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RARE DISEASES ORPHAN DRUGS

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

FOCUS ON:
RARE DISEASES GLOBALLY – HOW TO CREATE SOMETHING REALLY VALUABLE FOR THE SOCIETY TOGETHER

Dear friends,

Summer holiday season is still ongoing. But we have prepared for you some very interesting and serious materials to keep pace with the recent developments in the field of rare diseases and orphan drugs, which even in the hot month of August continue to take place.

The topic of the new edition is more than ambitious, but there are already substantial grounds in its favor. It's about the rare diseases at global level and how scientific miracles are literally becoming a reality in front of our eyes. Last month a recommendation for approval of the first gene therapy medicine was issued. This fact went unnoticed for the general public and mass media, but for the millions of patients in the world affected by rare diseases, for their families, for their doctors it is an event of landmark character. Today gene therapy opens doors for unsuspected possibilities that in the future may lead to effective treatment of hundreds, even thousands of rare diseases. It is something that we all strongly hope. This whole giant progress of science would not be possible without the global partnership and cooperation that exist for rare diseases. It is unthinkable to seek any solution to this huge problem independently and only on own efforts. Together, however, we can all give the society something priceless – a chance for a better life.

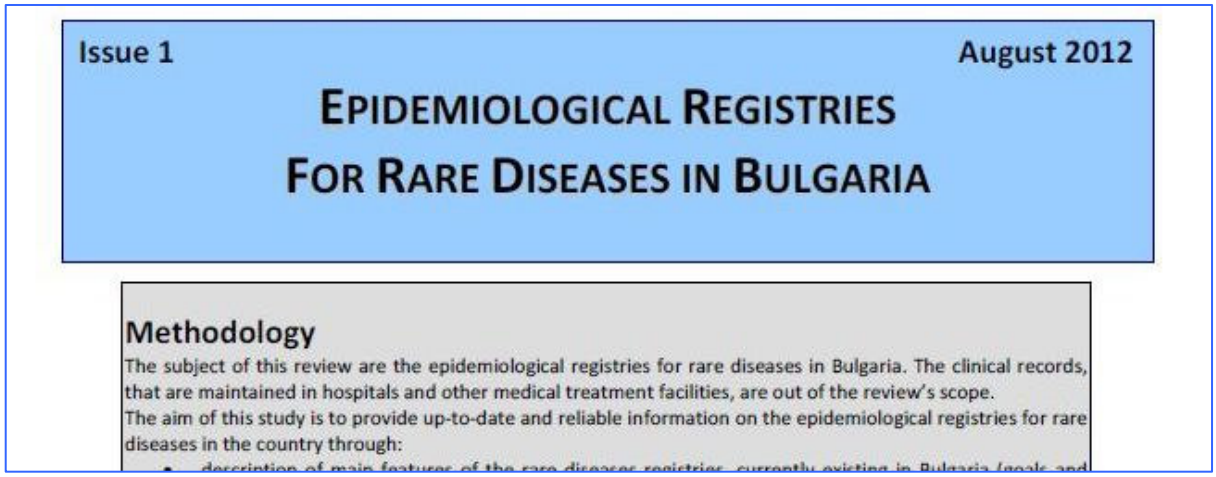
We are very pleased to discuss the topic of the global initiatives on rare diseases with three world-renowned experts in this field – Dr. Steven Groft (USA), Prof. Hanns Lochmüller (UK) and Prof. Yukiko Nishimura (Japan) (p. 6-11). We are extremely grateful for the contribution they made to "Rare Diseases & Orphan Drugs". We are also including interesting materials on rare diseases registries (p. 2) and spina bifida (p. 12-13).

Finally we would like to remind you that the 3rd National Conference on Rare Diseases is in a month time – on 14-15 September in Plovdiv. Do not miss the most important rare diseases event in Bulgaria for 2012!

HAVE A NICE TIME WITH "RARE DISEASES & ORPHAN DRUGS"!

EPIDEMIOLOGICAL REGISTRIES FOR RARE DISEASES IN BULGARIA

ICRDOD is expanding its thematic series of reviews on rare diseases in Bulgaria. After the highly acclaimed "Rare diseases and the public health system" and "Access to orphan drugs", a new report is now published to your attention.


Issue 1 August 2012

EPIDEMIOLOGICAL REGISTRIES FOR RARE DISEASES IN BULGARIA

Methodology

The subject of this review are the epidemiological registries for rare diseases in Bulgaria. The clinical records, that are maintained in hospitals and other medical treatment facilities, are out of the review's scope.

