

Hereditary C1-inhibitor esterase deficiency: a rather well defined entity

Deficiența ereditară de C1-inhibitor esterază: o entitate destul de bine definită

Dumitru Moldovan^{1, 2*}, Eniko Mihaly², Florin-Dan Popescu³,
Géza – Attila Szöllösi⁴, Minodora Dobreanu⁵

1. University of Medicine and Pharmacy Tîrgu Mureș, Mureș County Hospital, Internal Medicine Clinic, Allergology and Clinical Immunology Department,

2. Rețeaua Română de Angioedem Ereditar,

3. University of Medicine and Pharmacy "Carol Davila" Bucharest, Allergy and Clinical Immunology Department, Hospital "Nicolae Malaxa", Bucharest, Romania,

4. Klinik für Innere Medizin, Ilmenau Bereich 2, Ilmenau, Germany,

5. University of Medicine and Pharmacy Tîrgu Mureș, Dept Clinical Biochemistry – Immunology, Mures Emergency County Hospital

Abstract

Hereditary angioedema (HAE) is a rare disease, associated with quantitative or qualitative genetic deficiency of C1-esterase inhibitor (C1-INH) caused by different mutations within an abnormal C1-INH gene on chromosome 11. During attacks, endothelial cells in postcapillary venules contract, which allows fluid and plasma proteins to leak between them. Bradykinin, produced by HM kininogen by the unopposed enzyme kallikrein and factor XII, is important, as C1-INH is the major inhibitor of these proteases. Symptoms include recurrent skin swellings, abdominal and laryngeal attacks. Recurrent abdominal pain attacks have been reported to occur in majority of cases. Laryngeal edema is responsible for death in 20-30% of untreated cases. The disease has often been misinterpreted by clinicians. Symptoms of recurrent swellings and crampy abdominal pain lasting for days, with serum samples showing reduced C1-INH function or antigen, often below 20%, accompanied by low C4 values are hallmarks of HAE. A suggestive family history is obtained in most cases. Conversely, a laboratory test of C1-showing compatible values with HAE in only one single person should raise awareness of dealing with in vitro artifacts or acquired angioedema. In some cases, a full equipped complement laboratory is needed for a right diagnosis, but genetic tests are not compulsory. The aim of this review is to increase the awareness of HAE among colleagues, in order to refer these patients to a specialized center.

Keywords: hereditary angioedema, C1-inhibitor esterase concentration and function essay

*Corresponding author: Dumitru Moldovan, 1 Marinescu street, 541103 Tîrgu Mureș, Romania
Tel. / fax.: +40 265 215 004, E-mail: moldovan.dumitru@gmail.com

Rezumat

Angioedemul ereditar (AEE) este o boală rară, caracterizată prin deficiența genetică cantitativă sau calitativă a C1-inhibitor esterazei (C1-INH) cauzată de diferite mutații într-o genă C1-INH anormală pe cromozomul 11. În timpul atacurilor, celulele endoteliale din venulele postcapilare se contractă, ceea ce permite ca plasma să extravazeze. Bradikina, eliberată de HMW-kininogen de către kalikreină și factorul XII necontracarat, este importantă, C1-INH fiind inhibitorul major al acestor proteaze. Simptomele includ tumefieri cutanate recurente, atacuri abdominale și laringiene. Atacurile dureroase abdominale sunt prezente în aproape toate cazurile. Edemul laringian este responsabil de decesul a 20-30% din cazurile netratate. Afecțiunea este deseori greșit interpretată de clinicieni. Trăsăturile definitorii ale AEE sunt tumefierile cutanate și durerile colicative abdominale recurente care durează câteva zile, scăderea funcției sau concentrației de C1-INH, deseori sub 20%, însoțite de valori scăzute ale C4. O anamneză familială sugestivă este obținută în majoritatea cazurilor. Invers, o determinare de laborator a C1-INH compatibilă cu AEE la o singură persoană, trebuie să ridice suspiciunea unui artefact in vitro sau a angioedemului dobândit. În unele cazuri, pentru diagnosticul corect, este necesar un laborator de complement complet echipat, dar testele genetice nu sunt obligatorii. Scopul acestui referat este de a crește atenția colegilor cu privire la AEE, cu scopul de a îndruma acești pacienți către un centru specializat.

