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ORIGINAL ARTICLE

Hereditary Angioedema Due to C1-Inhibitor Deficiency in Romania: First National Study, Diagnostic and Treatment Challenges

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ABSTRACT

Background: Hereditary angioedema (HAE) is a rare genetic potentially life-threatening disease characterized by episodic non-pruritic subcutaneous and submucosal edema attacks in different parts of the body. **Objective:** To assess the status of Romanian HAE patients after the recent introduction of a new therapy through a nationwide program. **Methods:** This cross-sectional observational study included patients from the Romanian HAE Registry. **Results:** The study included 84 patients with HAE type I (91.7%) and type II (8.3%). The mean delay in diagnosis was 2.4 years in children and 16.7 years in adults (p=0.019). Stress and tiredness were the most frequent trigger factors. The majority of the HAE episodes involved subcutaneous (89.3%), abdominal (77.4%), genital (51.2%), facial (41.7%), and laryngeal (39.3%) symptoms during the preceding 12 months. One or several misdiagnoses were reported in 83.33% patients and 44.1 % of the patients were subjected to or proposed unnecessary surgery during abdominal episodes. Plasma-derived C1-INH (pdC1-INH) and recombinant C1-INH (rhC1-INH) were respectively used in 10 (11.9%) and 13 (15.5%) of the HAE patients for life-threatening attacks over the past 12 months. Forty-three (51.19%) patients practiced home treatment with subcutaneous injection of the bradykinin B2-receptor antagonist for acute HAE attacks. **Conclusion:** The significantly lower delay observed in children suggests an improvement in the awareness of C1-INH-HAE among physicians in recent years. The management of HAE in Romania has been somewhat enhanced as the majority of HAE patients have recently gained access to pdC1-INH, rhC1-INH, and bradykinin B2-receptor antagonist.

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Keywords: Angioedema, Diagnostic Errors, Hereditary, Romania

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INTRODUCTION

Hereditary angioedema (HAE) caused by C1 esterase inhibitor (C1-INH) deficiency is a rare, life-threatening autosomal dominant condition with an estimated prevalence of 1:50,000 in the general population (1,2). The low C1-INH concentration leads to excessive levels of bradykinin, the principal mediator of angioedema (3). HAE types I and II develop as a result of reduced C1-INH levels (85%) and dysfunctional C1-INH (15%), respectively (4). In some patients with normal C1-INH (HAE-nC1-INH), the disease is associated with mutations in F12 gene (HAE-FXII). Although mutations in the angiopoetin-1 gene or plasminogen gene have also been reported, the underlying genetic alterations remain unknown in most cases (5). The clinical picture is defined by recurrent episodes of painful and usually disabling swellings in subcutaneous and/or submucosal tissues, involving body sites such as limbs, face, intestinal tract, or airway (6). Untreated laryngeal edema in HAE patients entails an extremely high risk of asphyxiation, hence death (7). Abdominal attacks may result in symptoms identical to those observed during intestinal occlusion syndrome and may be associated with ascites and hypovolemic shock (8,9). Because of its rarity, HAE is frequently misdiagnosed or remains **undiagnosed** for years, leading to higher rates of morbidity and mortality (4,5).
The main objective of this study was to characterize HAE patients from the Romanian HAE registry as far as demographics, clinical and laboratory findings, treatment availability and use, and the physical, psychological, and social burden of the disease following the introduction of new therapies through a nationwide state-supported program. We further aimed to assess the extent of diagnosis and disease management challenges faced by HAE patients in Romania.

