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RARE DISEASES ORPHAN DRUGS

Official Newsletter of the Bulgarian Association for Promotion of Education and Science (BAPES)

Dear friends,

FOCUS ON:

RARE DISEASES REGISTRIES

IN SEARCH OF ANSWERS

Today is probably the only day in the year when rare diseases are among the headlines. Today is a moment of hope for the future and belief that things can happen for rare diseases in our country. We would like to take this opportunity to thank all the patients, their families, medical professionals and the National Alliance of People with Rare Diseases for their efforts today to celebrate Rare Disease Day across the country with a range of information, education and charity events. We would like also to send a special message to the whole society. Rare diseases are not just minor statistics. These are thousands of children, young people and adults, their families and friends. For them, a rare disease is not flying balloons and taking a picture once in a year. For them it is daily, continuous suffering and difficulties, many of which are due to the ignorance and the misunderstanding of the health institutions and the public. Now, it is a good time for each of us to promise to be a better person and not to turn head away when someone has a problem and needs help.

Despite these strong emotions today, "Rare Diseases & Orphan Drugs" has chosen a different cover story for the first issue in 2013. We have chosen what might be the answer in our opinion, or at least the beginning of the solution to this very complex problem – the registries for rare diseases. It may seem strange, but up-to-date and accurate information is the first step in tackling rare diseases. Without it, many patients with rare diseases will continue to be invisible for the system and therefore no specific actions would be undertaken to help them. You will read more about registries and their advantages from a globally recognised expert on this subject – Dr. Manuel Posada from Spain. Finally, our Rare Diseases Library features one of the "common" rare diseases – Duchenne muscular dystrophy.

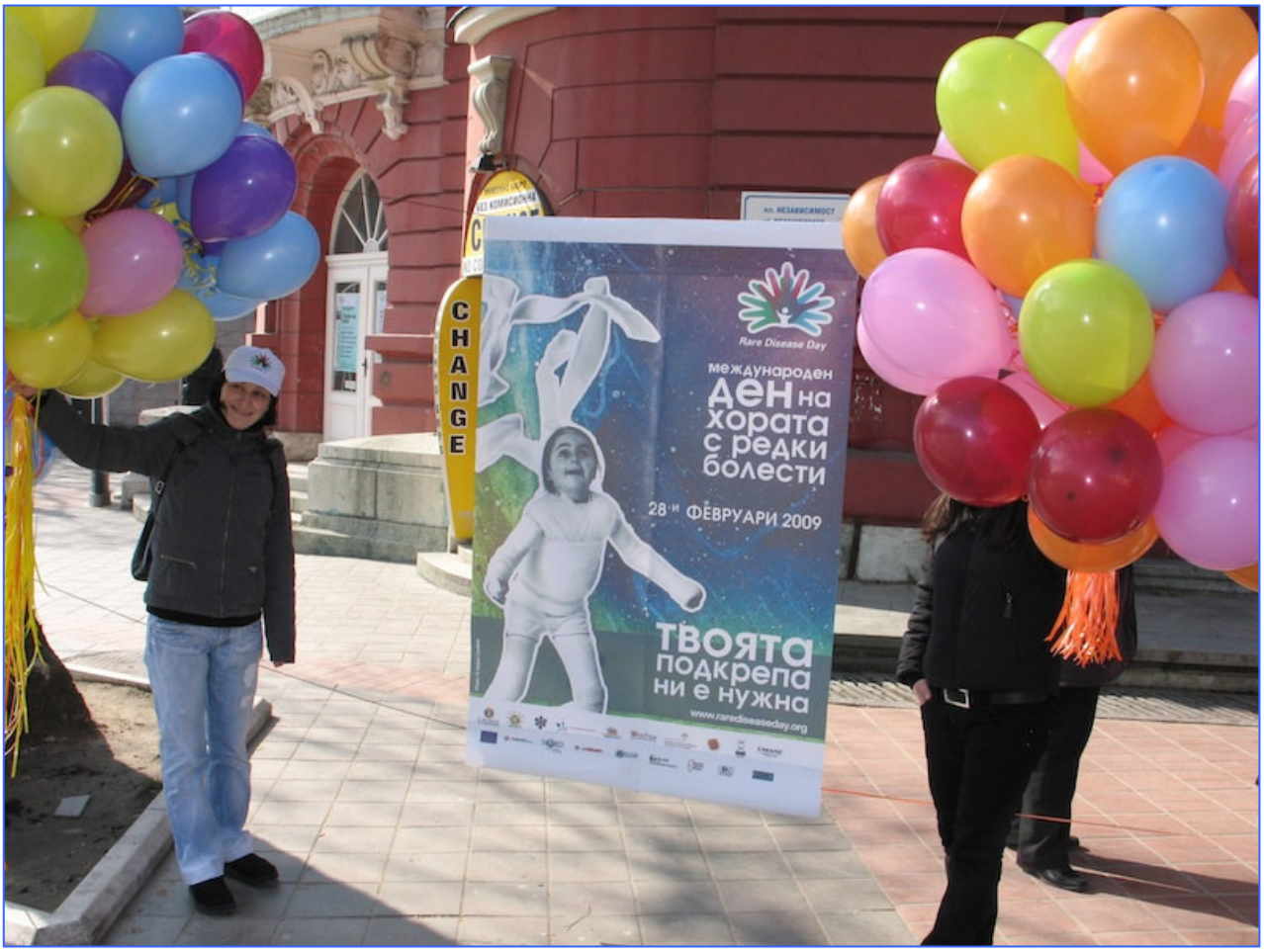
BE HEALTHY AND BE IN SOLIDARITY!

