Determinants of Disease Activity in Adults With Hereditary Angioedema due to C1-Esterase Inhibitor Deficiency

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J Investig Allergol Clin Immunol 2024; Vol. 34(6): XX-XX
doi: 10.18176/jiaci.1009

Key words: Hereditary angioedema. Disease activity. Health-related quality of life. C1-inhibitor. HAE-QoL.

Palabras clave: Angioedema hereditario. Actividad de enfermedad. Calidad de vida relacionada con la salud. HAE-QoL.

Hereditary angioedema due to C1 inhibitor deficiency/dysfunction (HAE-C1INH) is a potentially life-threatening disease [1] with variable clinical expression. It increases disease burden and impairs health-related quality of life (HRQOL) [2]. Some studies have reported clinical data and complement values as possible predictors of disease activity/severity, and disease activity has been shown to decrease HRQOL [3-5]. Disease activity and HRQOL should be regularly evaluated [6].

The objective of this study was to identify the determinants of disease activity in adults with HAE-C1INH to improve disease management and HRQOL.

An observational and prospective study was performed in patients aged ≥18 years with a confirmed diagnosis of HAE-C1INH [1] between April 2016 and May 2018. Demographic data, clinical data, and complement levels (C4, C1INH protein, C1INH functional) measured at diagnosis and during the 6 months before inclusion in the study were collected. The recall period was 6 months. Disease activity and HRQOL were assessed using the Hereditary Angioedema Disease Activity Scale (HAE-AS) [7] and Hereditary Angioedema Quality of Life (HAE-QoL) questionnaire [8], respectively. The statistical analysis was performed using IBM SPSS Statistics for Windows Version 22.0 (IBM Corp.). The study protocol was approved by the local ethics committee (PI-2297).

We included 88 patients (56% women) with confirmed HAE-C1INH. Of these, 81.9% had had angioedema attacks in the previous 6 months, and 33% of patients had an HAE-AS score >12. The demographic data, clinical characteristics, complement levels, total HAE-AS score, and total HAE-QoL score of the sample are shown in Supplementary table 1. Disease activity measured by HAE-AS was similar in males (9.58 [3.38]) and in females (10.63 [3.54], P=.165). Besides, HAE-AS score was negatively correlated with age at onset of symptoms (ρ=–0.273, P=.015). However, there was no significant correlation between the total number of angioedema attacks in the previous 6 months and the age at onset of symptoms (ρ=–0.204, P=.080).

The HAE-AS score was higher in patients receiving long-term prophylaxis (LTP) than in those who were not, although the difference was not significant (11.08 [3.34] vs 9.70 [3.49], P=.08). Similarly, while there were no significant differences in HAE-AS between the different types of LTP, the score was higher in patients taking intravenous pdC1INH (Supplementary table 2).

Regarding complement levels at diagnosis, there were no differences between women and men, as follows: C4 (7.1 [4.3]

Table. Comparison Between Complement Levels in Patients With and Without Angioedema Attacks in the Previous 6 Months.

	Angioedema attacks in the previous 6 months[a,b]		
	No (n=15)	Yes (n=68)	*P* Value
C4 at diagnosis, mg/dL No. Mean (SD)	15/15 9.73 (4.55)	59/68 7.28 (4.02)	.044
C1INHF at diagnosis, % No. Mean (SD)	9/15 20.59 (9.31)	26/68 20.83 (10.14)	.951
C1INH at diagnosis, mg/dL No. Median (IQR)	14/15 9.12 (7.90- 12.70)	53/68 7.82 (5.18-11.00)	.059
C4 (previous 6 mo), mg/dL No. Mean (SD)	15/15 6.20 (2.95)	67/68 6.99 (3.35)	.400
C1INHF (previous 6 mo), % No. Mean (SD)	15/15 25.25 (6.64)	65/68 20.70 (10.88)	.125
C1 INH (previous 6 mo), mg/dL No. Median (IQR)	14/15 7.37 (4.45-9.06)	63/68 6.91 (5.03-8.56)	.984

Abbreviations: C1INH, C1 inhibitor protein; C1INHF, C1 inhibitor functional activity.
[a]Data on angioedema attacks was missing in 5 patients.
[b]Normal range: C4, 14-60 mg/dL; C1INHF, >50%; C1INH, 16-33 mg/dL.

vs 8.5 [4.1], *P*=.131), functional C1INH (20.3 [10.1] vs 21.5 [9.0], *P*=.705), and C1INH protein (*P*=.389). C4 levels at diagnosis were significantly lower in patients who had experienced angioedema attacks than in those who had been asymptomatic during the previous 6 months (*P*=.044, Table). C1INH levels at diagnosis were also lower in patients with angioedema attacks than in asymptomatic patients in the previous 6 months, although the difference was not statistically significant (*P*=.059). However, there were no differences regarding functional C1INH.

No statistically significant differences were observed for complement levels between patients with LTP and those without LTP (Supplementary table 3). Likewise, no differences in complement levels were found between patients taking the different types of LTP (Supplementary table 4).