MATERIALS AND METHODS

Patients. The present study was designed as a cross-sectional observational study. Current and retrospective data were obtained, with the participants recruited from the Romanian Registry of HAE. Patients diagnosed with C1-INH HAE between 2008 and 2018 were included in the study. C1-INH HAE diagnosis was established corroborating positive family history, typical clinical manifestations, and laboratory confirmation of decreased C1-INH level or activity. The HAE severity based on the frequency of the attacks was defined as severe, moderate, mild, and asymptomatic if the patients had experienced 12 or more, 4-11, 1-3 attacks, and no attacks, respectively, during the last 12 months (10).
Measures. Serum concentrations of C1-INH and C4 were quantified using nephelometric assays (BN Prospec, Siemens Healthcare GmbH) while functional C1-INH was measured by functional enzyme-linked immunosorbent assay (MicroVue functional C1-inhibitor, Quidel Corporation) on an automated ELISA analyzer (Adaltis, Italy). The reference values for C1-INH antigen, C1-INH function, and C4 were 0.21-0.39 g/L, >40%, and 0.1-0.4 g/L. For each patient, the following information was collected from the medical records of the Romanian Registry of HAE: basic demographic data, family history, age at onset of the first symptoms and at diagnosis, plasma levels of C1-INH, and C4 at diagnosis.
A structured questionnaire was developed in collaboration with the experts of Romanian HAE Reference Centers. Table 1 presents the variables collected through a telephone

interview between 01.07.2018-01.10.2018. This study included both children and adults. For the children, the questionnaire was answered by at least one parent with no input from the child. Verbal consent was obtained from all patients or underage patients' parents.

Table 1. Variables collected through the telephone interview from the Romanian HAE patients.

Clinical data	Data related to treatment	Data related to misdiagnosis and mistreatment	Quality of life related data	Data related to emergency treatment
- Number of HAE attacks in the last 12 months **- Type of HAE attacks in the last 12 months** **- Precipitating factors for HAE attacks** **- Comorbidities**	- Long term prophylaxis received - Adverse effects of the prophylactic treatment - Acute treatments received during the last 12 months - Availability of home treatment - Satisfaction of HAE patients with current home treatment	- Number of misdiagnoses - Types of misdiagnoses - Number of needless surgical operations performed - Number of needless surgical operations proposed	- Number of missed workdays in the last 12 months - The limitations of HAE on work and study - The influence of HAE on patients' decision about having children - The influence of HAE on patients' ability to establish relationships - The influence of HAE on patients' resenting guilt for possibly transmitting the disease to their offsprings	- Time to the closest emergency department - Need for emergency tracheotomy in the last 12 months - The usefulness of medical referral letter from the HAE Center of Reference when patients interact with other physicians

Ethicals. Ethical approval was obtained from the Human Research Ethics Committee of George Emil Palade University of Medicine, Pharmacy, Science, and Technology of Targu Mures (ref.no.224/2018).

Statistical Analysis. Means and standard deviations were calculated for continuous variables while absolute and relative frequencies were calculated for categorical variables. Continuous variables with normal distribution were compared using student t-test and those with non-gaussian distribution were compared using the Mann-Whitney test. The threshold value for statistical significance was set at 0.05.

RESULTS

Of the 108 patients registered in the Romanian Registry of HAE, 84 participated in the telephone interview (response rate 77.77%). Twenty-four patients were not included because they either refused to participate or did not answer the call. The study population included 46 females (54.8%) and 38 (45.2%) males, 6 (7.1%) children or adolescents, and 78 adults (92.9%). Seventy-seven patients (91.7%) had type I while 7 (8.3%) had type II HAE. A family history of HAE was reported by 66 patients (78.6%)

