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RESEARCH ARTICLE

Assessing the control of the disease on current treatments available in Romania for hereditary angioedema patients

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Background: Acute treatment must be permanently accessible for every patient diagnosed with hereditary angioedema (HAE). In many cases this type of therapy does not provide/offer sufficient control of the disease, so long-term prophylaxis (LTP) is recommended. In the case of regular and prolonged/extended administration of drugs, the route of administration is essential. The aim of the investigation was to assess the control of HAE among patients in Romania receiving the available medications, while also examining potential correlations within the outcomes.

Material and methods: A phone call was made to all adult patients registered in the Romanian HAE Registry. Patients with confirmed diagnosis of HAE who had at least one angioedema attack in the last three months were asked to complete, online, the angioedema control test (AECT) for one- and three months respectively. AECT scores were calculated according to the authors' instructions.

Results: A total of 121 patients were contacted. Of these, 83 complies with the eligibility criteria and 56 completed the questionnaires (response rate 67.4%), 18 (32.1%) men and 38 (67.9%) women. Acute, home administered treatment with Icatibant or pdC1-INH was available for every patient during the study time. Nine (14.5%) participants used LTP too, with pdC1-INH. These treatments ensured an adequate control of the disease in only 13 patients (21%) in case of the three-month AECT, of whom 2 used LTP. The one-month questionnaire showed a well-controlled disease in 14 patients (23%), from which only 1 was on prophylactic therapy.

Conclusion: In most Romanian HAE patients, the available drugs do not offer a proper control of the disease. Even though a first-line drug for LTP is available, its administration route by intravenous injections makes it inconvenient for many patients, highlighting the necessity for new, easy-to administer drugs for HAE patients from our country.

Keywords: angioedema, hereditary angioedema, quality of life, on-demand, long-term prophylaxis

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Introduction

Hereditary angioedema (HAE) is a rare inherited disorder characterized by recurrent episodes of nonpruritic, nonpitting oedema that can affect any body part [1]. The most common location of the swelling is the skin (91% of patients), with over 80% of cases occurring in the extremities (hands, arms, feet and legs) [2]. Submucosal oedema of the gastrointestinal tract (abdominal attack) is manifested by severe pain, nausea, vomiting, and ascites formation and is present in approximately 73% of patients [3]. While upper airway swelling is less frequent (≤ 1% of all attacks) [4], it is the most dangerous clinical manifestation of HAE due to the risk of asphyxiation. Therefore, early diagnosis and the availability of specific treatment are indispensable for all patients with a confirmed diagnosis of HAE [5].

HAE should be suspected in every patient with recurrent episodes of angioedema without wheals [6]. The low levels of C1-INH (function and/or antigenic level), caused by mutations in the SERPING1 gene, are the laboratory parameters that confirm the diagnosis of HAE with C1-INH deficiency (HAE-C1-INH) [7]. If these parameters cannot be determined, a low level of C4, together with a positive family history, can help in the diagnosis establishment, with the mention that in 25% of cases, a de novo mutation can appear [8].

A genetic test is recommended only in particular cases for HAE-C1-INH, in contrast to HAE with normal levels of C1-INH (HAE-nC1-INH), where testing for gene variants known to be associated with these forms of HAE (factor XII, angiopoietin-1, plasminogen, kininogen, myoferlin or heparin sulphate 3-0-sulfotransferase 6), should be performed [9, 10, 11, 12]. However, the genetic cause of HAE-nC1-INH is unknown in many cases [13].

Because bradykinin is the most important mediator in HAE, the conventional treatment with antihistamines, corticosteroids, or epinephrine is ineffective so, replacement therapy with C1-INH or the bradykinin-kallikrein system-blocking agents should be used [5].

Excepting Ecallantide, which is not approved in UE, all the other specific drugs (pdC1-inh, rhC1-inh, Icatibant) used for on-demand treatment are available in Romania. Based on the international treatment guideline recommen-

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dations, these medications can be used by self-administration in our country too.