BECAUSE EVERYONE IS UNIQUE ON HIS/HER OWN…

JUST AS RARE DISEASES ARE

Introducing and explaining rare diseases is a simple and complicated taks at the same time. It is easy in terms of statistics – a rare disease affects no more than 5 in 10 000 people in Europe. It sounds emotionless and reassuring because it seems like a distant threat that can not happen and therefore there is no need to think about this problem. Unfortunately, it is how the mass consciousness works.

But we should not blame and should not be mad at the people... because people… that is us. Each health issue deserves serious attention and understanding. Rare diseases require something more because of their specificity. Suddenly, out of the blue rare diseases come into people's lives and from now on everything is different. Rare diseases mean everyday problems and challenges which people face all alone or only with the support of closest relatives. Since the medical science has no effective answers yet, the health system is not at all adapted and the society is committed to "more important" tasks.



Rare Disease Day in Varna, 2009 © Elena Eneva

Of course some people may ask, "Why rare diseases? Aren't there more important issues to resolve?" Urgent problems will always exist but rare diseases have a very important nuance. It is the right and the reality to be different. From a genetic point of view, everyone has a unique combination of genes. Whether we will be tall or curly haired – it is not up to us, we are born this way and develop ourselves using what we have been primary given. Rare diseases occur in the same manner. Everyone is born with a certain number of "defective" genes that can not be changed. Whether at some point in life rare diseases will occur or not, no one can predict. But one thing is sure – no one is exempt from the possibility that it may happen to him/her.

Nevertheless, a person should not and can not be deprived of the most basic right – to be himself/herself, to dream, to seek and find happiness in life. Unfortunately, in Bulgaria the diagnosis of a rare disease is not only a stigma. It is an immediate end to the dreams of the affected and his/her family. This means missed talent and untapped potential both for the person and the society. It is reasonable to ask whether today everything has to rely on special and exceptional cases in order to have some positive changes, so people with rare diseases could receive equal opportunities and equal treatment like anyone else.

Rare Disease Day in Pleven, 2010 © Todor Mangarov

This year, on the 28th of February, people with rare diseases in Bulgaria will come together to mark again the Rare Disease Day. But it would be neither to remind all of us and the health system in particular how much we owe them. Nor to talk about the daily difficulties that they have to deal with. They would like to show that by virtue of chance, we are all different and have different personalities. Just like the nodes in the thread of the traditional martenitsa that people with rare diseases will bind on this day in Varna. Each node comes different and no two are alike. But in order to have a strong thread, all nodes must be tightly interconnected, no matter large or small, tight or loose, red or white thread. Ultimately we are all one thing and we can go forward only if we stand together and support each other.

Rare Disease Day would be marked on February 28 for a sixth time. The motto of the initiative this year is “Rare Diseases without Borders”. In Bulgaria, the organizers from the National Alliance of People with Rare Diseases will draw the public attention on the problems of rare diseases patients and on improving health care for rare diseases. A series of information, education and charity events will take place. On February 28 patients with rare diseases will fly balloons in front of the Ministry of Health in Sofia, followed by an official press conference. The Second Balkan Conference of Patients with Rare Diseases, entitled “Communication and Support to Patients, Based on Modern Technologies” will be held in April in Sofia. Besides Sofia, a series of rare diseases events will be organised throughout the county – Plovdiv, Varna, Burgas, Stara Zagora, Pleven and Sandanski.

