Acta Med Croatica, 71 (2017) 157-162 *Original Paper*

IMPROVEMENT IN THE MANAGEMENT OF RARE DISEASES IN CROATIA BASED ON THE PROTOCOL FOR HEREDITARY ANGIOEDEMA

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Rare diseases affect up to 6%-8% of the population and pose a challenge to healthcare professionals and healthcare system. Hereditary angioedema is a rare life-threatening, debilitating disease characterized by recurrent edema attacks. It is essential to establish the diagnosis as quickly as possible. The Healthcare Network was created in order to prevent mistreatment of hereditary angioedema. This study evaluated the usefulness of the Hospital Information System and the Healthcare Network in urgent management of hereditary angioedema. The Instructions for Hereditary Angioedema that contain information on the diagnosis, instructions for treatment, preventive measures prior to a dental procedure, endoscopy or surgery under general anesthesia, available regimens and storage location in the Hospital, specialist's telephone number in emergency, and name of the family member to be contacted, were implemented in the Hospital Information System, Šibenik General Hospital as a protocol for urgent management. Data on the treatment before and after implementation of the Instructions for Hereditary Angioedema were compared. Comparing medical decisions before and after implementing the Instructions for Hereditary Angioedema in the Hospital Information System revealed that following implementation of the Instructions, correct therapy was administered more often (p=0.006, Fisher exact test) and short-term prophylaxis applied more often before medical procedures (p=0.011, Fisher exact test). Healthcare Network raised the physician awareness of this disabling and potentially fatal disease, led to accurate diagnosis and timely treatment, enabled short hospital stay, prompt recovery, and reduced absenteeism from work due to hereditary angioedema. With specific modifications, it could also be extrapolated to other rare diseases.

Key words: hereditary angioedema, emergency, management instructions, burden of illness

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INTRODUCTION

Accurate diagnosis and timely treatment of 5000-8000 known rare diseases that affect up to 6%-8% of the population is a challenge to healthcare professionals and system. Around 80% of these diseases are of genetic origin, occur in childhood and persist for life, posing considerable burden upon the individuals and their families (1). Hereditary angioedema (HAE) is a rare, life-threatening, debilitating disease characterized by variable clinical presentation of recurrent edema attacks that can affect different body regions (2). Attacks are usually triggered by infections, trauma or stress, by medications such as oral contraceptives with

estrogen or angiotensin-converting enzyme (ACE) inhibitors, or by procedures such as endoscopies and general anesthesia with intubation (3). HAE can present as robust abdominal pain leading to unnecessary diagnostic (computed tomography scans, laboratory tests) and/or exploratory procedures, such as surgery. Skin and face swelling may be disfiguring or disabling. However, life-threatening upper airway obstruction is the most troublesome symptom of HAE, especially in children with small airway diameter. It can cause death by asphyxiation, even at the first presenting attack (1-3). HAE is an autosomal dominant disease caused by mutations in the C1-INH gene, *SERPING1* (4). Low levels of the C1 inhibitor occur in type I C1-INH-HAE, whereas normal levels of ineffective C1 inhibitor cause type II C1-INH-HAE (5-10). The type of HAE in patients with positive family history and normal C1 inhibitor level and function (nlC1-INH-HAE) occurs in a group of patients with a mutation in the coagulation factor XII gene (FXII-HAE), or the cause of HAE remains unknown (U-HAE) (4).

In Croatia, HAE often remains undiagnosed, which leads to inappropriate treatment, mostly with corticosteroids and antihistamines that are not effective in HAE (11,12). In the emergency department (ED) or during triggering procedures, it is essential to establish the diagnosis as quickly as possible, so that the specific therapy for HAE can be administered to resolve edema (13).

This was the first study analyzing the awareness of HAE among patients and physicians in Croatia. In addition, usefulness of the Hospital Information System and Healthcare Network in the emergency management of HAE was evaluated.

PATIENTS AND METHODS

The largest number of clinically well-defined HAE patients were found in the catchment population of the only hospital in the Šibenik-Knin County, Croatia. Fifteen patients from two families were diagnosed with Type I C1-INH-HAE. In 12 of them, the diagnosis was substantiated with at least one major clinical presentation (laryngeal edema, abdominal pain, subcutaneous angioedema) and one laboratory criterion (C1 inhibitor level). In three asymptomatic patients aged 5, 14 and 20 years, decreased levels of C1 inhibitor were found. All of them share the same mutation in *SERPING1* (14). To evaluate the awareness of the C1-INH-HAE diagnosis among patients and physicians, history data were collected from electronic medical records available in the Hospital Information System (HIS) from 2012 to 2014, before creating the Healthcare Network (HN) and during a 22-month period after creating the HN. Also, subsequent treatment introduced by physicians was observed. This study was conducted in accordance with the amended Declaration of Helsinki. The study and the creation of the HN were approved by the Hospital Ethics Committee and all participants or minors' relatives gave their informed written consent.