Cuvinte cheie: angioedem ereditar, concentrația și funcția C1-inhibitor esterazei

Introduction

Hereditary angioedema (HAE) is a rare genetic disease, clinically characterized by recurrent, self-limiting episodes of marked edema involving the skin, the gastrointestinal tract, and other organs and might be fatal due to edema of the larynx. The prevalence of HAE is estimated between 1/50,000 and 1/100,000 (1-4). Since the disease is very rare, the patients remain undiagnosed for many years. Due to serious complications caused by attacks and progress in management, HAE must be clearly recognized.

The first medical documents about HAE belong to Heinrich Quincke (1882) and Sir William Osler (1888) (1). In 1962, before any of the complement defects were known, Landerman et al. suggested that symptoms might be due to dysregulation of the kinin system. HAE reached its own identity in 1963, when Donaldson and Evans demonstrated the C1-INH deficiency in HAE patients' plasma (1, 4, 5, 6). Due to impressive scientific progress achieved over the last decades regarding this rare disease, HAE is now a well defined clinical entity.

Symptoms usually appear early in life and are normally accompanied by a family history. The disease is inherited in an autosomal

dominant manner. The spontaneous mutation rate is about 25% and 150 different C1-INH gene mutations have been described. Only heterozygous individuals are described and the mutants can transmit the deficient gene to their offspring (1, 3, 4, 7).

Pathogenesis of HAE

C1-INH is the main regulator of the early activation steps of the classical complement pathway. Hepatocytes are the main source of C1-INH. It also regulates the contact phase coagulation and the fibrinolytic cascade. It inhibits factor XII by 90% and kallikrein and plasmin by 42%. In the case of a C1-INH deficit, any endothelial trauma will produce an overactivation of both the contact phase of coagulation and classical complement pathway and this will lead to the release of large quantities of bradykinin and kinin-like substances (1-5). The end result is increased vascular permeability and massive local uncontrolled edema. Although there was some debate as to the exact component that contributes to the angioedema, it is now well accepted that bradykinin is the main mediator of the increased vascular permeability (*Figure 1*) (4, 6, 7).

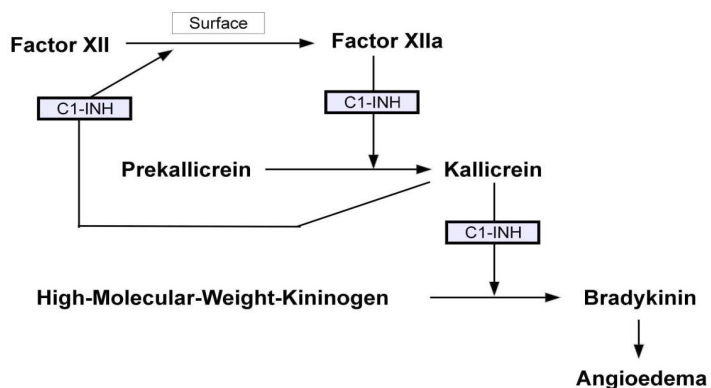


Figure 1. Bradykinin, the main mediator in HAE

It is important to stress that histamine is not involved in HAE pathogenesis. Similarities to allergic conditions and inappropriate framing as part of the urticaria-angioedema syndrome frequently lead patients with HAE to be considered allergic and treated with antihistamines and corticosteroids, proved to be ineffective in this disorder (1, 4).

Clinical manifestations

HAE is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous or submucosal edema typically involving the extremities, genitalia, trunk, face, tongue, bowel or larynx (*Figures 2 and 3*). Symptoms usually



Figure 2. An example of asymmetric swelling of the hands.

begin in childhood (50% in the first decade of life), worsen around puberty, and persist throughout life. Severity is not predictable (1, 2, 8).

Untreated patients may have attacks every 7 to 14 days on average, with the frequency ranging from virtually never to every 3 days. There is considerable variation in the severity of hereditary angioedema, even within kindred. Results of observational studies suggest that minor trauma and stress are frequent precipitants of swelling episodes, but many attacks occur without an apparent trigger.

Pregnancy has a variable effect on disease severity, but attacks are rare at the time of delivery (1, 3, 8).

Many attacks are preceded by a prodrome (usually a tingling sensation), and approximately a third are accompanied by erythema marginatum (*Figure 4*), a nonpruritic, serpiginous rash. It is important to mention the HAE patients that have no urticaria (1, 3, 4, 8).

