

Short Communication

Characteristics of rare diseases

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Abstract

The interest in the issues of rare diseases as well as in orphan drugs and products used in the treatment of patients with these conditions, is gradually increasing. Still, it is necessary to broaden the knowledge of many aspects of this extremely rich and complex subject. The purpose of this paper is to present some of clinical and other issues related to the rare diseases. The general information is sequentially provided to a better understanding of specific nature and complexity of the problems of these diseases. Clinical description based on Polish data is made and then political and legal issues in relation to ongoing programs, initiatives and plans for both the European Union and Poland are presented.

Introduction

Rare diseases, according to the definition adopted in the EU, are those diseases whose incidence in a population is less than 1 in 2,000 (5 in 10,000) [1]. Most often they are serious genetic diseases caused by gene mutations and chromosomal aberrations, including rare cancers, auto-immune diseases and congenital birth defects, some infectious diseases and other related to environmental factors and a large part of diseases of unknown etiology. They are of heavy and often chronic nature endangering lives of patients and lead to a significant physical impairment or intellectual disability. Rare diseases in large part, cannot be treated effectively but, in many cases, their effects can be mitigated [2,3].

Rare diseases are a huge group of heterogeneous disorders that can affect practically every system and organ [4]. They cause deterioration in the quality of life of patients who may be unable to learn and do professional work, which, in turn, has a destructive influence on their financial situation and life in general.

The number of these diseases is determined at the level of 5,000 to 7,000 – 8,000 [European Medicines Agency], which may mean that about 29-30 million people in the EU (from 27 million to 36 million, or 6% - 8% of the population) and 25 million in the United States suffer or will suffer from rare diseases [5,6]. Lack of accurate data is related to the fact that detailed records of patients with rare diseases are not kept.

Many rare diseases occur with a frequency of less than 1 in 50,000 (in the UK they are called ultra-rare diseases), which means that patients with these diseases are particularly isolated and have the greatest difficulties [7].

The occurrence of some rare diseases in a population of 100,000 [8]:

- protoporphyria erythroleukemia: 50;
- Guillain-Barre syndrome: 47;
- scleroderma (systemic sclerosis): 42;
- Marfan syndrome: 30;
- retinitis pigmentosa: 30;
- multiple myeloma: 30;

- α 1-antitrypsin deficiency: 30;
- juvenile idiopathic arthritis: 25;
- atresia of the esophagus: 25.

Still, there is no classification of rare diseases. The international system of classification of diseases (ICD) used in most countries is not useful for these diseases. The European Commission and the World Health Organization (WHO) launched a joint study to develop a universal classification of rare diseases. Research on various conditions, including epidemiological studies gives partial information on the prevalence of rare diseases and often is not supported by appropriate methodology. In many cases, there is a lack of adequate biochemical and genetic studies [9].

In many cases, it is still difficult to get access to specialized diagnostic tests, which results in delays in correct diagnosis and lack of effective treatment, causing the prognosis to be uncertain or unfavorable.

An example of this are studies of eight rare diseases – Crohn's disease, cystic fibrosis, Duchenne muscular dystrophy, Ehlers-Danlos syndrome, Marfan syndrome, Prader-Willi syndrome, tuberous sclerosis and fragile X syndrome - conducted in 17 European countries [10]. In 25% of cases, delayed diagnosis of the disease, after the appearance of clinical symptoms, ranged from 5 to 30 years. Before obtaining a correct diagnosis, 40% of patients were misdiagnosed which led to inappropriate treatment, 16% had surgery, 33% did not receive proper medication, only 10% were under the care of a psychologist because it was suspected that the symptoms of patients were of psychosomatic nature. 25% of patients were looking for additional help in other centers, including foreign ones (2%). Every third patient was not happy with the way of forwarding information about the diagnosis and its treatment.

These studies show that the level of diagnostics and medical

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knowledge about rare diseases is not sufficient. The consequence of this may also be the risk of complications and later consequences of the disease.