When the acute treatment does not offer adequate control of the disease, long-term prophylaxis (LTP) is recommended to reduce the frequency, severity, and duration of the attacks [5]. Substitution with pdC1-INH or plasma-kallikrein-inhibitor agents can be administered for this purpose.

The intravenous form of pdC1-INH, administered twice a week, became available in Romania in September 2021. Due to the frequent intravenous puncture use over a long period, this treatment was accepted by only a small number of patients. Starting from this fact, we carried out this study to assess the control of the disease on the current treatments used by the Romanian HAE patients to evaluate the need for innovative, easy to-administer, LTP drugs.

Material and Methods

The study was designed as a noninterventional survey of adult patients with a confirmed diagnosis of HAE (low level of C1-INH antigenic and/or activity together with low level of C4 and/or positive family history), registered in the Romanian Hereditary Angioedema Registry.

A phone call visit was made for these patients in March 2022 to evaluate the frequency of the attacks and treatment availability for the last three months. Those with more than one attack in the assessed period (last three months) were asked to complete the Angioedema Control Test (AECT) for one- and three months, respectively. For patients who gave their consent, the AECT questionnaires were sent electronically.

AECT is a 4-item patient-related outcome (PRO) tool used in patients with recurrent angioedema. The four questions refer to the attacks frequency (question1) together with their consequences on the patient's daily life (question 2), the unpredictability of the attacks (question3) and, the used treatment efficiency (question 4). Answers are predetermined using a 5-point Verbal Rating Scale (VRS), and the score ranges are similar for all responses (0-4 points) [15]. The obtained score allows the assessment of the disease control level at a given time [14].

Information regarding socio-demographic data (age, sex, HAE type, age at first symptoms, age at diagnosis, and recommended treatment) were collected from the Romanian HAE Registry.

The study was conducted in compliance with the requirements set forth in the Declaration of Helsinki and was approved in March 2021 by the IRB of the George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures, Romania (Decision no. 1306/19.03.2021).

Data analysis

Absolute and relative frequencies were computed for socio-demographic variables. One and three-month AECT scores were calculated according to the authors' instructions [14].

AECT association with sex, HAE type, and residence were checked using the Mann-Whitney test. The correlations between AECT scores, on the one hand, and age, age at first symptom and age at diagnosis, on the other hand, were checked using the Spearman correlation test. The statistical significance threshold was set at 0.05.

Results

At the time of the study, 121 adult patients were registered in our registry of which 83 responded to the phone call.

Sixty-eight patients had at least one HAE attack in the last three months, and 57 had the possibility to receive, complete, and resend electronically the questionnaires. One patient did not give his consent.

A number of 56 patients (response rate 67.4%) completed the questionnaires, of which 18 (32.1%) were men and 38 (67.9%) were women. The age of patients varied between 18 and 69 years (mean age 41.6), and 42 (75.0%) lived in urban areas. The reported mean (SD) age at onset of first symptoms and age at diagnosis were 12.8 (8.6) and 31.9 (12.8) years, respectively, with a mean delay in diagnosis of 19 (12.7) years. Fifty patients suffered from HAE type 1 (89.3%) and six (10.7%) had HAE type 2 (Table 1).

Acute treatment with Icatibant or pdC1-INH was available for home-administration to all respondents in the evaluated period. LTP with pdC1-INH, in a dose of 1000UI twice a week, was used by nine patients (14.5%).

These types of therapies assured a well-controlled disease for the three-month AECT in only 13 patients (23.2%), of whom two used LTP. When AECT was used for the evaluation of the last month, the results showed an adequate disease-control in 14 patients (25.0%), from which only one was on LTP.

The means and standard deviations of scores per individual AECT questions and the total scores at one and three months are presented in Table 2.