Data collection-Hospital Information System

In 2009, the Šibenik General Hospital, among the first in Croatia, implemented the HIS (IN2, Zagreb, Croatia). HIS supports all aspects of hospital business: medical (medical documentation management), economic (invoicing), and business (hospital business monitoring through reports). The following information systems are directly connected to the HIS: Business Information System (material and financial accounting), Laboratory Information System (laboratory test acceptance and validation), and Radiology Information System (radiological images acceptance). In December of 2014, Instructions for HAE were implemented in a new, improved version of the HIS. The name of each C1-INH-HAE patient was marked with a red exclamation mark on the screen at the moment of signing up at any work site in the Hospital, thus notifying the physician about the patient's condition. The Instructions contain information on the C1-INH-HAE diagnosis, instructions for treatment, preventive measures prior to a dental procedure, endoscopy or surgery under general anesthesia, available regimens and storage location in the Hospital, emergency specialist's telephone number, and the name of the family member to be contacted. There is also a warning for the physician not to prescribe ACE inhibitors or oral contraceptives, as well as a notice of any comorbidities such us drug allergy.

To evaluate the awareness of the C1-INH-HAE diagnosis among patients and healthcare professionals, information given by the patient about the C1-INH-HAE diagnosis and subsequent treatment by physicians were observed and analyzed in the HIS Archive. Data about treatment in the 2012-2014 period were compared to data collected during the 22-month period after implementation of Instructions for HAE (test version in December 2014, permanent version in January 2015).

Healthcare network

The Healthcare Network was created in order to prevent mistreatment of HAE. Patients were educated about the nature of their condition and given an identification card with an individual plan of C1-INH-HAE treatment. To prevent adverse events, a letter

containing information and instructions about children with C1-INH-HAE was sent to schools and kindergartens. E-mail communication between patients and HAE specialist continues on an ongoing basis. The Instructions for HAE were implemented in the Hospital Information System (HIS), Šibenik General Hospital. The benefit of Healthcare Network was evaluated by analyzing data in the HIS, finding data on already established C1-INH-HAE diagnosis and treatment of HAE attacks.

Statistical analysis

Data were processed by use of the SPSS version 20 software. Statistical analysis of data was performed using descriptive statistics. Variables were tested by Fisher exact test. The level of statistical significance was set at $p<0.05$.

RESULTS

Followed by available electronic medical records in the HIS (before implementing the Instructions for HAE in the HIS) from 2012 to 2014, three of 15 (20%) C1-INH-HAE patients visited the Šibenik General Hospital Emergency Department (ED) for a total of 12 HAE attacks. The main symptom for emergency treatment was abdominal and laryngeal swelling followed by facial and skin edema. According to the HIS, only one C1-INH-HAE patient who visited ED for HAE attack gave information about the illness, although the C1-INH-HAE diagnosis had already been established in all of them. The C1-INH-HAE diagnosis was never reported during abdominal edema attack. Short-term prophylaxis was not applied on 2 occasions: before giving birth and gastroscopy, triggering an abdominal edema attack. All patients except for one patient having reported diagnosis on two occasions were treated with corticosteroids and antihistamines during laryngeal edema attacks. Abdominal attacks were treated with antibiotics, analgesics, or symptomatic therapeutics. One urgent tracheotomy was performed during laryngeal edema attack. During regular visits to physicians for chronic disease follow-up (hypertension, diabetes) before creating HN, only 4/15 (20.6%) patients informed about the C1-INH-HAE diagnosis. One patient experienced several massive laryngeal edema attacks during ACE inhibitor therapy for hypertension, once ending in urgent tracheostomy. Recognized as acute abdomen, one patient was almost subjected to laparotomy during an abdominal edema attack before the edema spontaneously resolved. Until 2015, esophagogastroduodenoscopy was performed three times on the same patient without short-term prophylaxis. During pregnancy, one female patient experienced abdominal edema attacks 3 times. Treatment was always symptomatic with no evidence of C1-INH-HAE diagnosis noticed by her obstetrician. Joint swelling was treated in one patient as polyarthralgia with a recommendation of immunology testing for rheumatoid arthritis. One patient experienced massive facial edema attack after a dental-oral procedure. Although she had the physician's letter proving the C1-INH-HAE diagnosis and the drug given by her physician to be applied in case of a life-threatening swelling, the drug was not administered.