The aim of this study is to provide up-to-date and reliable information on the epidemiological registries for rare diseases in the country through:

"Epidemiological registries for rare diseases in Bulgaria" focuses on the topic of registries. Epidemiological registers are an organised system for collection, storage, retrieval and dissemination of a clearly defined set of epidemiological data, collected on identifiable individuals for a specific and specified purpose. The analysis includes a description of the main characteristics of this type of database (goals and objectives, benefits and value, key factors in planning, launching and management of epidemiological registries for rare diseases), a presentation of European and international recommendations and guidelines in this area and a summary of available information on the existing registries for rare diseases in the country by May 2012.

The full text of this review, as well as the previous editions of the series can be found on the website of ICRDOD in the section "Publications".
http://www.raredis.org/?page_id=2044&mel=5&smel=52&lang=en

ICRDOD would like to express special gratitude to Prof. Elisaveta Naumova ("Alexandrovska" University Hospital, Sofia) and Assoc. Prof. Alexey Savov (National Genetic Laboratory, Sofia), who have supported the preparation of this review, providing information on the epidemiological registries managed by them.

NATIONAL REGISTRY OF ADULT PATIENTS CML	
Rare disease's name (ICD-10 code)	Chronic myeloid leukemia (C92.1)
Year of launch	2010
Year of latest update	2012
Number of patients from latest update	328
Distribution by age	Adults – 328
Distribution by sex	Male – 163; Female – 165
Territorial scope	Nationwide
Coordinator	Dr. Tsonka Miteva, DD Information Centre for Rare Diseases and Orphan Drugs, Plovdiv
Bibliography	1. Stefanov R, Mihaylov G, Gercheva L, Hadzhiev E, Marinova-Goranova V, Tsvetkov N, Bogdanov L, Raynov J. Epidemiology of CML in Bulgaria – a pilot study (in Bulgarian) . Social Med and Health Management, 2010; 1:7-13. 2. Miteva Ts, Iskrov G, Popova L, Stefanov R. Epidemiological registries for rare diseases. 2nd National conference for rare diseases and orphan drugs – conference proceedings book, 2011; p. 149.

RARE DISEASES ON THE GLOBAL STAGE – WHAT IS GOING ON IN EUROPE

The first half of 2012 is already behind us and it's time to draw the balance. The past six months have confirmed the emerging trend in recent years that rare diseases are one of the main points in global public health's agenda. This fully applies to the European Union, which together with the USA, Japan, Australia and Canada continue to play a locomotive role in this field.

What is going on in Europe and where the Member States came with the passage and implementation of national plans for rare diseases?

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An undisputed breakthrough not only in scientific and political, but in purely practical aspect is the recommendation of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) for authorisation of Glybera (alipogene tiparvovec) for marketing in the European Union. It is intended to treat lipoprotein lipase (LPL) deficiency in patients with severe or multiple pancreatitis attacks, despite dietary fat restrictions. LPL deficiency is an ultra-rare inherited disorder estimated to affect no more than 1-2 people per million. Due to a defective gene, patients with this disorder cannot produce enough LPL, an enzyme responsible for breaking down fats. The big news here is that Glybera is the first gene-therapy medicine to be recommended for authorisation in the European Union. Gene therapy medicines have the potential to cure genetic disorders by replacing a defective gene with a working copy, thus helping the body to recover functionality. The vast majority of rare diseases are genetic, so this recommendation represents a major progress in science and practice, which gives hope to millions of patients and their families. The CHMP's opinion on Glybera will now be sent to the European Commission for the adoption of a marketing authorisation.

MORE ON GENE THERAPY

Each of us carries within both normal and some „defective" genes. Usually we do not know about it until the disease-related genes occur to us or our relatives. The majority of the nearly 8 000 rare diseases are caused by defective gene, each of which is associated with various degree of seriousness. Approximately 6-8% of human population sooner or later develops a disorder due to genetic defect.

The human genome (genetic matrix) is the full set of instructions, encoded in DNA, for the development and functioning of the human organism. Establishing the sequence of the 3 billion nucleotide pairs that make up human DNA is a prerequisite for developing new ways of diagnosis and treatment of various diseases. Today, science has put its efforts primarily on the development of gene therapy that tries to influence on phenotype manifestation of genetic compositions, providing normal functioning copies of defective or missing genes. As a beginning, scientists are attempting to induce genes in human cells, thereby treating diseases caused by single-gene defects like cystic fibrosis, hemophilia, muscular dystrophy and sickle cell anemia. The main difficulty is how to transfer large DNA fragments and place them on the right place.