Tabel 1. Socio-demographic data (age, sex, HAE type, age at first symptoms, age at diagnosis, and recommended treatment)

Patient characteristic		Value
Sex		
	Female	38 (67.9%)
	Male	18 (32.1%)
Age (mean)		41.6
Age at first symptoms (mean)		12.8 (8.6)
Age at diagnosis (mean)		31.9 (12.8)
Diagnosis delay		19 (12.7)
HAE type		
	1	50 (89.3%)
	2	6 (10.7%)
Residence		
	Urban	42 (75.0%)
	Rural	14 (25.0%)
LTP		
	Yes	9 (16.1)
	No	47 (83.9)

Table 2. Means and standard deviations of score per individual AECT questions and the total scores at one and three months

Test	Individual question scores				Total score
	Q1	Q2	Q3	Q4	
AECT 1-month, mean (SD)	1.5 (1.2)	1.5 (1.2)	1.5 (1.3)	2.8 (1.1)	7.0 (3.5)
AECT 3-month, mean (SD)	1.3 (1.1)	1.4 (1.1)	1.3 (1.2)	2.9 (0.9)	6.9 (3.3)

The results of correlation tests examining the relationship between the 1-month and 3-month AECT scores on the one hand, and age, age at first symptoms, and age at diagnosis on the other hand, are presented in Table 3.

Table 3. Correlations between AECT scores vs. age, age at first symptoms, and age at diagnosis

Variable	AECT at 1 month		AECT at 3 months	
	Spearman rho	P-value	Spearman rho	P-value
Age	-0.1866	0.1724	-0.09977	0.4686
Age at first symptom	0.272	0.0445	0.4141	0.0017
Age at diagnosis	-0.1627	0.2353	-0.06204	0.6527

Discussions

We investigated 56 adult patients from the Romanian HAE Registry to evaluate the control of their disease on currently used treatments. For this reason, the 1-month and 3-month AECT whereas used. A score of ≥10 points, obtained by the sum of the marked scores, indicates a well-controlled disease, and a score of less than 10 points is considered a poorly controlled disease. The overall score ranges from zero to 16 points.

Our study showed a mean age at onset of first symptoms of 12.8 years, which is consistent with previously published data (11.5 years in a multinational patient survey published by Mendvil and his group (16) and 12.5 years in an American survey [17].

Our data show a significant correlation between the age at first symptoms and AECT scores for one-month (rho=0.272, p=0.445) and three-months respectively (rho=0.4141, p=0.0017). In contrast with these we do not find a correlation between the determined AECT scores and the age of patients and age of diagnosis. To our knowledge, there are no published data on such correlations, so we can only speculate that age at first symptom has a negative impact on achieving adequate disease control. Therefore, it will be of interest to confirm our results.

The higher prevalence of HAE type 1 (89.3% of the patients) over HAE type 2 (10.6%) in our group confirmed the findings from several other countries such as Italy (87% type1/13% type 2), Greece (80.5% type1/ 17% type2), and Brazil (95.2% type 1/4.8% type2) [18].

The 19-year delay in diagnosis found among our patients is higher than reported by other researchers, such as the German group with 15.0 years [19] or the American group with 8.4 years [17].

This result might be attributed to the fact that in most of our patients the diagnosis was established in the period when HAE was little known by the Romanian physicians in one hand and C1-INH level determination at that time was not available in our country in the other hand.

During the study period, the home-administered on-demand treatment was available for all respondents, and nine patients used LTP. Despite these conditions, our results show adequate control of the disease (>10) only in a small number of patients, 13 (23.2%) for the last three months and 14 (25.0%) for the last four weeks period, with the mean score of 6.9 (±3.3) and 7.00 (±3.5) respectively (Table 2.) Furthermore, of the nine patients on LTP only in two, (with score of 10 in both patients) respectively in one patient (score of 14) the disease was well controlled on the available dose (1000UI twice a week).

These data are consistent with those published in a multinational survey of 242 patients [16], with 62.4% of them on LTP, where the majority (81.8%) had a score of AECT for 3 months less than 10, with the mean 3-month AECT score of 8.00, indicating a poor control of the disease.