For more information, please visit the official website of NAPRD (http://rare-bg.com/).

RARE DISEASES REGISTRIES

IN SEARCH OF ANSWERS

In the one of the very first issues of "Rare Diseases & Orphan Drugs" we have presented the rare diseases registries and their situation in Bulgaria. After two years we return again to this topic for several reasons, most importantly because this problem is still relevant. There is no national registry for rare diseases in Bulgaria and rare diseases remain an "enigma" for health authorities.

During the month of Rare Disease Day society tends to act more on these issues, but usually it is confined to solemn promises and official photos. "Rare Diseases & Orphan Drugs" has always aimed to present this issue as a complex that requires a multifaceted and sustained action. It is what rare diseases people and their families need. The lack of systematic information was and remains the main obstacle. Despite being completely reasonable, without real, actual data all rare diseases requests look inappropriate in the overall context of our country's healthcare. That is why the number one task of the ongoing National plan for rare diseases was to create a national registry for rare diseases and to provide epidemiological data on rare diseases in Bulgaria.

This is the other reason why we return to the subject of registries. Less than a year before the official end of the plan, this goal is not only unrealised, but it even seems more hopeless. This should have served as a foundation for the overall development of the programme and for finding effective solutions to all rare diseases problems accumulated in the country.

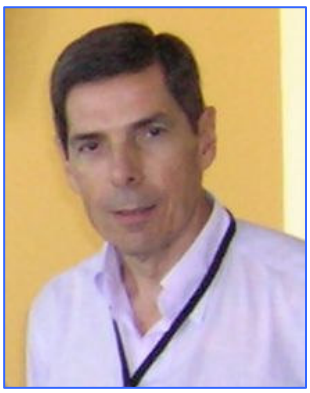
So, on Day of Rare Diseases let's wish to be healthy, but also to have more power to address this important issue. Because one particular activity helps just one particular patient, but the overall registry will help all affected, without dividing them into children and adults, from small and large settlements, regardless of the specific rare disease.

In support of this appeal we present you the opinion one of the leading researchers in the field of epidemiology of rare diseases and longtime head of the Institute for Rare Diseases Research in Madrid – Dr. Manuel Posada.

Our team takes this opportunity to thank Dr. Posada for his support!

May you briefly introduce yourself to our readers?

My name is Manuel Posada. I am the Director of the Institute of Rare Diseases Research (IIER) at the Institute of Health Carlos III (ISCIII), a governmental research institute in Spain. I am a physician, specialist in Internal Medicine and also in Preventive Medicine and Public Health.



Dr. Manuel Posada

First of all, is there a particular reason for you to be involved in rare diseases activities? When did you first "face" the rare diseases?

During my training for getting the Internal Medicine specialty, I had the opportunity of care and diagnosis a lot of people with rare diseases, because the hospital was at that time a national center for several pathologies. Some years later, I had to face on a severe epidemic of rare disease cases due to an external toxin, the Toxic Oil Syndrome. It is an autoimmune disease which shows during its natural history features, simulating several other rare diseases such as primary pulmonary hypertension, scleroderma, polyneuropathies, hypereosinophilia syndrome, etc.

In 1999 I was involved in the first European Action Plan of Rare Diseases, then in the Rare Diseases Task Force, EC and at that time, I was already into this interesting field. I have been working in several projects and actions at both European and National levels.

What are the differences between registries for rare diseases and registries for common diseases?

From the methods to be used, there are no major differences between these two types of diseases registries. However, rare diseases registries have some extra difficulties because of the rarity and the lack of expertise of our physicians. At the same time, rare diseases have not been well recognised in the international classifications of diseases (WHO-ICDs family) and this is very problematic for epidemiologists because we cannot capture all the information about these cases. Therefore, we have to define new system codes and classifications, specificly for rare diseases and promote their use by both health authorities and physicians.

From your own country's experience, what are the biggest advantages of rare diseases registries?

We are conducting a major strategy regarding rare diseases registries in Spain. This has been possible thanks to the International Rare Diseases Research Consortium (IRDiRC), which is providing funds for this strategy. Our project is called "Spanish Rare Diseases Registries Research Network" (SpainRDR) (www.spainrdr.isciii.es). This network comprises two different methods: i) the use of population-based registries, which are addressed by our Spanish Autonomous Regions, but with a great consensus and a central repository and, ii) the patient registries, where medical societies and research networks are responsible for data collection, data entry and also research about their specific rare diseases registries.