The swelling classically worsens gradually over the first 24 hours, and then slowly subsides over the subsequent 48 to 72 hours. The arms, legs, hands, feet, and abdomen are



Figure 3. Facial edema in a patient with type 1 C1-inhibitor deficiency



Figure 4. Serpiginous rash (*erythema marginatum*) in HAE

the most common sites of swelling. Attacks may start in one location and then spread to another before resolving (1, 8).

Abdominal attacks are characterized by crampy pain, but may include vomiting, diarrhea, nausea and meteorism. Among patients with HAE, recurrent abdominal pain attacks have been reported to occur in >90% of cases (8, 9). These attacks can mimic surgical

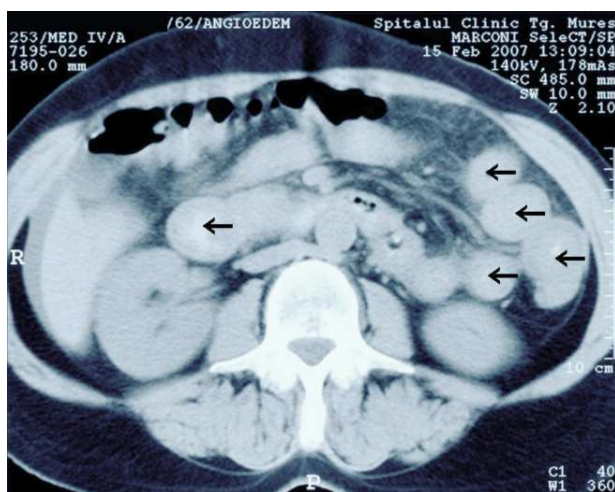


Figure 5. Abdominal CT scan showing an impressive bowel edema (arrows) during a severe abdominal attack

emergencies and, before a diagnosis of HAE is established, patients frequently undergo unnecessary appendectomy or exploratory laparotomy (14%-34%) (1, 8, 9). Ascites and edema of the intestinal wall can be detected by abdominal ultrasound (10) or CT scan (Figure 5). A shift of fluids into the interstitium or peritoneal cavity during abdominal attacks can cause clinically significant hypotension. A history of these surgeries increases the suspicion of HAE (9).

Oropharyngeal swelling is less frequent, but over half of patients have had at least one episode of laryngeal angioedema during their lifetime (1, 2, 4). Laryngeal edema poses the greatest risk for patients with hereditary angioedema. Asphyxiation caused over 30% of deaths among patients suffering from this disease in the past. Even today, patients occasionally die from asphyxiation, particularly in the absence of a proper diagnosis (11).

Patients remain uncertain when the next attack may appear and whether an episode will affect the skin, the gastrointestinal tract, the larynx or any other site (5, 6).

Rare clinical symptoms are collapse, dysuria, hemorrhagic diarrhea, acute pancreatitis, tetany, intussusception, pleural effusions, headaches, aphasia, hemiplegia and seizures, possibly due to localized brain tissue edema (1, 9).

Diagnosis

The HAE diagnosis is suggested by a history of recurrent peripheral angioedema, abdominal and laryngeal attacks. It has to be noted that there is no urticaria. In 30% of cases HAE attacks can be preceded by an erythema marginatum or serpiginous rash, that can be misinterpreted as urticaria (1, 2, 3, 4, 7, 9). Family history is present in 80% of cases (Figure 6), the rest of 20% representing the novel mutation. C4 is low in almost all cases, even between attacks (1, 2, 3, 7).

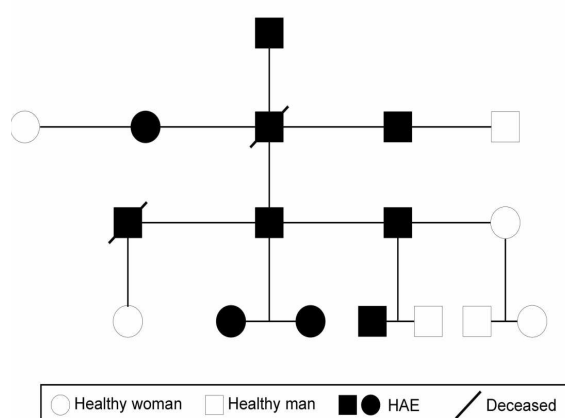


Figure 6. Pedigree of a family with HAE type I

The frequency of attacks increases during puberty. The age at the first HAE symptoms onset is below 20 years of age in 85 % of cases and the frequency of attacks seems to decrease in the elderly (1, 3). The attacks are variable from 1 per week to 1 per year and the duration of an attack is between 2 and 8 days (1, 3, 4, 7).

