

CONTRIBUTIONS TO THE MANAGEMENT OF HEREDITARY ANGIOEDEMA DUE TO C1-INH DEFICIENCY IN ROMANIA

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Introduction: Rare diseases have become a priority for healthcare in Europe, Canada and the USA. The European Commission encourages research regarding the diagnosis and treatment of rare diseases, which are considered public health priorities. Hereditary angioedema (HAE) is a rare genetic condition that affects the quality of life among patients, and can rarely be the cause of asphyxiation due to upper airway obstruction. Up to 30% of patients with HAE die from untreated laryngeal attacks. Abdominal attacks can be the first and only manifestation of HAE that persist for a long time, often leading to differential diagnosis. All over the world, HAE is under-diagnosed and under-treated. Diagnostic errors result in unnecessary suffering and surgery, as well as preventable deaths.

In Romania, these patients are in the care of the National Pilot Centre for Hereditary Angioedema from the Mureș County Clinical Hospital, which was officially recognized by the Ministry of Health as a Center of Expertise for patients with HAE. The Center of Expertise coordinates the Romanian HAE Registry (RRAEE) and the national treatment program in collaboration with the Romanian Foundation of HAE. In Romania recombinant C1-INH and plasma derived C1-INH may be administered since 2015 in case of laryngeal, facial or abdominal HAE attacks in the emergency services of the counties and county residences where there are patients with registered HAE. Since April 2017, by order of the Ministry of Health, establishing a national program for treatment of HAE attacks, patients with this disease can be treated at home with Icatibant, a competitive and selective antagonist of the bradykinin B2 receptor.

Purpose: The choice of HAE management in Romania as a research topic is justified both in terms of topicality and from a practical point of view. This approach intends to increase the interest of specialists in this rare condition, to increase the enrollment rate in RRAEE of already diagnosed cases, to improve the monitoring of patients with HAE in Romania, to facilitate collaboration with other referral centers in Europe and to contribute to international research. Studies on the situation of HAE patients in Italy, Brazil, Denmark, Sweden, Greece, Spain and Iran have been published in the literature of the last 10 years. In the last decade, remarkable progress has been made in countries such as Italy, Germany, Denmark, the Netherlands, Hungary and France in diagnosing a large number of patients with this rare disease. The same happened with the therapy of HAE attacks and with the prophylactic treatment. Other countries, such as Greece, Brazil, the Balkan countries, including Romania, had the same trend, although with different degrees of delay. To date, there has been no published systematic retrospective assessment of cases in Romania and no analysis of molecular genetics. The first study proposes a systematic retrospective evaluation of HAE cases in Romania, the registration and processing of statistical data on the clinical characteristics of the disease, the quality of life of patients, data on emergency treatment and diagnostic errors. The second study had as main objective the evaluation of diagnostic errors and their consequences in patients with HAE from Romania, emphasizing the importance of correct and early diagnosis of this orphan disease for effective management. The third study concerns molecular genetic determinations and possible correlations between the disease phenotype and the type of SERPING1 gene mutations.

Material and method: In order to meet the objectives of this research, three different studies were performed on groups of patients diagnosed with C1-INH-HAE from Romania. Subjects included in the three studies were recruited among the 108 patients included in the RRAEE. The diagnosis of HAE due to C1 inhibitor deficiency was based on the family and / or personal history of recurrent angioedema without urticaria associated with antigenic and / or functional C1-INH deficiency. Serum concentrations of C1-INH and C4 were quantified by nephelometric methods (BN Prospec, Siemens Healthcare GmbH), while the level of functional C1-INH was measured using enzyme-linked immunosorbent assay (MicroVue C1 functional inhibitor, Quidel Corporation) using the automatic ELISA analyzer (Adaltis, Italy).

The data from the study were collected from the medical files from RRAEE and with the help of a structured questionnaire, developed in collaboration with the experts of from the HAE Expertise Center in Romania. Peripheral blood samples were collected from 28 patients, 22 index cases and 6 first-degree relatives diagnosed with this disease and were sent to the Department of Immunology and Histocompatibility, School of Medicine, University of Thessaly for genetic analysis. Genomic DNA was isolated and mutations in the SERPING1 gene were detected by sequencing after PCR amplification of all exons and exon / intron boundaries, followed by long-term PCR and MLPA to identify large genetic rearrangements.