Examples of rare diseases are inborn errors of metabolism (IEM) [11]. They occur in different populations with a frequency 1 in 1,400 – 1 in 5,000 births. In studies conducted in Italy, it was found that from the group of 1,935 patients with IEM examined from 1985 to 1997 only 11% survived infancy to adulthood [12].

In the case of some metabolic diseases (IEM) and other rare diseases, population neonatal screening is possible, allowing for detection of a disease before the onset of dangerous clinical symptoms (especially damage of the central nervous system), which allows, in some cases, for early introduction of appropriate and effective treatment and prevention activities. An example of such neonatal screening is the screening for phenylketonuria (PKU) and congenital hypothyroidism conducted in many countries, including Poland [13]. These tests and early treatment should be carried out in specialized centers with appropriate diagnostic and therapeutic facilities. There is therefore a need for a network of specialized centers of reference dealing with complex diagnosis and treatment of patients with rare diseases.

An important feature of many rare diseases, in addition to a low incidence of various illnesses, is their different clinical picture, difficult to predict: process and speed of the development of symptoms and the occurrence of complications and consequences. Much of it is applicable for children and there is often no possibility of effective treatment.

In most cases, despite the great advances in medicine, there is still no possibility of effective treatment in patients with rare diseases, but it must be noted that in some rare diseases, when they are detected early and the right treatment is used, very good results can be obtained to ensure patients a normal life [14]. Rare diseases have negative impact on patients and their families, disrupting the welfare, social and economic aspects of their lives.

Rare diseases in Poland - clinical description

Epidemiological data about rare diseases in Poland are incomplete because an accurate, complete register, based on their structured classification is not kept. The following is a brief description of selected groups of rare diseases in Poland. More complete data and information about particular groups of diseases and disease entities can be found in the professional medical literature.

- Birth defects. In Poland, annually about 3% of children are born with at least one congenital malformation, and in 0.7% of newborns malformation syndrome occurs. Polish Registry of Congenital Malformations estimated the number of children born with a malformation to be: from 459 in 2008 to 254 in 2009. One of the major subgroups of rare diseases are chromosomopathies that are illnesses caused by the wrong number and / or structure of chromosomes [15,16]. They are characterized by a severe clinical course, the most commonly being a syndrome of congenital defects of: heart and large vessels, kidneys, central nervous system, which are often associated with intellectual disability [17].

- Metabolic diseases. In Poland annually 150-350 children are born with inborn, genetic, metabolic diseases. One of the most common of these, phenylketonuria is detected in neonatal screening tests which, after confirming the diagnosis, allows for very early introduction of dietary treatment based on the following low phenylalanine diet. Thanks to this, patients can be ensured correct physical and psychomotor

development and normal life [13].

- Neuromuscular diseases are another large group of rare diseases. The total frequency of their occurrence in the population is estimated at 1 in 800 – 1 in 1,000. The hardest, while the most common form of muscular dystrophy, is Duchenne's muscular dystrophy with a prevalence of 1 in 3,000 live-born boys. The disease is incurable and most boys die before the age of 20 [18].

- Phacomatoses. This group includes more than 30 diseases. The most common disease is the neurofibromatosis type 1 (NF-1), which occurs with a frequency approximately 1 in 2,500 births. Another disorder is tuberous sclerosis, multiple organ disease often occurring with an intellectual disability and refractory epilepsy. The prevalence of tuberous sclerosis in the population is estimated at about 1 in 10,000, but in children under five is higher and is about 1 in 4,300 [19].

- Dysraphies are inborn defects of central nervous system, which occur in Poland with a frequency about 1-3 in 1,000 births, most often in the form of a meningomyelocele [20].

- Inherited neurodegenerative diseases. In Polish population, the most common of these disorders is Huntington's disease, with a prevalence of approximately 1 in 20,000. The main symptoms are uncontrolled movements and progressive intellectual disability. With time symptoms intensify. Movement coordination disorders, caused by changes in the cerebellum, are the main clinical symptom of another group of neurodegenerative diseases - spinal cerebellar ataxia (SCA). Currently, this group has more than 20 classified units. In total 0.1% of population may be affected [21].