The most common form of genetic engineering involves insertion of a functional gene at an unspecified location in the host genome.This is accomplished by isolating and copying the gene of interest, generating a construct containing all the genetic elements for correct expression and then inserting it into a random location in the host organism. Other forms include gene targeting and knocking out specific genes via engineered nucleases.

Insertion of DNA into cells can be achieved by several methods. Two main classes are through recombinant viruses (also called biological nanoparticles or viral vectors) and through so-called "naked" DNA or DNA complexes (non-viral methods).

The concept of gene therapy as an innovative therapeutic approach was born in the 70s of last century. In 1972 Friedmann and Roblin published a paper – "Gene therapy for human genetic disease?", suggesting the promising future of gene therapy. Both, however, called first to focus on security and safety and not to rush to human studies. So, it's in 1990 when the first approved gene therapy case in the United States took place. It was a treatment for an immune system deficiency. Despite effects being only temporary, the treatment was considered successful.

Since then, gene therapy has been studied and tested experimentally for many medical conditions. Although early clinical failures led some people to dismiss gene therapy, recent clinical successes in retinal disease Leber's congenital amaurosis, X-linked SCID, adrenoleukodystrophy, chronic myelogenous leukemia and Parkinson disease, as well as increasing number of scientific publications and growing investments in this field are a clear sign of success.

Like any revolutionary idea, gene therapy raises certain social and ethical issues too. A large number of serious diseases could be genetically treated, but gene therapy could also be used to treat inherited physical traits and genetic dispositions, determining the extent of development and realisation of the human. This could be considered as a violation of fundamental human rights, because each one's uniqueness and dignity are inalienable. The possible abuse of gene therapy raises a number of concerns such as the revival of eugenics and the idea of a pure race. Opponents of gene therapy insist on the right of future generations to inherit intact engineering-free genetic material. Of course, to date all these are rather hypotheses, but in the process of development of gene therapy they must be cleared both legally and psychologically.

Although the idea of gene therapy has emerged relatively recently for the general public, today's scientific advances in this area give hope for millions of people. What will happen remains to be seen, but the future is certainly very exciting.

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Traditionally the Scientific Secretariat of the EU's Committee of Experts on Rare Diseases (EUCERD) publishes in July its annual report on the activities in the field of rare diseases in Europe. Perhaps the most interesting part in this year's edition is the one on the individual actions of Member States. While the trend is strongly upward at EU level, national activities greatly vary. The Second French national plan is no doubt the most outstanding among the national rare diseases measures. It was launched in 2011 with a budget of 180 million euros. This represents a substantial increase in plan's funding. The fact that the French government devotes so many resources for the establishment and strengthening of rare diseases medical and social services in times of crisis is a clear demonstration of the enormous value of these activities. Unfortunately, to date still few Member States have started partially implementing their national plans and strategies. Most are still in process of consultation and discussion. This situation keeps staying already too long and in our view it is definitely not a good indicator of the interaction and performance of EUCERD with the Member States.

Maybe the idea for the establishment of European Agency for rare diseases, composed of independent experts and with broader power, which was commented in the previous edition of "Rare Diseases & Orphan Drugs" is worth discussing, as it may be a solution to this problem. After years of excellent work of the Rare Diseases Task Force at the Commission, today its successor EUCERD looks too passive. However, EUROPLAN project 2, which officially starts in September, may partially compensate it. The first part of this European project has produced excellent results and now it is up to improve communication and collaboration on rare diseases at various levels in Europe.

And if EUCERD struggles to keep the desired pace, the European Commission continues its strategical policy to create an improved environment and conditions for solving rare diseases problems. Currently, the Commission has adopted a proposal to boost clinical research in Europe by simplifying the rules for conducting clinical trials. The new legislation will take the form of a regulation. This will ensure that the rules for conducting clinical trials are identical throughout the EU. This significant legislative change is perhaps the better approach for harmonising and creating a more coherent and unified Europe. In particular, it will make it easier to conduct multinational clinical trials in Europe. It will include an authorisation procedure for clinical trials which will allow fast and thorough assessment of the application by all Member States concerned and will ensure a single assessment outcome, simplified reporting procedures, more transparency on participant's recruitment, as well as a possibility for the Commission to conduct controls in Member States and other countries to make sure the rules are being properly supervised and enforced. The legislative proposal is expected to come into effect in 2016.