Results and conclusions: Our study provides the most up-to-date picture on the diagnosis and treatment of Romanian patients with HAE after the recent introduction of new therapies through a national program. Our data confirm an increased prevalence of HAE type I (91.7%) over HAE type II (8.3%), data that are consistent with the results obtained in several countries. A delayed onset of the disease is characteristic of Romanian patients with HAE (15.6 years), however our recent results suggest improvements in the diagnosis of HAE, patients are now diagnosed at a younger age and with reduced delays between the onset of symptoms and correct diagnosis (2.4 years). In our cohort of patients, the extremities and the gastrointestinal tract were most frequently affected as a result of HAE attacks.

Approving long-term prophylaxis treatment in Romania is a crucial step in reducing the frequency of attacks. Progress in HAE management in Romania is obvious. In the past, treatment options have been limited, but today, most patients with HAE have gained access to treatments with plasma-derived C1-INH concentrates, a recombinant C1-INH, a bradykinin B2 receptor antagonist. The availability of bradykinin B2 receptor antagonist home treatment has led the vast majority of patients to report feeling safer than before.

Attacks are triggered by seizures, fatigue, tissue damage, infections, exertion and, in women, menstruation. These observations are in line with previous studies on HAE.

Due to the unpredictable and fatal nature of HAE attacks at the laryngeal level, adequate emergency care is critical. The reported cases describe the recognition of HAE as a diagnosis, the assessment of HAE as a serious disease and that the management of specific medicines are factors that need to be improved in the Emergency Department. The recent approval of the use, in Romania, of the home treatment with Icatibant, in case of acute attacks, is a crucial step for the reduction and prevention of mortality caused by laryngeal HAE attacks.

Misdiagnosis and mismanagement are common problems in HAE management. Our study highlighted that patients with HAE were often misdiagnosed, most commonly with allergic angioedema, gastritis or appendicitis. These observations are consistent with the literature to date. National education programs are essential to raise awareness among patients, relatives and doctors in the Emergency Department and to improve access to appropriate treatment.

Abdominal attacks can be the first and only manifestation of HAE for a long time, often causing problems with differential diagnosis. Gastroenterologists and other physicians should add intestinal angioedema to their list of potential causes of unexplained abdominal pain and transient ascites and request C1-INH. Referring patients to an HAE Center of Expertise that provides specialized treatment, care and education can dramatically improve their quality of life, prevent further invasive procedures and can save lives.

The types of mutations in Romanian patients show an unusual distribution, with a significantly higher proportion of missense mutations and splice defects (61.22%, respectively 22.4%), a lower frequency of nonsense mutations and frameshift mutations, as well as larger gene rearrangements than in other populations. The analysis of the mutation in the case of our patients contributed significantly to the management of affected families, by confirming the diagnosis and identifying relatives who could themselves be carriers of this mutation, 53% of our cases were identified by family screening. There is a more severe reduction in C1-INH levels in carriers of other than missense mutations, as also noted by other authors. With significant variations in each group, neither the age of onset nor the calculated score indicating clinical severity demonstrated significant differences. Clinical severity cannot be strictly related to the type of mutation.

In Romanian patients with HAE type II, only missense mutations were observed.

RRAEE offered the possibility to analyze clinical / paraclinical data from registered patients, and the results of the study can be used to familiarize clinicians with this orphan pathology, which would facilitate proper diagnosis and treatment, thus leading to lower mortality and morbidity rate.

Considering that this rare disease is an autosomal dominant inherited condition family screening is necessary for all first-degree relatives. RRAEE is the consequence of cooperation with renowned experts in Europe and international cooperation continues with the accession to the Global Registry of HAE which aims to evaluate and compare epidemiological and clinical data of patients with HAE in participating countries, identify new standards in patient management with the intention of significantly improve the quality of life of these patients.

Keywords: rare disease, hereditary angioedema due to C1-INH deficiency, home treatment, Global Registry of HAE