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Rare Diseases in Croatia – Lesson Learned from Anderson-Fabry Disease

Rare diseases, also referred to as orphan diseases, have a very low incidence and include diseases that occur at a prevalence of less than 5 cases per 10 000 people in the overall population (1). New rare diseases are discovered every year, and some of today's known diseases in this category have patient populations of fewer than a hundred (2).

In a country like Croatia (population of 4.5 million), most physicians do not see a single patient with a rare disease during their entire career. Hematologists, pathologists, and other specialists in main hospital centers would probably see not more than one case in several years.

Rare diseases are mostly genetic. Many of them are life-threatening or chronically debilitating. The prevalence of rare diseases may vary between different populations. In some populations they may be slightly more frequent than in others, which is especially true for genetic, infectious, or malignant diseases. For example, cystic fibrosis is very rare in Asia but relatively common in Europe. Other diseases, such as many rare forms of cancer, have no apparent pattern of distribution but are simply rare in most countries. European Organization for Rare Diseases (EURODIS) estimates that there are between 5000 and 8000 distinct rare diseases affecting 6-8% of the population (3).

From a societal point of view, many patients and families affected by a rare disease are often isolated and thus vulnerable to stress. The life expectancy of patients with rare diseases is significantly reduced. Many of them have disabilities that may become a cause for discrimination, which in turn might reduce educational, professional, or social opportunities for these persons. The research on rare diseases is scarce. The lack of specific health policies and the scarcity of expertise translate into delayed appropriate diagnosis and difficulty of access to care.

National health care services for diagnosis, treatment, and care of patients with rare disease differ significantly in terms of their availability, expertise, and quality. In Croatia, most rare diseases are infrequently diagnosed, and when diagnosed they are not given special treatment and attention. The awareness about rare diseases remains low among Croatian physicians and health care system organizations. The need for creating an infrastructure that would enable early access to existing treatment by establishing a special fund for expensive therapies has only rarely been recognized (4). A special fund was established on the principle that the society cannot accept discrimination and the fact that certain individuals are denied the benefits of medical progress because the illness they have is rare or costly. The main goal of this fund is to ensure equal access to treatment for all such patients. The most striking progress was made in the field of lysosomal storage diseases, but gradually more and more diseases are included.

Lessons learned from Anderson-Fabry disease

Anderson-Fabry disease is an X-linked disorder characterized by a deficiency of α-galactosidase (5). The incidence of the disease is 1:40 000 among men and 1:114 000 in the overall population (6). Anderson-Fabry disease is a multisystemic disorder characterized by an accumulation of globotriasilceramide in the endothelium of the hearth, kidney, brain, skin, and other organs. Alpha-galactosidase is an enzyme involved in lipid metabolism, and its deficiency causes lipid accumulation in various cells leading to cell death. The disease is usually diagnosed by peripheral blood sampling and measurement of α-galactosidase activity in leukocytes. Like many other genetic diseases, Anderson-Fabry disease is readily diagnosed and treated at the Zagreb University Hospital Center. However, due to the nature of the disease, some patients suffering from Anderson-Fabry disease had been seen by 7 to 10 different specialists on average before a diagnosis was finally made (7).

One of the main characteristics of the disease is the appearance of red spots (angiokeratomas) on the skin of the lower abdomen and genital regions. In early childhood, patients with Anderson-Fabry disease experience bouts of pain and/or acroparesthesia, recurrent febrile episodes, and heat and cold intolerance. An inability to sweat and corneal clouding is also often encountered. Older patients have the same symptoms but develop proteinuria followed by kidney failure. Transient ischemic attacks, cerebrovascular stroke, myocardial infarctions, left ventricular hypertrophy, and hearing loss are common complications (8,9). Without appropriate therapy, most patients die in the fourth to fifth decade of life (10).

The diagnosis of Anderson-Fabry disease should be considered in younger patients presenting with crebrovascular stroke, left ventricular hypertrophy, or kidney failure of unknown origin. The knowledge about Anderson Fabry disease increased over past few years and today we know that women are not only carriers, but also the patients due to the random inactivation of the X-chromosome (11). Today, there are two effective treatment options – enzyme replacement therapies with agalsidase alpha or agalsidase beta – available for most patients diagnosed with Anderson-Fabry disease (12,13). The treatment costs are covered by the "Expensive Drug Fund" of the Croatian Institute for Health Insurance, which also covers the costs of treatment of some other rare diseases like Morbus Gaucher and mucopolisaharidoses and some more common diseases like malignant lymphoma, breast carcinoma, tuberculosis, AIDS, juvenile arthritis, colon carcinoma, multiple sclerosis, and others.

