hereditary Angioedema

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Discussion

HAE-AS provides a linear measure that makes it possible to assess the activity of C1-INH-HAE. The scale was specifically developed for C1-INH-HAE and was found to have satisfactory reliability and construct validity. Therefore, HAE-AS might prove useful for analyzing the determinants of the severity of C1-INH-HAE in future studies.

Reliability is satisfactory [26]. Furthermore, items were locally independent and formed a unique dimension, indicating that the HAE-AS measures only 1 construct and supports items being taken together and assigned a single score. Adequate fit was achieved by removing 2 of the 14 items included in the initial questionnaire. The item “treatment maintenance in the last 6 months” appeared to be measuring a different construct, whereas “attack frequency in the last 6 months” was identified as a redundant item (fit residual = -4.778), possibly because this item is the sum of the items regarding attacks by location.

Seven of the 12 items refer to the number of angioedema attacks in the previous 6 months. The number of attacks was previously used as an indicator of disease severity/activity in clinical trials [27-30], case series [22,30], and some nonvalidated clinical scores of disease severity or disease activity [1,17,31]. Moreover, the number of angioedema attacks has been found to be a determinant of HRQOL in C1-INH-HAE [11].

Rasch analysis also provides an item hierarchy (Figure S1), showing that facial attacks, upper airway attacks, and attacks at “other locations” account for the highest activity, whereas peripheral attacks and good general health account for the lowest clinical activity. Laryngeal or upper airway attacks had previously been described by patients as the most severe type of attacks [32] and had been considered indicative of more severe disease in some disease severity scales [33]. Two items expressing the impact of the disease on the patient’s life (item 10, days not attending school/work due to C1-INH-HAE in the last 6 months; and item 12, impairment in everyday work and activities due to pain in the last month) are located in the middle of the activity score. In other words, these items are endorsed even by patients with only mild-to-moderate disease. The disruption caused by the disease in everyday life has been described elsewhere [13,32,34,35]. In summary, the item hierarchy reflects the content validity of the scale.

HAE-AS was free from the bias associated with several group characteristics, namely, sex, age, family history, and C1-INH-HAE type. However, small sample sizes prevented DIF analysis by country, and further studies are called for. The HAE-AS linear measure presented a normal distribution, thereby allowing for the use of parametric statistical analysis. The scale also showed good discriminative ability by sex and age at onset of symptoms, which are not subject to item bias. As expected, women and patients with early onset of symptoms, in whom disease activity was more pronounced, presented higher HAE-AS scores [5,31,36,37].

Insofar as convergent validity is concerned, there was a significant and moderate-to-high relationship between the HAE-AS scale and HRQOL measures. As hypothesized, a higher C1-INH-HAE activity score on the HAE-AS scale is associated with a more pronounced impact on the patient’s life and, thus, lower HRQOL. We observed a stronger association between HAE-AS and the SF-36v2 mental component than the physical component. Similarly, a previous study showed that, following treatment, changes were greater in the SF-36 mental component than in the physical one [9], possibly because, as demonstrated in both longitudinal and cross-sectional studies of C1-INH-HAE patients, the SF-36v2 mental component is more sensitive to changes than the physical component.

The HAE-AS showed a stronger association with HAE-QoL than with SF-36v2, probably because both HAE-AS and HAE-QoL were specifically designed for C1-INH-HAE, and thus, both capture important disease features that are not covered by a generic QOL measure such as the SF-36v2. Indeed, the SF-36v2 failed to capture sex or age differences in a study on C1-INH-HAE and QOL [10]. Therefore, HAE-AS and HAE-QoL are recommended for studying C1-INH-HAE.

An ROC curve was used to determine a cut-off for assessing responses that indicated a high degree of severity of C1-INH-HAE. This cut-off showed acceptable sensitivity, specificity, and predictive values and could prove to be extremely useful for research or clinical practice.

HAE-AS is the first validated scale developed specifically for measuring C1-INH-HAE activity. The Angioedema Activity Score (AAS) [15] is a validated scale for measuring angioedema activity and could potentially be used to prospectively measure disease activity in any kind of angioedema. Although the period it refers to may be as long as needed, it was actually designed and validated to measure disease activity for only 1 month. A 6-month evaluation period, as is the case with HAE-AS, could be more suitable for C1-INH-HAE, in which the general frequency of follow-up visits is once every 6-12 months and the frequency of angioedema attacks varies greatly from month to month [1,6,7,13,14]. Another drawback is that patients are required to complete the AAS on a daily basis, an onerous task that can result in poor adherence. Finally, data from a large international sample reveal a lack of knowledge about the psychometric properties of the AAS according to the Rasch model and classic test theory [15].

Our study is subject to a series of limitations. First, as C1-INH-HAE is a rare genetic disease, it was not possible...
to obtain a random sample. However, the multicenter nature of the study and the relatively large sample size broadened the applicability of our findings. Second, further studies are needed to assess other psychometric features such as test-retest reliability, sensitivity to change, and concurrent validity with the AAS score. Nevertheless, the good reliability and precision, and proven ability to discriminate between groups, even with respect to severity, indicate that the scale’s sensitivity to change might also be appropriate for making comparisons over time or according to type of treatment. Third, patients might not accurately remember their disease activity during the previous 6 months. Further studies should compare patients’ reports with clinical records. It would also be interesting to evaluate the HAE-AS in patients with nonhereditary angioedema. Therefore, HAE-AS presents several strengths and some weaknesses and leaves room for improvement, as is the case with almost all outcome measures reported by patients.

In conclusion, we present the first validated scale developed specifically for measuring C1-INH-HAE activity. HAE-AS is a short, psychometrically sound questionnaire that provides a linear measure of disease activity, with satisfactory reliability and good content and construct validity, as well as discriminative validity. We recommend the use of HAE-AS in future studies on C1-INH-HAE.

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Conflicts of Interest

Dr. Teresa Caballero is an investigator from the IdiP AZ program for promoting research activities. The remaining authors declare that they have no conflicts of interest.

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