whereas 18 patients (21.4%) were not aware of any family members with HAE. The patients' mean age at the time of the telephone interview was 39.4 years (SD 16.7). Their mean age at the onset of the first symptoms was 13.9 years (SD 10.8) in the group as a whole, 11.6 years (SD 7.7) in females, and 16.6 years (SD 13.3) in males (p=0.036). The mean age at the time of diagnosis was 29.5 years (SD 16.0) in the group as a whole, 29.3 years (SD 16.6) in females, and 29.8 years (SD 15.5) in males (p=0.88). The mean delay of diagnosis from the first symptoms was 15.6 years (SD 14.4) for the group as a whole, 17.7 years (SD 15.8) in females, and 13.2 years (SD 12.2) in males (p=0.162). The mean delay in diagnosis was 2.4 years (SD 2.1) in children and 16.7 years (SD 14.4) in adults (p=0.019). During the previous year, 4 patients (4.76%) had no attacks and 80 (95.23%) experienced attacks of angioedema. Among these, 55 subjects (65.47%) had severe, 17 (20.23%) had moderate, and 8 (9.52%) had mild HAE attacks while 4 (4.76%) were asymptomatic. Table 2 depicts the number of patients having HAE attacks over the past year by type of attack and the mean number of attacks per patient. The self-reported frequency of factors triggering HAE episodes is presented in Figure 1.

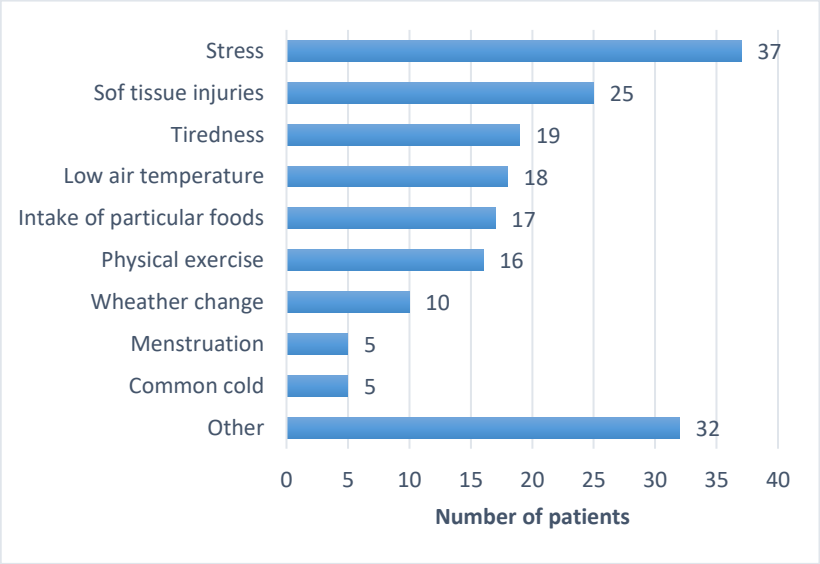

Figure 1. Commonly reported trigger factors in HAE patients in Romania.

The mean C1-INH value was 0.01 g/L (SD 0.01), C1-INH function was 32.18% (SD 40.37), and the mean C4 value was 0.98 g/L (SD 1.63). As far as treatment is concerned, pdC1-INH and rhC1-INH were respectively used in 10 (11.9%) and 13 (15.5%) of the HAE patients for life-threatening attacks involving the airway or gastrointestinal tract in the emergency department over the preceding 12 months. At the time of telephone interview, a total of 43 patients (51.2%) practiced home treatment with subcutaneous injection of the bradykinin B2-receptor antagonist for acute HAE attacks. Four patients (9.3%) felt very much safer, 37 (86.0%) felt sensibly safer, and 2 (4.6%) felt as safe as before home treatment. The use of fresh-frozen blood plasma to manage acute attacks was reported by 14 patients (16.7%) in the last 12 months.

Table 2. The number of patients having HAE attacks during the last 12 months and the mean number of attacks per patient.

Type of attack	Number of patients	% patients	Mean number of attacks per patient	Standard deviation
Peripheral	75	89.3	14.86	15.58
Abdominal	65	77.4	12.25	15.08
Genital	43	51.2	2.61	5.38
Facial	35	41.7	1.70	3.95
Laryngeal	33	39.3	1.23	2.76
Multiple type	71	84.5	-	-

