I. GENETICS

RARE DISEASES – A MAJOR PROBLEM OF PUBLIC HEALTH

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Abstract

A rare disease is a disease that affects less than 1 of 2000 individuals. The term "orphan disease", used especially in France, confers to rare diseases political and social dimensions, trying to transmit the need of patients to be taken into consideration their existence, as rare as it would be the disease. Today it is being reported that exists over 8000 of this kind of diseases. Numerous and complex, rare diseases are less known by the medical corps and by the authorities of the health care system. These diseases are connected with all medical specialties and there are of an extremely variable gravity in accordance with patient and disease. Since the rare diseases affects over 25 million individuals in Europe, the Health Care Committee of UE seems to become more and more preoccupied to rehabilitate the research in this domain, to create an educational climate of the medical corps, patients and general population, with the announced purpose of ensuring conditions for a correct and early diagnosis of these diseases. All these strategies must be adopted in our country as well with the sustained effort of National Alliance of Rare Disease from Romania (ANBRaRo), by creating and unrolling The National Plan for Rare Diseases.

Key words: rare diseases, orphan drugs, patient and parent organizations

Definition

"A rare disease (RD) is a disease that occurs infrequently or rarely in the general population". In Europe a disease is considered rare when it affects less than 5 in 10,000 citizens. This figure can also be expressed as 500 rare disease patients out of 1 million citizens. A RD is also called an "orphan disease", a term that is usually used in France and it gives to RD political and social dimensions trying to transmit the solicitation of patients not to be forgotten even if their disease is very rare. Also, RD are orphan of treatment, recognition and proper care.

Frequency

Despite the rarity of each RD, "about 30 million people have a RD in the 25 EU countries", which means that 6% to 8% of the total EU population are RD patients. Considering that in Romania the frequency is similar to other EU countries we can appreciate that 1,3 million citizens are affected by RD and over 1,2 million do not obtain an accurate diagnosis, so they do not benefit of adequate information about the disease, access to qualified specialists and proper treatment. For this reason RD represents a major public health problem as well in Romania as in all EU countries which made from this subject a priority in healthcare programs and research programs of the European Union.

Quoting from the Background Paper on Orphan Diseases for the "WHO Report on Priority Medicines for Europe and the World" (7 October 2004): "Unfortunately, the epidemiological data that are available are inadequate for most RD to give firm details on the number of patients with a specific RD. In general people with a RD are not registered in databases. Many RD are summed up as "other endocrine and metabolic disorders" and as a consequence, with few exceptions, it is difficult to register people with a RD on a national or international basis, and in a reliable, harmonized way". In 1995 World Health Organization (WHO) reviewed about five thousand RD, but today 6000 – 7000 RD have been found and five new diseases are described every week in the medical literature.

Common characteristics of RD

RD concern all medical specialties and their gravity differ widely in accordance with the disease and the patient. The disease can be discovered at birth or in childhood (for 50% of RD the onset of the disease occurs in childhood), but in many cases the first symptoms appear in adult age. In patients with RD are affected physical capabilities, mental abilities, behavior and sensorial capacities. Many disabilities can coexist, can be severe and it determines an important handicap. The impact on life expectancy varies greatly from one disease to the other: some RD cause death even before birth or at birth while others are compatible with a normal life if diagnosed in time and properly managed and/or treated. RD are severe to very severe, progressive, chronic, often degenerative and life-threatening and most of the time leads to the lifetime care necessity. The quality of life of RD patients is frequently compromised because of the loss of autonomy. It is also present a psychosocial burden for patients and their families due to lack of therapeutic hope. For most of these diseases there are no efficient treatments, but in some cases symptoms can be treated to improve quality of life and life expectancy. Fighting isolation and

despair the patients and their families need attention and emotional support.

Etiology

80% of RD has identified genetic origins, involving one or several genes or chromosomal abnormalities. They are generally inherited and transmitted from one generation to another, but they can also be derived from de novo gene mutation or from a chromosomal abnormality. The other 20% of RD are caused by infections (bacterial or viral), allergies, or are due to degenerative, proliferative or teratogenic (chemicals, radiations, etc) causes. Some RD are also caused by a combination of genetic and environmental factors. But for most RD the etiological mechanism are still unknown due to lack of research in this domain.