Successful development of the Rare Disease Patient Organization

The Croatian Society of Patients with Rare Diseases is a non-profit organization established in November 2006 as a successor of the Croatian Society for Inherited Metabolic Diseases, which in itself was a derivative of the Croatian Society for Mucopolysaccharidoses and Similar Diseases (*www.rijetke-bolesti.hr*). The history of the Society illustrates the need for expanding the scope of work from one specific rare disease to all inherited metabolic diseases and, finally, to all rare diseases. Members of the Society are not only patients suffering from various rare diseases, but also non-profit organizations (NGOs) devoted to particular problems of those affected by rare diseases. The Society for Rare Diseases has been joined by other organizations, such as Association for Persons with Prader-Willy syndrome, the Croatian Organization

for Cystic Fibrosis, the Croatian Organization for Osteogenesis Imperfecta, and Dystrophic Epidermolysis Bullosa Research Association. Other established rare disease patient organizations are currently in the process of joining the Croatian Society of Patients with Rare Diseases. While these organizations have worked for years on solving various problems of patients with specific rare diseases, the umbrella society provides a platform for working together as one network for rare diseases. As the joint efforts increased, it became essential to strengthen the cooperation with other non-governmental organizations. The main goal of the society is to improve the quality of life of patients suffering from rare diseases and their families. The Society of Patients with Rare Diseases had numerous activities over the past two years, including the launch of the first rare disease Web site (*www.rijetkebolesti.hr*) bringing information about the organization, rare diseases in general, and other member organizations. In 2007, the Society organized the first local Meeting on Rare Diseases, during which patients and their family members, physicians, NGO workers, and government officials met and discussed essential issues concerning rare diseases. A series of public activities under the name "Give me a hand" was organized with the main goal to inform and educate citizens about rare diseases and to raise funds for future activities. On February 29, 2008, the Society celebrated the European Rare Disease Day.

The first steps in the positive direction have been taken to build a health care infrastructure for rare diseases. Nevertheless, further progress is still depending on NGOs and there is still a need for more structural and transparent regulations.

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References

1 The portal for rare diseases and orphan drugs. Available from: http://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN. Accessed: September 25, 2008.

2 Baric I, Fumic K, Hoffmann GF. Inborn errors of metabolism at the turn of the millennium. Croat Med J. 2001;42:379-83. Medline:11471189

3 Eurordis. What is a rare disease? Available from: http://www.eurordis.org/secteur.php3?id_rubrique=1. Accessed: September 25, 2008.

4 Mrsic M, Stavljenic-Rukavina A, Fumic K, Labar B, Bogdanic V, Potocki K, et al. Management of Gaucher disease in a post-communist transitional health care system: Croatian experience. Croat Med J. 2003;44:606-9. Medline:14515422

5 Shin SH, Kluepfel-Stahl S, Cooney AM, Kaneski CR, Quirk JM, Schiffmann R, et al. Prediction of response of mutated alpha-galactosidase A to a pharmacological chaperone. Pharmacogenet Genomics. 2008;18:773-80. Medline:18698230 doi:10.1097/FPC.0b013e32830500f4

6 Desnick RJ. Prenatal diagnosis of Fabry disease. Prenat Diagn. 2007;27:693-4. Medline:17533632 doi:10.1002/pd.1767

7 Kudumija B, Mrsic M, Dits S, Matijevic V, Thune S, Bozina K. Classical type of Fabry disease without angiokeratomas – a case report [in Croatian]. Lijec Vjesn. 2007;129:396-400. Medline:18383742

8 Hauser AC, Lorenz M, Sunder-Plassmann G. The expanding clinical spectrum of Anderson-Fabry disease: a challenge to diagnosis in the novel era of enzyme replacement therapy. J Intern Med. 2004;255:629-36. Medline:15147526 doi:10.1111/j.1365-2796.2004.01300.x

9 Whybra C, Kampmann C, Krummenauer F, Ries M, Mengel E, Miebach E, et al. The Mainz Severity Score Index: a new instrument for quantifying the Anderson-Fabry disease phenotype, and the response of patients to enzyme replacement therapy. Clin Genet. 2004;65:299-307. Medline:15025723 doi:10.1111/j.1399-0004.2004.00219.x

10 Schaefer E, Mehta A, Gal A. Genotype and phenotype in Fabry disease: analysis of the Fabry Outcome Survey. Acta Paediatr Suppl. 2005;94:87-92. Medline:15895718 doi:10.1080/08035320510031045

11 Wang RY, Lelis A, Mirocha J, Wilcox WR. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. Genet Med. 2007;9:34-45. Medline:17224688

12 Keating GM, Simpson D. Agalsidase Beta: a review of its use in the management of Fabry disease. Drugs. 2007;67:435-55. Medline:17335299 doi:10.2165/00003495-200767030-00007

13 Hughes DA, Elliott PM, Shah J, Zuckerman J, Coghlan G, Brookes J, et al. Effects of enzyme replacement therapy on the cardiomyopathy of Anderson-Fabry disease: a randomised, double-blind, placebo-controlled clinical trial of agalsidase alfa. Heart. 2008;94:153-8. Medline:17483124 doi:10.1136/hrt.2006.104026