HAE symptoms may be induced by triggering events, such as minor trauma, surgery (even dental anesthesia), stress, oral contraceptives, pregnancy, menstruation, infections, autoimmune disorders, ACE inhibitors (1, 3, 4, 8). Fatal laryngeal attacks have been reported following tooth extraction. In several cases

no triggers can be found, and attacks are unpredictable. In many patients extensive dental work may be carried out without complication and conversely minor work may sometimes precipitate an attack (1, 3, 7, 8).

If clinically there is a suspicion of C1-INH deficiency, screening with serum C4 and C1-INH proteins (*Table 1*) is recommended. If serum C4 and C1-INH antigenic proteins are both low and acquired angioedema (AAE) is not suspected, then the diagnosis is compatible with type 1 HAE (85% of cases) (1, 3, 4). If a case of suspicion of AAE is possible (later onset of symptoms, age over 40, no family history, associated with lymphoproliferative disease or, less commonly, autoimmunity), then serum C1q antigenic protein testing is required (1, 3, 4, 12). If low, the diagnosis is highly compatible with AAE. If C4 is normal or low and C1-INH antigenic protein normal but clinical suspicion is strong, it is recommended to obtain a C1-INH functional assay. If C1-INH functional activity is low and has a normal or elevated C1-INH antigenic protein type 2 HAE diagnosis is likely (1, 2, 3, 4). If C4 antigenic protein and C1-INH functional assays are both normal, this rules out types 1 and 2 HAE, but it does not rule out the recently described type 3 HAE or estrogen dependent angioedema, with

Table I. At-a-glance comparison of C1-INH function and complement protein concentration in HAE, AAE and ACE inhibitor-induced angioedema

Condition	C-Inh Antigen	C1-Inh Function	C 1q	AntiC1-Inh	C4
HAE 1	↓	↓	N	-	↓
HAE 2	N/↑	↓	N	-	↓
HAE 3	N	N	N	-	N
AAE 1	↓	↓	↓	-	↓
AAE 2	N/↓	↓	↓	+	↓
ACE Inhibitor-induced AE	N	N	N	-	N
Idiopathic	N	N	N	-	N

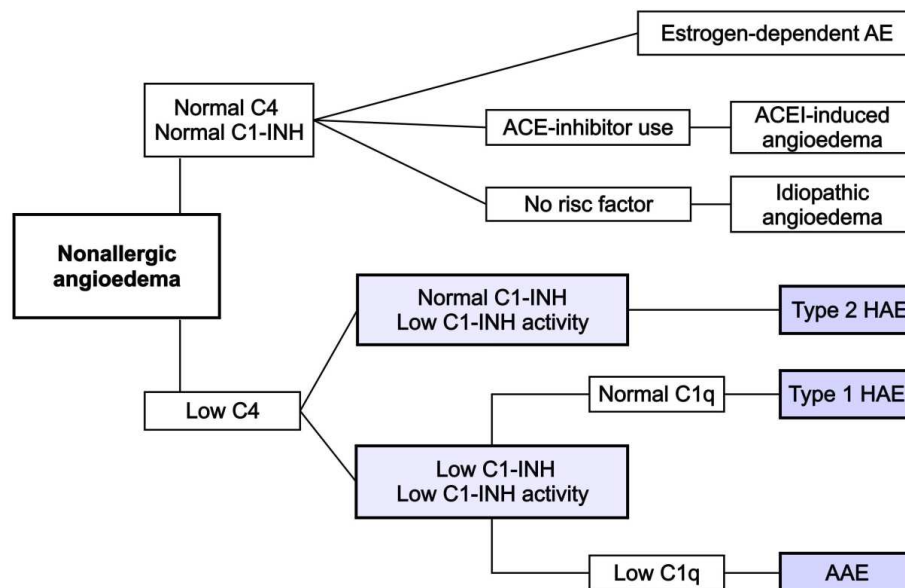


Figure 7. Algorithm of HAE diagnosis

normal C1-INH protein and function occurring mainly in women (13). The same is true for ACEI-related angioedema. Genetic testing is not necessary to confirm the diagnosis of HAE types 1 and 2. However, genetic testing may be necessary to investigate type 3 (4, 13).