In another study published by Zarnowski et al., the AECT revealed an insufficient control of the disease (score <10) in 15/37 HAE-C1-INH patients (20 were on on-demand treatment and 17 with LTP, mainly pdC1-INH), with a significantly higher AECT value in those on LTP. [19].

Data published by Fijen et al. regarding AECT on 69 patients with HAE revealed a well-controlled disease in 64.7% of them. In this group, 59% of patients were on LTP.

Overall, regarding AECT for 1 month and 3 months respectively, 36/37 of patients reported experiencing angioedema “often” or “very often”; 31/26 reported experiencing “much” or “very much” impairment in quality of life due to angioedema; 33/38 reported being “much” or “very much” bothered by the unpredictability of their angioedema; and 41/44 reported that their angioedema was “well” or “very well” controlled by their current treatment.

This is the first national assessment regarding the control of the disease of the Romanian HAE patients since specific drugs have been available, namely since 2015. Because between 2015 and 2021, only acute treatment was accessible, this evaluation was not justified, with no other treatment possibilities.

In September 2021, when the intravenous form of pdC1-inh for LTP became available, all registered patients were informed about this treatment modality. However, it was accepted and initiated only in a small number of patients (16% from of the 56 evaluated patients). This fact can be explained by the restriction of face-to-face visits during the COVID-19 pandemic period, on the one hand, and the frequent venous puncture (twice weekly) on

the other hand. The latter is proven by the fact that the number of patients included in this type of treatment did not increase even after the pandemic, although our results show that the used treatment does not offer good control of their disease. This fact suggests that, in the case of chronic disease, the route of administration of the drug is an essential aspect in the acceptance of treatment, frequent intravenous administration being at a disadvantage.

Study limitations

This study has some limitations. First, the survey was only offered online and responses were self-reported without third-party confirmation, which may lead to bias. In addition, the online administration of the questionnaire limited the participation of those who do not have access to the internet as well as those who are less comfortable using technology. A second limitation is the relatively small sample size inherent to surveys in rare diseases. A third limitation could be considered the fact that, a single questionnaire was used with the same questions and possible answers, asked for two different but overlapping periods, which may lead to bias. Future studies would benefit from the regular assessment of disease control over a medium or even long period, especially through the availability of other treatments dedicated to LTP.

Conclusion

In most Romanian HAE patients, the available drugs do not offer a proper control of the disease. Even though a first-line drug for LTP is available, its administration route by intravenous injections makes it inconvenient for many patients, highlighting the necessity for new, easy-to administer drugs for HAE patients from our country. Findings from this study indicate the continuing need for improvements in care for patients suffering from HAE. These results are the first step of a long-term survey to evaluate the progress of disease control and, thereby, the improvement in the quality of life of these patients, together with the assessment of the effectiveness of new innovative drugs.

Authors contributions

NAB - Conceptualization and design, systematic literature research, data analysis and interpretation, writing – original draft, writing – review & editing.
IN - Data curation, statistical analysis, writing – review & editing.
VN - Data curation, formal analysis, methodology, writing – review & editing.
DD - Formal analysis, methodology, writing – review & editing.
All authors approved the final version of the manuscript.

Conflict of interest

None to declare.