The mean (SD) total HAE-QoL score (n=84) was 100.8 (23.9 [range, 32.0-134.0]). Women had worse HRQOL than men (94.5 [26.1] vs 108.7 [18.9], *P*=.07). HAE-QoL scores were significantly lower in patients with angioedema attacks (97.0 [23.2]) than in asymptomatic patients during the previous 6 months (122.9 [8.7], *P*<.0001). Furthermore, patients who were on LTP also had HAE-QoL scores indicating greater impairment (92.8 [24.5]) than patients who were not on LTP (104.6 [22.8], *P*=.03). The total HAE-QoL score was negatively correlated with the total number of angioedema episodes in the previous 6 months (ρ=–0.397, *P*<.0001) and with HAE-AS (–0.649, *P*<.0001).

In this observational study, low C4 levels at diagnosis were associated with higher disease activity. In contrast, Kelemen et al [4] analyzed the possible association between baseline complement levels and disease severity and found significantly lower baseline functional C1INH levels in patients with moderate and severe disease than in patients with asymptomatic and minimally severe disease. However, this relationship was not demonstrated with C1INH, C4, or CH50. Other authors also found an association between disease activity and C4 levels. A negative correlation between C4 and functional C1INH levels and the annual number of attacks and the number of pdC1INH vials administered per year has been reported [9]. Similarly, a study that included 162 HAE patients found lower C4 levels in patients with a high number of angioedema attacks not receiving LTP [10]. In addition, a retrospective descriptive study from our group that included 112 HAE-C1INH patients reported similar results, namely an association between angioedema attacks in the previous year and the most recent C4 assessment [11], although we did not find such a relationship with current C4 levels in this study.

As previously described [3,11,12], we found a negative correlation between disease activity and age at onset of symptoms. Moreover, earlier onset has been correlated with both lower C1INH antigen level and functional C1INH [12].

In this study, HRQOL was poorer in females than in males. While similar to data from previous reports, the difference was not significant [13]. Moreover, disease activity measured by HAE-AS and angioedema attack frequency did not differ between females and males. Accordingly, Nordenfelt et al [13] did not find sex differences in disease activity measured using the Angioedema Activity Score, although the authors attributed these findings to the older age of their female participants and, probably, low sex hormone levels.

In our study, HRQOL was affected by disease activity. Two recent studies also reported this negative association using the HAE-QoL [14,15]. In contrast to previous reports [15], we found that patients receiving LTP had poorer HRQOL than patients without LTP. This could be because patients receiving LTP often have greater disease activity than those receiving exclusive on-demand treatment or because of the characteristics of the LTP available at that time.

In summary, earlier onset of symptoms correlated with greater disease activity, and C4 levels at diagnosis were lower in patients who had experienced angioedema attacks in the previous 6 months. In addition, HRQOL was negatively affected by disease activity.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

Nieves Prior and Teresa Caballero are developers of the HAE-AS and HAE-QoL.

Teresa Caballero has participated on advisory boards from Austria, BioCryst, CSL Behring, KalVista, Novartis, Pharming NV, Pharvaris, and Takeda and is a member of speakers' bureaus for CSL Behring, Novartis, Pharming and Takeda. She has received grants or honoraria from BioCryst, CSL Behring, Kalvista, Novartis, PharmingNV, and Takeda and funding to attend conferences and educational events from BioCryst, CSL Behring, Novartis, Pharming, and Takeda. She is a clinical trial/registry/study investigator for BioCryst, Biomarin, CSL Behring, IONIS, KalVista, Novartis, Pharming NV, and Takeda and a researcher on the Instituto de Investigación Hospital Universitario La Paz (IdiPAZ) program for promoting research activities.

Rosario Cabañas has participated on data safety monitoring boards or advisory boards for CSL-Behring, Biocryst, Novartis, and Takeda Pharmaceuticals and has received grants or contracts from Takeda Pharmaceuticals, CSL Behring, and AEDAF. She has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Pharming NV and Novartis and funding to attend meetings and/or travel from Takeda Pharmaceuticals, CSL-Behring, Pharming NV, and Novartis.

Nieves Prior has participated on data safety monitoring boards or advisory boards for CSL-Behring, Biocryst, Novartis, and Takeda Pharmaceuticals. She has received grants or contracts from Takeda Pharmaceuticals, CSL-Behring, and Byocrist and payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Takeda Pharmaceuticals, Pharming NV, and Novartis. She has received funding to attend meetings and/or travel from Takeda Pharmaceuticals, CSL-Behring, Pharming NV, and Novartis.

María Pedrosa has participated on data safety monitoring boards and advisory boards from Byocryst and Takeda Pharmaceuticals. She has also received payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, and educational events from Takeda, CSL Behring,

and Novartis and funding to attend meetings and/or travel from Takeda Pharmaceuticals, CSL-Behring, and Novartis. She is a clinical trial/registry/study investigator for Pharming, Takeda, CSL-Behring, Novartis, and Biocryst.

Elsa Phillips-Anglés has been a clinical trial subinvestigator/study coordinator for Takeda Pharmaceuticals and Biocryst.

The remaining authors declare that they have no conflicts of interest.

Previous Presentations

Presented as a poster at EAACI 2019.

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Manuscript received March 3, 2024; accepted for publication March 26, 2024.

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