Prevention

Because most of the RD are genetically determined and have a great risk of recurrence it is very important for us to know if and how we can prevent these diseases. The concept of prevention is not new. The prevention can be collective by using general measures pointed to a certain disease (vaccine, control to detect breast or uterine cancers) and which is based on general criteria (age, sex, season, local or national epidemiological status). Unlike the collective prevention, in RD's pathology the prevention is frequently individual; the selection of risk patients and the prevention depends of the genetic features of each individual. The new possibilities of genetic diagnosis permitted the progressive implementation of some public health programs. These programs have started a new concept of predictive medicine which covers different situations the diagnosis being determined to subjects in good health. The most used prevention methods are connected with antenatal diagnosis, screening tests, in fact with the existence of a functional healthcare system that includes well trained specialists, diagnosis and counseling centers, an informed population, adequate sanitary laws, funds to support expensive investigations, quality of medical attendance, multidisciplinary supervision. The fight against genetic diseases must be based on an integrated and exhaustive strategy associating an optimum prevention and treatment, methods to aware the community, detection in population, genetic counseling and the possibility of an early diagnosis.

Specialty drugs for RD ("orphan drugs")

Orphan drugs are medicinal products intended for the diagnosis, prevention or treatment of RD. People who have RD have not had research attention in past decades because the potential market for new drugs to treat RD is small. It is important to underline that many RD are transmitted along different generations and therefore investing in the fight against RD today may be a very profitable investment. In 1999 the European Union adopted a Regulation, based on experience in the United States, aimed at promoting the development of drugs for patients suffering from RD. Pharmaceutical and biotech companies that market an orphan drug received a variety of financial assistance, a guaranteed 10 year-monopoly on drug sales, protocol assistance so they are constantly researching and developing new medications. Clinical evaluation of orphan drugs is restrained by the small number of patients available for clinical trials. In many cases, surrogate criteria are used instead of clinical endpoints. New drugs, with documented efficacy and safety, are now available for patients who previously had no effective treatment options. Access to these drugs varies greatly from one European Union Member State to another, mainly because of the high annual treatment costs so that patients in many European countries cannot benefit.

What do patients with RD need?

- *Access to correct diagnosis*: it is very important to have an early and accurate diagnosis to prevent highly risk delays and inaccurate treatments due to wrong diagnosis
- *Basic information* about the disease and where to obtain help
- *Scientific knowledge* in order to develop therapeutic tools, therapeutic strategy and therapeutic products (medicinal products and appropriate medical devices)
- *Social integration:* patients with RD are often stigmatized, isolated, excluded from social community, discriminated for insurance subscription and professional opportunities
- *Quality healthcare*: RD patients need most of the time a multidisciplinary team: physiotherapist, nutritionist, psychologist, logoped,organ specialist, etc. Unfortunately, sometimes patients live for several years without competent medical attention or they are treated during many months or years for another more common disease. They remain excluded from the health care system even after the diagnosis is made.
- *Social benefits and reimbursement* so that the patients and their families can cover the high cost of the few existing drugs and care
- *Equities in availability of treatment and care*: new treatments are often unavailable even in the EU countries because of delays in price determination and/or reimbursement decision, lack of experience of the physicians and the absence of treatment protocols.

A delayed diagnosis has sometimes dramatic consequences:

- other children with the same disease in the family,
- parental splitting when a child with a RD is borne,
- lack of support from family members,
- clinical complications even leading to the death of the patient,
- distrust in the healthcare system.

The entire family of the patient is affected by the disease and becomes marginalized psychologically, socially, culturally and economically vulnerable. In order to help RD patients and their families face the future psychological support is greatly needed. This kind of support can be offered by family and friends, but also by specialists, support groups and electronic email discussion groups which link patients and also families and medical personnel.