We have learned about this strategy several things such as the SpainRDR registry can provide high quality information for making decisions by our health policy makers. They can use this information for health planning, particularly for reference centres designation, information dissemination, providing resources and orphan drugs policy developments.

On the other side, patient registries have provided a wonderful open window for physicians, involved in rare diseases but not so well connected with other types of researchers. At the same time, several rare diseases have currently new physicians involved not only in the patients' care but in their registries and research.

What lessons could you recommend for a country like Bulgaria regarding rare diseases registries?

It is very important to adopt an overall health policy regarding rare diseases registries because the major difficulty of the registries is that it is neither easy nor viable for one rare disease registry to survive for a long time. Sustainability is the major challenging task and health policies should develop some strategy to face it on.

What's your message to "Rare Diseases & Orphan Drugs" readers?

It is not so easy to summarise all in one single message what I could say about these two linked topics. However, I could suggest the following issues:

- To be aware about problems arisen and limits (scarce of validity) of some types of the decisions, which apparently are showing as good promises with premature results. In medical science the knowledge is continuously increasing, but not all apparently progresses are valid for the patients;
- To concentrate all efforts in sustainable activities throughout a previous deeply analysis on risks and real benefits for the populations, and taken into consideration ethic rules. These efforts should be developed in a joint action between patient alliances and researchers;
- To promote rare diseases registries trying to involve all sectors and looking at the future while the sustainability of today and tomorrow is guaranteed.

DUCHENNE MUSCULAR DYSTROPHY

DEFINITION AND PREVALENCE

Muscular dystrophies are a group of diseases that have three features in common – inheritance, progressive development and specific type of weakness. Duchenne muscular dystrophy (DMD) is one of the most common neuromuscular diseases, inherited in an X-linked recessive manner. The most distinctive feature of Duchenne muscular dystrophy is a progressive proximal muscular dystrophy with characteristic pseudohypertrophy of the calves. Most boys with DMD walk alone at a later age than average and often parents are worried about the strange way their child goes. Only boys suffer from the disease. Prevalence in the population is 1 in 3 300-3 600. There are also female carriers of the mutation, but clinical symptoms are much less expressed.

ETIOLOGY

DMD is caused by a mutation in a gene located on the short arm of the X chromosome. Pathological gene determines severe deficiency or complete absence of a protein called dystrophin in membranes of muscle fibres. Dystrophin generally plays a role as “glue”. It has a stabilising function and maintains the integrity of the membranes of muscle fibres. Its absence leads to degeneration of muscle cells and increased muscle breakdown enzymes. Non-functional connective tissue grows on the site of the destroyed muscle cells.

DIAGNOSIS

A blood test (serum creatine kinase) may be done to help in the diagnosis of DMD. Creatine kinase is an important chemical in muscle fibres and there is normally a small amount of it in the blood serum, in DMD, creatine kinase is found in greatly increased amounts in the serum. When there is reason to suspect DMD, a very high serum creatine kinase level makes the diagnosis probable. The diagnosis should be confirmed by muscle biopsy. Some doctors also recommend electromyography (EMG). The final diagnosis is based on immunohistochemical testing, recording a strong decrease or absence of dystrophin, and on a genetic analysis showing the mutation.

CLINICAL PICTURE

The progression of DMD leads to many physical symptoms that typically affect different parts of the body:

- overall weakness and fatigue;
- overdeveloped calves – one of the earliest signs is the enlargement or overdevelopment of the calves (“pseudohypertrophy”). During exercise, most people experience muscle hypertrophy and enlargement of muscles. In the beginning, the boys suffering from DMD also observe such enlargement. But instead of getting stronger, muscles are damaged fast and die due to non-functional or missing dystrophin. When this happens, other cells may respond by producing fibrous connective tissue with fatty deposits. This increases the size of the muscle and enlarges it, but it is filled with fat, not muscle cells;
- lordosis – inward curvature of a portion of the lumbar and cervical vertebral column;
- feet – the Achilles tendon is often contracted, pulling legs into an unnatural position and obstucting walking. Patients often have to wear braces, straightening ankle at night. Another DMD problem is the purple discoloration of the legs (“cold” feet). This happens due to the decreased muscle function of the legs and subsequent lowered blood circulation;
- limited flexibility of joints and tendons (contracture);
- scoliosis (curvature of the spine) – when in acute form, it may limit the functions of the lungs and upper limbs. Patients with DMD are increasingly turning to surgery for straightening the spine;
- respiratory problems – respiratory muscle function may be affected in a way that modifies the manner of inhaling and exhaling the air. With the progression of DMD, the diaphragm weakens and breathing becomes more difficult. Besides the problems with the lungs, weakened muscles that are responsible for