- Other monogenic diseases include Marfan syndrome, Noonan syndrome, Ehlers - Danlos syndrome, fragile X syndrome, congenital immune disorders, hemophilia A and B, and also achondroplasia and hypochondroplasia [22].

These groups of diseases have different clinical presentation, often progressive, chronic course which leads to physical and intellectual disabilities by creating a number of medical, social, economic and other problems and difficulties.

Political and legal issues of rare diseases

The subject of rare diseases was noticed as a serious health, social and economic problem in the European Union countries and in the world [23]. Significant steps were taken for more precise, better knowledge and understanding of, among others, medical and scientific basis, and consequently a number of initiatives, programs and tasks solved on the forum of the European Commission and in member states, including Poland.

The European Union

Rare diseases are one of the important issues of the public health programmes of the European Union: The development of strategies and mechanisms for exchange of information and coordination of activities at the transnational level.

In the EU budget for 2014-2020, the European Commission ensures funding to programs for health and consumer protection "Health for Economic Growth" and "The Protection of Consumers Programme." Their purpose is "Europe of healthy, active and aware of their rights citizens who can contribute to economic growth."

The program "Health for Economic Growth" refers to, among others, "cooperation at EU level concerning rare diseases, whose

aim is to improve the level of prevention, diagnosis and treatment of patients with rare diseases in the whole EU" [24]. An example of such cooperation could be an EU website of rare diseases (www.orpha.net), which is a very important database. Since April 2011, the Orphanet portal has also been running a website in Polish. Extensive information available under the Orphanet include data on:

- the descriptions of individual rare diseases - their genetic background, etiology, epidemiology, clinical course, available treatments, information on the classification (based on ICD-10), references to scientific databases such as OMIM, PubMed and MeSH;
- catalog of service providers, experts and specialized laboratories dealing with individual rare diseases;
- research and clinical studies conducted in different countries (they concern information on how to participate in these studies, test reports, and sponsors);
- orphan drugs and products;
- patients' organizations;
- scientific information in the field of rare diseases;

Orphanet regularly submits reports, and has its own newsletter.

In 2008 the European Commission adopted the Communication setting out a Europe-wide strategy supporting member states' efforts in ensuring the effectiveness of European action on rare diseases. In the following year, in response to a proposal from the Commission, the Council adopted a recommendation about the merger of scarce resources, so far dispersed in various EU member states. Joint actions are to enable patients and health care professionals to exchange expertise and information at international level - Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges (SEC (2008) 2713) (SEC (2008) 2712), Brussels, 11.11.2008 COM (2008) 679 final).

Special features of rare diseases, such as the limited number of patients and relatively small and difficult access to knowledge, including expertise about these diseases characterize them as a specific domain of very high European added value. International cooperation can help in popularizing this limited knowledge and combination of existing resources in a possibly efficient manner, so as to more effectively treat patients with rare diseases in all Europe.

Lack of adequate healthcare policies in the field of rare diseases and the scarce resources of specialized knowledge in this field, cause a delay in the diagnosis of these disorders and difficulties in accessing to appropriate care. This can lead to a significant deterioration of the physical, psychological and intellectual impairments of patients, inadequate or even harmful treatments and loss of confidence in the health care system. Patients with some rare diseases can lead a normal life if the disease is diagnosed early and if the appropriate treatment is introduced. The problems reported are critical barriers to improving the quality of life of thousands of patients with rare diseases.

Poland

In Poland The Commission for Rare Diseases, which is advisory body of the Minister of Health has been working since 2008. It consists of scientific experts, representatives of the Ministry of Health, the Office for Registration of Medicinal Products, Medical Products and Biocidal Products, the Agency for Health Technology Assessment in

Poland, the National Health Fund, the pharmaceutical industry and the organization of patients. The task of the Commission is giving opinion on the policy on rare diseases and reimbursement of orphan drugs and products, health care system organization, education, etc. This Commission has prepared the National Plan for Rare Diseases (NPChR) for the years 2013 to 2017, which, being a kind of „road map", defines very ambitious major tasks which are necessary to be implemented [25]:

- classification and establishment of a register of rare diseases - improvement of the diagnosis through dissemination of screening and genetic tests and the establishment of a system of reference centers;
- adequate health care and treatments for patients with increased access to highly specialized medical procedures, including pharmacotherapy and expensive technologies and appropriate rehabilitation;
- providing comprehensive, integrated social support for patients and their families;
- providing scientific information and medical and social education, development and the promotion of research;
- monitoring the implementation of the Plan in the following stages. Presented Plan points relate to many aspects and indicate in detail what actions should be implemented to achieve the main intended purpose, which is to improve the lives of patients with rare diseases in Poland.