Twenty-three of the 84 patients (27.3%) were on maintenance treatment with androgens, but none were receiving long-term prophylaxis with C1-INH. Seventeen (20.2%) patients received danazol and 6 (26.1%) received other androgens for long-term prophylaxis. None of the patients on maintenance treatment with androgens had experienced side-effects. No patient underwent tracheal intubation due to laryngeal edema over the previous 12 months. The mean time to the closest emergency room was 22.4 (SD 22.5) minutes among HAE patients. The specific medical referral letter from the HAE Center of Reference was deemed useful in the emergency room by 58 patients (69.9%). Thirty-two patients (38.1%) reported ED and other medical professionals who refused on all occasions to administer specific medications and/or did not agree with the patients' previously established HAE diagnosis. One or several misdiagnoses were reported in 70 patients (83.3%). The frequency of the most common misdiagnoses is shown in Figure 2.

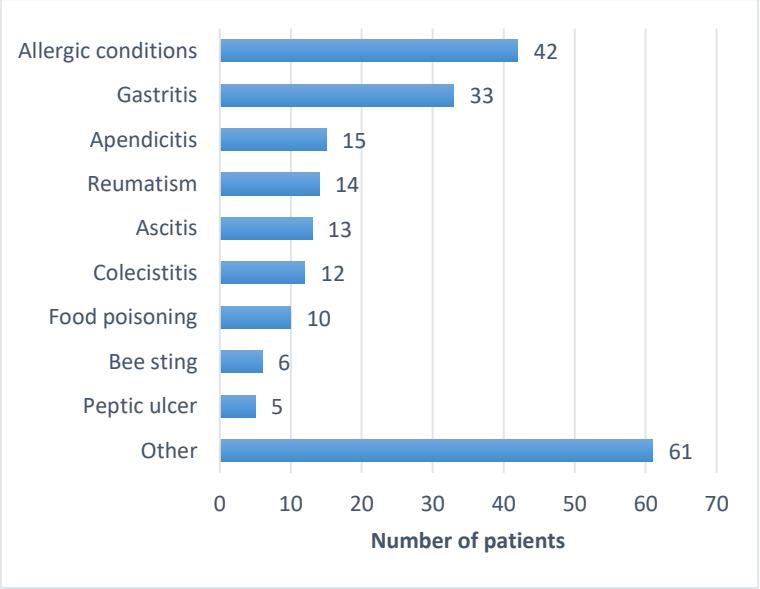

Figure 2. The frequency of the most common misdiagnoses reported by HAE patients from Romania.

Since the start of HAE symptoms, 37 patients (44.1%) had been subjected to or proposed unnecessary surgery during abdominal episodes. Table 3 illustrates the type and number of unnecessary performed and proposed surgery during abdominal episodes of HAE. The mean number of missed work or school days among Romanian HAE patients in the last 12 months was 9.3 days (SD 8.6).

Table 3. Reported unnecessary performed and proposed surgery among the HAE patients in Romania.

Surgical operations	Number of patients	% patients
Performed		
Appendicectomy	27	32.1
Cholecystectomy	11	13.1
Exploratory laparoscopy	4	4.8
Intestinal occlusion surgery	2	2.4
Subtotal colectomy	2	2.4
Stomach cancer surgery	1	1.2
Ovarian cyst surgery	1	1.2
Proposed		
Appendicectomy	13	15.5
Exploratory laparoscopy	13	15.5
Cholecystectomy	5	6.0
Perforated duodenal ulcer	2	2.4
Ovarian tumor surgery	2	2.4
Extra uterine pregnancy surgery	1	1.2
Liver cancer surgery	1	1.2
Stomach ulcer surgery	1	1.2
Colon cancer surgery	1	1.2

Having the disease was considered by 27 of the HAE patients (38.6%) as an important factor when deciding about conceiving a child and twenty-nine (39.7%) felt limited in their ability to establish a relationship with a partner due to the disorder. Furthermore, 48 of the patients (67.6%) experienced a sense of guilt or responsibility because of the possibility of transmitting this disease to their children. Twenty-eight patients (57.1%) reported limited work or study capacity.