RD patient and parent organizations

The scientific community's insufficient knowledge of RD and the minimal attention given to them by national authorities and the pharmaceutical industry has lead to the creation of associations of patients and parents. These were created as a result of experience gained by patients and their families who wants to gather, produce and disseminate the existing information on their disease and to make patients and parents voices heard. These support groups for patients are the most motivated and have the most important achievements in the advocacy activities. They have succeeded to influence the policies and to stimulate the medical research because of the personal involvement. In the world there are various forms of organization of the patients, from very small groups to very large organizations, it can be focused to support patients affected by one disease or can include patients with different pathologies and have members from one country or there are organized at the European or international level. Certainly, the best results are obtained by patients that are organized in networks because they speak for a great number of patients influencing the legislation and sharing the experience of all smaller groups.

The association of patients, parents, specialists represents the most beneficial way to interfere efficiently in changing conceptions, in modifying the health care strategies, but the most important, in improving the life quality of these patients. The Health Care Committee of UE seems to become more and more preoccupied to rehabilitate the research in the RD domain, to create an educational climate of the medical corps, patients and general population, with the announced purpose of ensuring conditions for a correct and early diagnosis of these diseases. All these strategies must be adopted in our country as well. In 2005 Romanian Prader-Willi Association opens The Information Center for Rare Genetic Diseases in Zalau, which is the first center of this kind in Romania and its purpose is to be a resource center for patients with RD, their families and specialists involved in the diagnosis and management of these diseases. Some patient and parent organizations from Romania (Romanian Prader-Willi Association, Williams Association, PKU Life for Romania, Thalassemia Association, etc) together with specialists and volunteers founded in August 2007 The National Alliance of Rare Diseases from Romania which is affiliated to other European networks. This project was sustained from European funds and the main purpose for this Alliance is to create and unroll The National Plan for Rare Disease. The Ministry of Public Health from Romania proved to be interested for an efficient partnership in promoting this plan and developing the specific activities for its implementation. Some EU Member State (Denmark, France, Italy, Sweden, Spain, UK) have developed such a plan with specific public policies on RD.

Access to information in RD

Today, patients, their families and medical personnel have access to many European information sources. Some of them are:

- **ORPHANET** – a database dedicated to information on RD and orphan drugs; access of this database is free of charge. Its aims are: to contribute to the improvement of the diagnosis, care and treatment of patients with RD, to optimize the correct use of clinical resources and to accelerate therapeutic development and research.
- **EURORDIS (The European Organization for Rare Diseases)** – a non-governmental patient-driven alliance of patient organizations and individuals active in the field of RD; represents more than 260 RD organizations in 29 different countries, covering more than 1.000 RD. It is dedicated to improve the quality of life of all people living with RD in all Europe. Its main priorities are: networking and empowering RD patient organizations, advocating and raising awareness, public health and health care policy.
- **RDTF (Rare Diseases Task Force)** – set up by the European Commission Public Health Directorate. Its aims are: to advise and assist this Commission in promoting the optimal prevention, diagnosis and treatment of RD in Europe and to provide a forum for discussion and exchange of views and experience on all issues related to RD.
- **EUROCAT (European Concerted Action on Congenital Anomalies and Twins)** - is a European network of population - based registries for the epidemiologic surveillance of congenital anomalies. Its objectives are: to provide essential epidemiologic information on congenital anomalies in Europe, to act as an information and resource center for the population, health professionals and managers regarding clusters or exposures or risk factors of concern, to provide a ready collaborative network and infrastructure for research related to the causes and prevention of congenital anomalies and the treatment and care of affected children.
- **NORD (National Organization for Rare Disorders)** - was created by a group of patients and their families involved in advocacy activities for the adoption of a regulation on research and development of orphan drugs, called the Orphan Drug Act. .NORD's website includes two databases: one on rare diseases, the other on rare disease organizations. For each disease, a list of relevant patient organizations is available.
- **ORD (Office of Rare Diseases)** - was created by the National Institutes of Health (NIH) to stimulate and coordinate RD research in the United States. Its information centre, called Genetic and Rare Diseases Information Center (GARD), supplies reliable and valid information to the public, researchers and health care providers, about any one of the more than 6,000 rare diseases known today.

Conclusions

The RD patient is the orphan of health systems, often without diagnosis, without treatment, without research. In this framework we must underline that there is always something useful that can be done in this domain. It is important to progress in all fields of activity: physiotherapy, nutrition, pain management, psychology, medical devices, advanced therapies and the main effort has to be done in order to stimulate research, to increase the existing knowledge.

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