The President of the National Health Fund has appointed the Coordinating Team for Ultra-rare Diseases. It was appointed in order to fulfill the instruction of the Minister of Health Regulation dated 30 August 2009 on the guaranteed treatments included in health programs (Journal of laws No, 140, item. 1148, as amended) to ensure that only scientific methods are used to include and exclude patients from therapeutic programs while obtaining full independence of the decision of the authorities providing health care financing from public funds. The Team is composed of practitioners, professors of medicine, having the appropriate knowledge and experience to make decisions about eligibility for the programs or exclusion from them.

The National Health Fund and the Ministry of Health do not have influence nor should have influence on decisions made in individual cases of patients. The criteria for inclusion and exclusion of patients from health programs/drug programs are governed by the law in the said regulation of the Minister of Health.

The current Status of Action on Rare Diseases Conducted in Poland is part of the Report of the Committee of Experts of the European Union for Rare Diseases on current state of Action on Rare Diseases in Europe, 2012 (EUCERD).

Additionally, taking into account precise legal analysis of various aspects of rare diseases, attention should also be drawn to granting patients with these diseases, as all patients, medical treatments according to the standards of medical treatment, which results, among others, from the Medical Profession Act and the Code of Medical Ethics.

Conclusions

Rare diseases are a very special category and a group of disorders, because the distinction has been made not because of the similarity of clinical symptoms, but due to the difficulties encountered by patients in accessing appropriate medical care and other forms of support. This often leads to social exclusion or marginalization of patients and their families. Despite the low frequency of occurrence of rare diseases, together they cover a large group of diseases, being a serious medical, social and economic problem.

Extensive topics related to rare diseases concern very different

disciplines and require a multidisciplinary approach, especially taking into account medical, epidemiological, scientific, legal, economic, social and other aspects.

Ongoing efforts for the sake of patients with rare diseases should be comprehensive to ensure smooth functioning of the system of care for patients and their families, ranging from diagnosis to the treatment, rehabilitation, psychological support and social care. This will improve the quality of life of patients and provide them with greater social integration.

The adoption of the National Plan for Rare Diseases resulting from the recommendations of the Council of the European Union, the extension of institutional activities related to the area of public health and social initiatives seeking innovative solutions to create a model of social support for patients and their families, with very high complexity of the issues regarding rare diseases, results in the need for a coherent, comprehensive, system operations and the adoption of comprehensive solutions. They should rely primarily on:

1) the adoption and consistent implementation of a coherent, comprehensive, long-term policies to support the operation and development of the system of aid for patients with rare diseases, their families and fully meet their specific needs the plan of these activities and their conduct at the government level should apply to the Ministry of Health and other departments such as social services and education.

2) creating a network of reference coordinating centers fully specialized in the overall diagnostic, therapeutic, rehabilitative, educational and popularizing these issues procedures;

3) solving problems related to the potential use in the treatment of orphan drugs and products for patients with rare diseases, especially concerning the refund of medical expenses;

4) expanding prevention activities such as screening tests, for example the introduction of new therapeutic treatment programs, with the option of a customised treatment, and rehabilitation;

5) supporting the activities integrating patients and their families, such as assisting in the patients' organizations, social initiatives and promoting knowledge and awareness, charity events, the foundation activities, etc.

6) using any forms of access to information and its transmission with the use of modern communication technologies;

7) active participating in all international initiatives, programs and activities, for example by the European Union relating to the subject.

Conflicts of interest

The author declares no conflict of interest.

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