DISCUSSION

This is the first nationwide survey of HAE patients in Romania; it was performed through collecting demographic, clinical, laboratory, and quality of life data after the recent implementation of the National HAE Program that secured access to home treatment with subcutaneous injection of bradykinin B2-receptor antagonist for acute HAE attacks. In Romania, HAE patients are monitored by the Romanian HAE Pilot Center which has recently been approved by the Ministry of Health as an HAE Center of Reference. This center coordinates the Romanian Registry of HAE and the nationwide state-supported treatment program (11). The Romanian Registry of HAE has

been available since 2008 and is currently merging into the Global HAE Registry. Our data have shown a higher prevalence of HAE type I (91.7% of the patients) over HAE type II (8.3%), confirming the findings from several other countries such as Italy (87% type I vs. 13% type II), Iran (63.6% type I vs. 36.7% type II), Greece (80.5% type I vs. 17% type II), and Brazil (95.2% type I vs. 4.8% type II) (12-15). The mean delay in diagnosis was 15.6 years in our study, higher than the reports of Roche *et al.* with 13.1 years (16), Nordenfelt *et al.* with 10 years (10), and Gómez-Traseira *et al.* with 8.5 years (17). The longer diagnostic delay in our study might be attributed to the rarity of the disease and the low awareness of physicians who first noticed the patients with HAE; therefore, it is necessary that specialists and primary care physicians make supplementary efforts to increase their knowledge of this disorder . An early HAE diagnosis may be life-saving since laryngeal edema may be fatal even at its first occurrence (18). Similar to an Iranian report (13), the delay in diagnosis was significantly shorter in children than in adults (2.4 vs. 16.7 years). Our findings may suggest improvements in HAE diagnosis over time, with patients now more commonly diagnosed at a younger age and the reduced delays between symptom onset and correct diagnosis. Almost all patients were symptomatic during the preceding 12 months. The most frequent episodes involved peripheral (89.3%) and abdominal (77.4%) symptoms while the laryngeal attacks were the least frequent (39.3%). The number of HAE episodes ranged from zero to well over a hundred in the past year. The frequency of attacks in our study was higher than a report from Denmark (19), but it was similar to the one found in Sweden (10). This finding could be ascribed to the unavailability of long-term prophylaxis treatments (pdC1-INH, attenuated androgens, and monoclonal antibody) among Romanian HAE patients. At the time of the study, none of the patients was undergoing long-term prophylaxis with pdC1-INH. This observation could be related to the high cost of the treatment. Romania is among those European countries where attenuated androgens are not licensed, hence not available. Nevertheless, a few individuals (27.3% of HAE patients) secure it from abroad and use it as an off-label medication. This figure is lower than the one reported in Spain (43.7%) (16) and Italy (39.8%) (12). The approval of long-term prophylaxis treatment in Romania is a crucial step to reducing the frequency of attacks. The percentage of Romanian HAE patients reporting unnecessary abdominal surgery since the start of HAE symptoms (58.3%) was higher than that reported by Bygum *et al.* (16.9%) (19) and Lunn *et al.* (approx. 20%) (20). The relatively higher number of invasive procedures found in Romanian HAE patients may be due to clinicians' inadequate knowledge concerning HAE clinical appearance. To prevent unnecessary operations or laparoscopies, physicians should add HAE on their list of differential diagnosis in cases with periodic abdominal pain combined with ascites. HAE treatment has been a challenge in Romania. Over the past ten years, three of the specific HAE treatments, namely pdC1-INH, rhC1-INH, and icatibant, have been registered. RhC1-INH and pdC1-INH have been administered since 2015 for laryngeal, facial, or abdominal HAE attacks in the emergency services. Since April 2017, the Romanian HAE patients have access to treatment with icatibant for acute HAE attacks througha national program. The availability of home-based treatment with icatibant has resulted in the vast majority of patients reporting feeling safer than before. Self-administered acute care can usually be given more promptly, thereby more rapidly reducing the episodes of possibly disabling swelling. Finally, this means fewer emergency room visits and decreased disease burden. The time from the beginning of upper respiratory symptoms to asphyxiation may be as short as 20 minutes (7),