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Of course, the promotion of clinical trials will not be at expense of quality and security. On July 1 new European legislation came into force, which significantly enhances monitoring of medicinal products. The new regulation and directive on pharmacovigilance strengthen EMA's powers in this area. For the first time ordinary citizens could directly report adverse reactions and side effects too.

All these policy measures affect all health care system, not only rare disease. But there are many new initiatives, which are entirely focused on rare diseases, such as the International Rare Diseases Research Consortium (IRDiRC). Gene therapy is just one example that rare diseases are the engine of modern science. However, to reach the stage of clinical trials and effective innovative therapies, basic research should be enacted first. Then these initial outcomes should be adequately transferred to clinical trials, finally to come to the creation of new drugs. That's why IRDiRC aims to serve as a global catalyst and united platform for research on rare diseases. This is a joint project of the European Commission and the US National Institutes of Health, launched in April 2011. In 2012 members of the scientific committees within IRDiRC were appointed and the initiative can now start working on full implementation of the target – the creation of 200 new therapies and diagnostic tools for most rare diseases by 2020. It may sound far-fetched to some, but given the pace of progress of bio- and nanotechnologies it is more than logical. An objective look at enterprises like IRDiRC, IMI (Innovative Medicine Initiative) and Framework Programmes for Research and Development points out enormous socio-economic benefits for European citizens – increasing the competitiveness of Europe to attract investment for science, modernising medical services and not last, creating new jobs and stopping the brain drain from the continent.

Rare diseases are already a global public health priority and this is an irrevocable fact. This result is not accidental and has its explanation. Rare diseases are a unique domain, in which actions reflect with great value on the society and all its members. This is not strictly limited and inapplicable elsewhere concept. This is a broad, innovative idea, which for a short period proved that it can serve as a model for action in all social spheres and helps millions of affected and their families. Now, it is important to continue this pace and more than ever to seek synergies and cooperation to make today's great scientific indicators be available to physicians and patients tomorrow.

RARE DISEASES –

HOW TO CREATE SOMETHING REALLY VALUABLE

FOR THE SOCIETY TOGETHER

Besides Europe, the USA and Japan have been the other two important "pillars" in the field of rare diseases. Historically, they are indeed the rare diseases pioneers considering the orphan drugs legislation in the USA in the 80s of last century. Today, however, everyone is aware that only global cooperation, communication and information sharing can provide answers to the many questions that are still unresolved. Hanns Lochmüller (Newcastle University), Stephen Groft (US NIH Office of Rare Diseases Research) and Yukiko Nishimura (The University of Tokyo) will tell their opinion on these rare diseases issues.

"Rare Diseases & Orphan Drugs" would like to take the opportunity to thank them for the interesting answers and contribution!

May you briefly introduce yourself to our readers?

Hanns Lochmüller

Hanns Lochmüller (HL): I am trained as a neurologist and see patients with muscle disorders in my clinic. For the last 20 years, I have been involved with research into the causes of and therapeutic approaches for muscle disorders. I am currently Professor of Experimental Myology at the Institute of Genetic Medicine, Newcastle University (UK). Several of my functions relate to my work with rare disorders: I am scientific coordinator of EuroBioBank (www.eurobiobank.org), chair of the executive committee of TREAT-NMD (www.treat-nmd.eu/contacts/hanns.lochmuller/), and chair of the interdisciplinary scientific committee of IRDiRC (http://ec.europa.eu/research/health/medical-research/rare-diseases/irdirc_en.html), and coordinator of RD-Connect (www.rd-connect.eu), a new European project creating an integrated platform for rare disease research.