coughing can allow bacteria and viruses in the lungs to grow, since coughing represents a normal defense that lungs use to clear excess mucus. Thus, a common cold could quickly develop into pneumonia in young men with DMD.

TREATMENT

At present there is no generally accepted treatment for the disease. Treatment is symptomatic by nature and aims to manage the problems that have already occurred. Myoblast transfer therapy and gene replacement with dystrophin minigenes are currently being investigated, however it is all at experimental level. Progressive development can be delayed by the application of physiotherapy. Patients are recommended high-protein diet and vitamin E intake.

REHABILITATION AND FOLLOW-UP CARE

Appropriate individual rehabilitation programme has a proven effect in managing the symptoms of DMD. Patients with DMD experience difficulties in many everyday activities. This is a direct result of reduced mobility and stability of posture, progressive deterioration of function of the upper limbs, and contractures. Specialists in physical and occupational therapy can help in dealing with these symptoms, using different methods.

Efforts and attention should be mainly aimed at the care of muscle extensibility and joint contractures. Medical specialists prepare a stretching programme which can be easily performed in a family environment too. It is important to maintain a good range of motion and symmetry in each joint. This helps to maintain the best possible function and prevent the development of fixed distortions. Effective management of contractures may also require the use of assistive devices for stretching, splinting and maintaining the posture. Night splints (ankle-foot orthoses) are used to help control contractures at ankles and longer leg braces (knee-ankle-foot orthoses) are useful at the stage when walking becomes very difficult or impossible. In some cases, surgery is recommended to extend the period of free walking.

The work with the patient's relatives should not be underestimated working. They have to be actively involved in all aspects of the rehabilitation programme. The family plays a vital role in supporting the patient and his subsequent reintegration into society.

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UPCOMING RARE DISEASES CONFERENCES, WORKSHOPS AND INITIATIVES

- **25 March – 2nd EUROPLAN II Workshop "Key Indicators for National Plans for Rare Diseases", Rome**
- **16-17 April – 1st International Rare Diseases Research Consortium (IRDiRC) Conference, Dublin**
- **12-14 June – 12th European Symposium on Congenital Anomalies, Zagreb**
- **17-21 July – 8th International Prader-Willi Syndrome Conference, Cambridge**
- **13-14 September – 4th National Conference for Rare Diseases and Orphan Drugs, Plovdiv**
- **19-23 October – Thalassemia International Federation World Congress, Abu Dhabi**

RARE DISEASES BEST PRACTICES

A new major rare diseases European project started in 2013. RARE-Bestpractices is a four-year project (2013 – 2016), co-funded by the Seventh Framework Programme of the European Union (FP7). The project is coordinated by Dr. Domenica Taruscio, Director of the National Rare Diseases Centre at the Italian National Institute of Health and brings together a team of high level of experts in the area of clinical practices guideline, systematic review, health technology assessment, health policy, epidemiology and public health in the field of rare diseases. The consortium has 15 partners across Europe, including BAPES.

Dr. Taruscio explains, "The project RARE-Bestpractices intends to respond to the information needs of health professionals, patients, policy makers in the field of rare diseases, by creating a system of easily accessible resources for the development, evaluation, dissemination and implementation of guidelines for clinical practice. A major challenge in the care of patients with rare diseases of yesterday and today is the full and continuous access to accurate and up to date information on the treatment options."

The project aims to improve the clinical management of rare diseases by undertaking a series of specific activities. Important aspect is the organisation of courses intended to serve as an introduction to guidelines development process and evaluation, taking into account challenges in developing guidelines for rare diseases identified within the project.

For further information, please visit the project's official website
http://www.rarebestpractices.eu/.

Editorial Box

This newsletter is prepared and published by the Bulgarian Association for Promotion of Education and Science (BAPES). The Information Centre for Rare Diseases and Orphan Drugs (ICRDOD) and Medical Centre "RareDis" are projects of BAPES (www.raredis.org).
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