Followed by available electronic medical records in the HIS (after implementation of the Instructions for HAE), from January 2015 until October 2016, 11/15 (73%) C1-INH-HAE patients visited a physician in the Šibenik General Hospital. Six patients were examined for chronic disease follow-up (diabetes, hypertension) or acute diseases such as stenocardia or obstructive bronchitis, but four of them reported the C1-INH-HAE diagnosis on 16/29 (55%) occasions. Five patients visited the ED on seven occasions because of a C1-INH-HAE attack, all of them reported the C1-INH-HAE diagnosis, and appropriate therapy was applied for 6/7 (85%) attacks. Despite medical history, notice to the physician in the HIS and Instructions for HAE, abdominal edema attack was misdiagnosed as acute gastroenterocolitis and treated erroneously. Short-term prophylaxis before dental-oral procedures, endoscopies or general anesthesia were undertaken 12 times in 12 procedures.

According to the Instructions for HAE implemented in the HIS, an anesthesiologist suggested attenuated androgen danazol to a patient for 5 days before an operation in spinal anesthesia, and on-demand therapy (icatibant) was prepared in case of necessity. Although education through Healthcare Network was obtained, one patient reported the HAE diagnosis at 4/6 visits to a pediatrician for asthma exacerbation. Due to tagging in the HIS, management was accurate on all occasions. Due to physical exertion, one patient experienced an abdominal and skin (hand) edema attack at work. Within an hour, on-demand therapy was applied and the patient got back to work.

Comparing medical decisions before and after implementing HAE instructions through the HIS, correct therapy was given more often ($p=0.006$, Fisher exact test) and prophylaxis was applied more often before medical procedures ($p=0.011$, Fisher exact test). HAE diagnosis was not more often reported by patient to a physician ($p=0.045$, Fisher exact test) (Table 1).

Table 1
Differences between hospital visits, reported hereditary angioedema diagnosis and applied therapy in two observed period: before (2012-2014y) and after (2015-2016y) implementation of HIS

HIS	No (%) of occasions in HN			p*
	2012 – 2014.y	2015 -2016.y	Total	
No of visits				
HAE attack	12/36 (33%)	7/29 (24%)	19/45 (42%)	0.584
Other	24/36 (67%)	22/29 (76%)	26/45 (58%)	
Reported HAE diagnosis				
Yes	14/36 (39%)	16/29 (55%)	19/45 (42%)	0.219
No	22/36 (61%)	13/29 (45%)	26/45 (58%)	
Preventive therapy applied				
Yes	0	12/12 (100%)	12/14 (85.8%)	0.011
No	2/2 (100%)	0	2/14 (14.2%)	
Emergency therapy				
Appropriate	2/12 (16.6%)	6/7 (85,8%)	8/19 (42%)	0.006
Inappropriate	10/12 (83.4%)	1/7 (14.2%)	11/19 (58%)	

Values are number of patients.
* Fisher's Exact test. Y-years.
HAE - hereditary angioedema
HIS - Hospital Information System
HN - Healthcare Network