C1-INH functional assays vary and standardization of functional assays is strongly recommended as well as establishing specialized laboratories capable of accurately measuring C1-INH function (7).

To sum up, HAE is classified in three phenotypes:

1. type 1 (approximately 85% of cases), characterized by impairment or absence of C1-INH protein,
2. type 2, with normal C1-INH levels, but impaired or absent activity, and
3. type 3, with normal C1-INH activity, while clinical symptoms are present.

The clinical features of these types of HAE are indistinguishable. The differential diagnosis of nonallergic angioedema is shown in Table 1 and Figure 7.

Management

It is important to stress that treatment with corticosteroids, antihistamines and adrenaline is not effective in HAE attacks or prevention (1, 14). Current treatment of patients with HAE includes long-term prophylaxis and treatment of acute attacks.

Preventive treatment consisting of attenuated androgens (danazol and stanozolol) with a good response in the majority of patients, e.g., reduces the number and severity of the attacks. However, a number of side effects were reported, but only at high doses (virilization in females, weight gain, and even liver carcinoma). Use in children, teenagers, and women in child-bearing age is problematic (15, 16). Long-term administration of tranexamic acid is less effective, but shows fewer side effects (14).

Acute attacks can be efficiently treated with C1-INH concentrate derived from human plasma, which has to be injected intravenously (1, 3, 4, 7, 14). Bradykinin receptor 2 antagonist Icatibant proved to be a good alternative (4,



Figure 8. www.haenet.ro, the site for information regarding HAE in Romania, both in Romanian and English

14). In countries where these drugs are not available fresh frozen plasma remains the single choice. The recombinant human C1-INH and plasma kallikrein inhibitor are currently being investigated as potential therapies for attacks of HAE (14).

Romanian Network for Hereditary Angioedema

Our first efforts to implement the modern management of HAE patients in this country have been started by attending the 4th Workshop for C1-inhibitor deficiency held in Budapest, in 2005 (17). With the sustained support of our collaborators, we started to build-up a national network, being aware that in the matter of rare diseases a network is the most appropriate solution (18). Until we built-up our own complement laboratory we were mainly supported by the Hungarian Centre for Hereditary Angioedema from Semmelweis University in Budapest, Hungary. Pharming Technologies Ltd from the Netherlands has also helped us with some of the infrastructure needed in our complement laboratory.

Since 2005, we have organized trainings for general practitioners, specialists in internal medicine, allergology and clinical immunology, pediatricians and dermatologists. Five workshops were held at the annual conferences of the above mentioned national societies (19). In 2006 we founded the "Romanian Hereditary Angioedema Network" aimed to provide assistance to HAE patients and colleagues. Our efforts and achievements so far can be found at www.haenet.ro (Figure 8) (18 - 20).

Presently we have registered 53 patients belonging to 19 families. Thirty six of them were enrolled in two consecutive clinical trials concerning the effect of two drugs on the acute attacks. An open-label study, still ongoing, is presently the sole therapeutic alternative for some of these patients, real orphans of our medical system. Fortunately, over these 4 years, according to our database (including patients who came at least once to our centre) nobody has died.

Desiderata

Romania is far behind many nations regarding the management of HAE. Our purposes for the near future are to build-up a national registry of HAE patients, to make their registration possible and ease the availability of drugs for the treatment of acute attack, to find new cases, to provide with further medical education for various specialists, to form a team work with the society for primary immunodeficiency and national alliance for rare diseases as well as with those of internal medicine, pediatrics, dermatology etc., empowering the quality of complement laboratories, especially of functional C1-INH and to initiate a patient association to better represent their interests.

In this context, we want to think we are a specialized centre with a sufficient case load to acquire the clinical expertise; we have personnel trained in this field, and an associated

laboratory, able both to measure the complement proteins and to provide interpretative comment on the results, preferably on site in view of the potential for sample degradation. We hope this article will be helpful in finding new cases, since there is still a lot to be done in discovering the remaining undiagnosed 150-250 patients expected to be in Romania, according to the prevalence rate of this rare disease. It is likely that most of these patients presently have a wrong diagnostic label. This misinterpretation is due to the rarity of the disorder and the scarcity of specialist centers on the one hand and insufficient clinical experience in managing the condition on the other hand.