References

1. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. Allergy. 2014;69(5):602-616. doi:10.1111/all.12380.
2. Magerl M, Sala-Cunill A, Weber-Chrysochoou C, Trainotti S, Mormile I, Spadaro G. Could it be hereditary angioedema? -Perspectives from different medical specialties. Clin Transl Allergy. 2023;13(9):e12297. doi:10.1002/clt2.12297.
3. Bork K, Anderson JT, Caballero T, et al. Assessment and management of disease burden and quality of life in patients with hereditary angioedema: a consensus report. Allergy Asthma Clin Immunol. 2021;17(1):40. doi:10.1186/s13223-021-00537-2.
5. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema - The 2021 revision and update. World Allergy Organ J. 2022;15(3):100627. doi: 10.1016/j.waojou.2022.100627.
6. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2017 revision and update. Allergy. 2018;73(8):1575-1596. doi:10.1111/all.13384.
7. Germenis AE, Speletas M. Genetics of Hereditary Angioedema Revisited. Clin Rev Allergy Immunol. 2016;51(2):170-182. doi:10.1007/s12016-016-8543-x.
8. Cicardi M, Zuraw BL. Angioedema Due to Bradykinin Dysregulation. J Allergy Clin Immunol Pract. 2018;6(4):1132-1141. doi: 10.1016/j.jaip.2018.04.022.
9. Bork K, Wulff K, Steinmüller-Magin L, et al. Hereditary angioedema with a mutation in the plasminogen gene [published correction appears in Allergy. 2018 Dec;73(12):2412]. Allergy. 2018;73(2):442-450. doi:10.1111/all.13270.
10. Bork K, Wulff K, Rossmann H, et al. Hereditary angioedema cosegregating with a novel kininogen 1 gene mutation changing the N-terminal cleavage site of bradykinin. Allergy. 2019;74(12):2479-2481. doi:10.1111/all.13869.
11. Ariano A, D'Apolito M, Bova M, et al. A myoferlin gain-of-function variant associates with a new type of hereditary angioedema. Allergy. 2020;75(11):2989-2992. doi:10.1111/all.14454.
12. Bork K, Wulff K, Möhl BS, et al. Novel hereditary angioedema linked with a heparan sulfate 3-O-sulfotransferase 6 gene mutation. J Allergy Clin Immunol. 2021;148(4):1041-1048. doi: 10.1016/j.jaci.2021.01.011.
13. Bork K, Machnig T, Wulff K, Witzke G, Prusty S, Hardt J. Clinical features of genetically characterized types of hereditary angioedema with normal C1 inhibitor: a systematic review of qualitative evidence. Orphanet J Rare Dis. 2020;15(1):289. doi:10.1186/s13023-020-01570-x.
14. Weller K, Donoso T, Magerl M, et al. Validation of the Angioedema Control Test (AECT)-A Patient-Reported Outcome Instrument for Assessing Angioedema Control. J Allergy Clin Immunol Pract. 2020;8(6):2050-2057.e4. doi: 10.1016/j.jaip.2020.02.038.
15. Weller K, Donoso T, Magerl M, et al. Development of the Angioedema Control Test-A patient-reported outcome measure that assesses disease control in patients with recurrent angioedema. Allergy. 2020;75(5):1165-1177. doi:10.1111/all.14144.
16. Mendivil J, Murphy R, de la Cruz M, et al. Clinical characteristics and burden of illness in patients with hereditary angioedema: findings from a multinational patient survey. Orphanet J Rare Dis. 2021;16(1):94. doi:10.1186/s13023-021-01717-4.
17. Banerji A, Davis KH, Brown TM, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. Ann Allergy Asthma Immunol. 2020;124(6):600-607. doi: 10.1016/j.anai.2020.02.018.
18. Gabos G, Nadasan V, Mihaly E, Dobru D. Hereditary Angioedema Due to C1-Inhibitor Deficiency in Romania: First National Study, Diagnostic and Treatment Challenges. Iran J Immunol. 2020;17(3):226-235. doi:10.22034/iji.2020.85416.1709.
19. Zarnowski J, Rabe M, Kage P, Simon JC, Treudler R. Prophylactic Treatment in Hereditary Angioedema Is Associated with Reduced Anxiety in Patients in Leipzig, Germany. Int Arch Allergy Immunol. 2021;182(9):819-826. doi:10.1159/000514973.
20. Fijen LM, Vera C, Buttgereit T, et al. Sensitivity to change and minimal clinically important difference of the angioedema control test. Clin Transl Allergy. 2023;13(9):e12295. doi:10.1002/clt2.12295.