DISCUSSION

Rare conditions typically remain undiagnosed or misdiagnosed, require new approaches and program, as proposed by Baynam *et al.* (15). In an Australian study, approximately 30% of patients saw more than six physicians before receiving correct diagnosis and 46% had received at least one incorrect diagnosis (16). HAE morbidity and mortality remain considerable despite the availability of diagnostic tests and specific treatments, representing a notable socioeconomic burden. HIS analysis also revealed social (unemployment, isolation) and emotional (avoiding partnership or parenthood, trepidation for affected children) burden, difficulties in education, and premature retirement of HAE patients, pointing to the need of structural changes in the healthcare system. As Otani *et al.* suggest, HAE management in emergency departments can be improved with a focus on recognition of HAE attacks and administration of effective therapies (17). Protocol for HAE is designed to test whether the Instructions for HAE implemented in the HIS are more effective than the usual practice (history findings, laboratory tests, clinical examination) in the urgent management of patients with HAE. To the best of our knowledge, a similar IT model for urgent diagnosis of rare diseases such as HAE has not yet been established. A group of French authors organized the SOS-HAE call center for HAE to address the handling of HAE attacks experienced at home (18). Due to the large number of C1-INH-HAE patients in the Šibenik General Hospital (the minimal prevalence in the Šibenik-Knin County with approximately 100,000 inhabitants is estimated to be 1 *per* 7500) including tourists, and the high frequency of laryngeal edema attacks, improving the management of HAE patients is needed. HAE is often misdiagnosed, which leads to inappropriate pharmacological therapies, thus potentially exposing the patients with laryngeal attacks to the risk of asphyxiation (14-19). The low rate of HAE diagnosis reported by patients with already established C1-INH-HAE in this study indicated the lack of awareness of HAE as a serious disease among HAE patients. Education through the Healthcare Network has insufficiently raised the awareness of HAE among patients, thus making the implementation of the Instructions for HAE in the HIS even more important. Before tagging in the HIS, all involved HAE patients except for one were treated with glucocorticoids and antihistamines for laryngeal edema, which are ineffective in HAE (21). In Croatia, specific therapeutics such as plasma-derived C1-INH, recombinant C1-INH and a bradykinin receptor B2 antagonist icatibant have recently been available for the treatment of acute HAE attacks and for short-term prophylaxis (plasma-derived C1-INH) before triggering procedures. Instructions for HAE implemented in the HIS have improved management during angioedema attacks, especially abdominal and laryngeal, raised the physician awareness of this disabling and potentially fatal disease, led to accurate diagnoses and timely treatment, enabled short hospital stay, prompt recovery, and reduced work and school absenteeism for HAE patients, thus highly improving their quality of life. These encouraging findings prompted a group of experts for HAE management in Croatia to recommend implementation of this model in the information systems of other hospitals (11). Studies analyzing the economic costs associated with acute attacks and long-term management of HAE estimated the total annual *per* patient cost at $42,000 for the average HAE patient (21). Further investigations should be conducted to analyze the implications of the Instructions for HAE implemented in hospital information systems compared to education costs for healthcare professionals in terms of socioeconomic costs for both healthcare services and patients.

CONCLUSIONS

The need for high level of knowledge and appreciation of rare diseases among patients and physicians has been noted. The Healthcare Network and the HIS have

improved the management of HAE and prevented adverse events. With specific modifications, it could easily be implemented for other rare diseases, since they all share the same challenge.

ACKNOWLEDGMENTS

The authors are grateful to all patients and their family members who participated in the study, to laboratory workers, and ENT and IT Departments of the Šibenik General Hospital.

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SAŽETAK

POBOLJŠANJE ZBRINJAVANJA BOLESNIKA S RIJETKIM BOLESTIMA U HRVATSKOJ - TEMELJENO NA PROTOKOLU ZA HEREDITARNI ANGIOEDEM

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Rijetke bolesti su izazov zdravstvenim stručnjacima i sustavima. Smatra se da 6-8 % populacije boluje od rijetkih bolesti. Nasljedni angioedem (HAE) jedna je od rijetkih bolesti, karakterizirana ponavljajućim napadima oteklina (edema) različitih dijelova tijela te se vrlo često ne dijagnosticira pravodobno, a težina ponavljajućih napadaja se pogoršava i za život je opasno stanje. Bitno je posumnjati na rijetku bolest i postaviti dijagnozu što je brže moguće. Ova je probna studija procijenila korisnost implementacije podataka o bolesnicima s HAE u Bolnički informacijski sustav (BIS) Opće bolnice Šibensko-kninske županije kao i primjenu protokola za hitno zbrinjavanje i formiranje mreže zdravstvene zaštite (MZZ). Upute u BIS-u za HAE sadrže podatke o dijagnozi HAE-a, upute za liječenje, preventivne mjere prije stomatološkog, endoskopskog ili kirurškog postupka (pod lokalnom/općom anestezijom); popis raspoloživih lijekova u hitnoći i mjesto njihove pohrane u bolnici; telefonski broj specijalista u hitnoći te ime člana obitelji (kontakt osoba). Podatci o liječenju prije primjene uputa za HAE uspoređeni su s podatcima prikupljenima u razdoblju nakon provedbe implementacije novog sustava. Uspoređujući medicinske odluke prije i nakon implementacije uputa za HAE u BIS-u, pravilna je terapija bila češće primijenjena (p = 0,006, Fisherov test), kao i kratkotrajna profilaksa prije medicinskih postupaka (p = 0,011, Fisherov test). Uspostava MZZ pospješuje informiranost medicinskog osoblja, pravilan odabir liječenja i zbrinjavanje bolesnika s HAE. Omogućuje brži oporavak, kraći boravak u bolnici i smanjenje radne odsutnosti bolesnika s HAE. Temeljem ove studije otvara se mogućnost primjene MZZ i za druge rijetke bolesti.

Ključne riječi: nasljedni angioedem, hitna pomoć, implementacija uputa