References

1. Agostoni A, Aygören-Pürsün E, Binkley KE, Blanch A, Bork K, Bouillet L, et al. - Hereditary and acquired angioedema: problems and progress: proceedings of the third C1 esterase inhibitor deficiency workshop and beyond. *J Allergy Clin Immunol.* 2004; 114:S51-S121.
2. Agostoni A, Cicardi M. - Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore).* 1992; 71:206-15.
3. Bowen T, Cicardi M, Bork K, Farkas H, Kreutz W, Zingale L, et al. - Hereditary angioedema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. *Ann Allergy Asthma Immunol.* 2008; 100(Suppl 2):S30-S40.
4. Zuraw BL. - Hereditary Angioedema. *N Engl J Med.* 2008; 359:1027-36.
5. Cicardi M, Bergamaschini L, Marasini B, Bocassini G, Tucci A, Agostoni A. - Hereditary angioedema: an appraisal of 104 cases. *Am J Med Sci.* 1982; 284:2-9.
6. Cicardi M, Bergamaschini L, Cugno M, Beretta A, Zingale LC, Colombo M, et al. - Pathogenetic and clinical aspects of C1 inhibitor deficiency. *Immunobiology.* 1998; 199:366-76.
7. Gompels MM, Lock RJ, Abinun M, Bethune CA, Davies G, Grattan C, et al. - C1 inhibitor deficiency: consensus document. *Clin Exp Immunol.* 2005; 139:379-94.
8. Bork K, Meng G, Staubach P, Hardt J. - Hereditary angioedema: New findings concerning symptoms, affected organs, and course. *Am J Med.* 2006; 119:267-74.
9. Bork K, Staubach P, Eckardt A, Hardt J. - Symptoms, Course and Complications of Abdominal Attacks in Hereditary Angioedema due to C1 Inhibitor Deficiency. *Am J Gastroenterol.* 2006;101: 619-27.
10. Farkas H, Harmat G, Kaposi PN, Karádi I, Fekete B, Füst G et al. - Ultrasonography in the diagnosis and monitoring of ascites in acute abdominal attacks of hereditary angioneurotic oedema. *Eur J Gastroenterol Hepatol.* 2001;13:1225-30.
11. Bork K, Barnstedt S. - Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. *Arch Intern Med.* 2001;161:714-18.
12. Cicardi M, Zingale LC, Pappalardo E, Folcioni A, Agostoni A. - Autoantibodies and lymphoproliferative diseases in acquired C1-inhibitor deficiencies. *Medicine (Baltimore)* 2003;82: 274-81.
13. Bork K, Barnstedt S, Koch P, Traupe H. - Hereditary angioedema with normal C1-inhibitor activity in women. *Lancet* 2000; 356: 213-7.
14. Farkas H, Harmat G, Gyeney L, Füst G, Varga L. - Danazol therapy for hereditary angio-oedema in children. *Lancet.* 1999;354:1.031-2.
15. Frank M.M. - Hereditary angioedema: a half century of progress. *J Allergy Clin Immunol.* 2004;3: 626-628.
16. Cicardi M, Zingale L. - The deficiency of C1 inhibitor and its treatment. *Immunobiology* 2007; 212:325-31.
17. Moldovan D, Todea Cs. - Hereditary angioedema: present and perspectives in Romania. 4th C1 Inhibitor Deficiency Workshop, Budapest, 29 April-1 May 2005. Abstract book, 40.
18. Moldovan D. Romanian Hereditary Angioedema Network - 5th C1 INH Deficiency Workshop, Budapest, 31 May-3 June 2007. Abstract book, 53.
19. Moldovan D, Dobreanu M, Popescu FD, Vieru M, Cristea A, Tătaru A. - The Romanian Network for Hereditary Angioedema. Present and perspectives - 1st Congress of the Rom Soc Allergol Clin Immunol. Tîrgu Mureş, pg. 40, April 26-28, 2007.
20. Szöllösi G, Mihály E, Moldovan D.- Romanian Hereditary Angioedema Network. *Allergy* 2007;62: S83:479.