underscoring the need for HAE patients to hold a personal supply of C1-INH concentrate or recombinant, icatibant or ecallantide at home to avoid fatalities. Transportation can pose a huge challenge in Romania. Our study showed that the average time to the closest ED was 22.4 minutes (up to a maximum of 120 minutes) among HAE patients. Given that laryngeal attacks can progress rapidly to respiratory arrest, patients may die as a result of laryngeal asphyxia while waiting for an ambulance. The approval of icatibant home treatment for acute attacks in Romania was an essential step towards reducing and avoiding mortality caused by HAE laryngeal attacks. No patient underwent tracheal intubation and there were no fatalities due to laryngeal edema over the past 12 months. Misdiagnosis and mistreatment are prevalent problems in HAE. Our study found that patients with C1-INH-HAE were more often than not misdiagnosed, most frequently with allergic angioedema, gastritis, or appendicitis. These observations are consistent with the results published by Zanichelli *et al.* (21). Remarkably, more than half of our patients with a family history of HAE received misdiagnoses. This finding puts forth a possible avenue for improved diagnosis by encouraging family members to proactively seek medical consultation on behalf of their relatives, thus facilitating diagnosis by primary care physicians. In 30.1% of the Romanian HAE patients, the specific medical referral letter from the Romanian HAE Reference Center was not useful in the emergency room, highlighting the dysfunctionality of the Romanian health system with major consequences concerning the HAE patients. Despite the ED physician being notified as to the particularity of the swelling, C1-INH HAE was not acknowledged by the medical personnel as a relevant diagnosis, leading to misdiagnosis and mismanagement of laryngeal edema with fatal consequences in certain cases (18). In several instances, ED physicians did not communicate with the HAE reference center at the time of admission to gain the particulars of any preceding history of HAE episodes. More than half of the Romanian HAE patients had been medicated with corticosteroids and more than a fourth with antihistamine, none of which is effective for HAE attacks and prescribed due to disease misdiagnosis. HAE diagnosis, appreciation of HAE as a serious disease, and medication management were identified as areas needing improvement. Every clinician, especially those working in EDs, should have a standardized approach to HAE and its management. Development and consistent implementation of ED triage and intervention algorithms may be conducive to reducing the number of lethal outcomes. A third of the HAE patients reported that the disorder impacted the direction of their education and/or career, caused frequent visits to healthcare institutions including missed workdays over the past 12 months, all of these representing a burden for the patient, the healthcare system, and society. Many patients either blame themselves for passing the disorder to their children or choose not to have one; meanwhile, the burden is much alleviated when patients benefit from up-to-date treatments, professional care, and home therapy (22-24). In Romania, the following were the first steps to guaranteeing increased awareness about HAE, prompt diagnosis, and adequate treatment of the condition: the recognition of HAE patients' association among the Ministry of Health, the publication of the national guideline for the diagnosis and treatment of HAE, the identification and development of reference centers, and the dissemination of information regarding HAE through lectures and articles in popular magazines. We expect that the diagnostic tools and therapeutic options available today will decrease the misdiagnosis and mistreatment of HAE. While the inherent limitations of a cross-sectional observational study based mainly on patient-reported data are to be considered, our investigation provides the

most up-to-date picture regarding the diagnosis and treatment of Romanian HAE patients after the recent introduction of new therapies through a nationwide program. In conclusion, our study brings to attention a long delay in diagnosis and a significant number of misdiagnoses and mistreatments. The significantly lower delay observed in children suggests an improvement in the awareness of C1-INH-HAE among physicians over the recent years. The management of HAE in Romania has been somewhat ameliorated as the majority of HAE patients have recently gained access to pdC1-INH, rhC1-INH, and bradykinin B2-receptor antagonist.

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