Stephen Groft

Stephen Groft (SG): My current position is the Director, Office of Rare Diseases Research (ORDR) in the National Center for Advancing Translational Sciences (NCATS) at the USA National Institutes of Health (NCATS). The goal of ORDR is to generate research activities in rare diseases research. My professional experiences in orphan products development and rare diseases research started in 1982 with the establishment of the FDA's Office of Orphan Products Development where I had review responsibility for identifying potential orphan products for neurologic and psychiatric disorders. My undergraduate and graduate training was in Pharmacy and I realized in the early 1960's the lack of adequate treatments for most disorders, especially those conditions with relatively small populations and for those conditions with very little available information beyond a description of the disease and expected outcomes. I also had the opportunity to be the Executive Director of the National Commission on Orphan Diseases from 1987-1989 in the Office of the Assistant Secretary for Health at the Department of the Health and Human Services. The Commission was charged to review activities after the implementation of the Orphan Drug Act in 1983 and to offer recommendations for a future direction for orphan products development and rare diseases research. In 1998, NIH initiated a Special Emphasis Panel on the Coordination of Rare Diseases Research. The goals included the task of developing strategies to foster a better coordination of research and development activities. Reports from these advisory groups are available on the ORDR website (http://rarediseases.info.nih.gov/Resources/Reports_Publications.aspx).

Yukiko Nishimura

Yukiko Nishimura (YN): My name is Yukiko Nishimura, Assistant Professor of Department of Intellectual Property and Social Application of Technology, Research Center for Advanced Science and Technology at The University of Tokyo, Visiting Lecturer of Institute for Integrated Cell-Material Sciences at Kyoto University, and Board Member of NPO Promotion Research for Intellectual Property (PRIP Tokyo). I have been working for Japan Patient Association, the biggest association related to NANBYO in Japan as a Chief of International Relations (NANBYO is a Japanese word for rare and intractable diseases). I have more than 9 years of university and 4 years of ministry working experiences and 8 years of administrative experience of NPO. I have conducted several research areas: technology transfer, intellectual property management, human resource development of IP/TT area, innovation management, and social application of technology. My targeting area is not only a single but also very interdisciplinary, and I have constructed unique and varied networks related to these area in the whole of Japan and Asian countries.

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?

HL: Most muscle disorders and many neurological conditions are rare disorders. Therefore, they have played a major part throughout my professional life. Many of them have a genetic basis which has been elucidated through advances in genetic and genomic research. Because of their rarity, they share similar challenges with other rare disorders from different fields of medicine.

SG: The absence of available diagnostics and treatments for most diseases has been a personal concern of mine for many years. The clinical outcomes of treatment with a new product can be immediately observable and dramatic for patients. The successful development of a new product requires overcoming the challenges of conducting research and developing compounds to meet the needs of the rare diseases community consisting of patients and their families, patient advocacy groups, and philanthropic foundations, healthcare providers, research investigators, the pharmaceutical, biotechnology and medical devices industry, and government research, regulatory, reimbursement agencies. Identifying resources that could be utilized by the rare diseases community is the key to collaborative efforts required for research and development activities for rare diseases and orphan products. Meeting these needs has resulted in professional and personal commitments that have guided me for most of my career.

As a child growing up in a small town and knowing most people, there was an awareness of those who had uncommon diseases with many special and unmet needs. Cystic fibrosis, childhood leukemia, brain tumors, Marfan syndrome, Polio, cerebral palsy, Parkinson's disease, and Multiple Sclerosis were a few of the diseases that I encountered very early in my life. I sensed that at some time in the future, I would have some involvement with patients and families with these diseases. When Dr. Marion Finkel, the first Director of the Office of Orphan Products Development at FDA, asked me to join the new office in 1982, it was an easy decision to join the very small initiative with an unknown and uncertain future.

YN: In 2004, Japanese Pharmaceutical Affairs Law has been revised, and then I found Japanese orphan drug market would be created in this revision. At that time, my main research area was making startups and technology transfer and I would like to attract talented researchers to rare disease research area for the orphan drug development. We gathered basic researchers who were interested in rare disease area and built a network. We had held regular workshops, however, we realized we need much further information from patients' side and also the world. Many of us are basic researchers, and we have no chance to hear from patient voice. We have attended the International Conference on Rare Diseases (ICORD) since 2008, and also started to contact to patient organizations. I never forget to participate in the patient meeting for the first time.

Our active period is only about 5 years. However, we have now strong relationships with Japan Patients Association, other patient groups on a global scale, universities, hospitals, pharmaceutical companies (including from mega pharmaceutical to biotech startups) and their associations, and Japanese ministries (Ministry of Health, Economy, and Education) based on the relations of trust. We have published over 20 papers in this field, and several policy recommendations to Ministries. We hope to make a "Hub" for orphan drug development promotion and to build a portal of this area to the world from Japan

What's your explanation of the growing interest in rare diseases topics?

HL: There are numerous possible explanations. Through better and faster ways of communication, patients with rare diseases can connect much better with other patients affected by the same condition and have successfully come together in patient organisations and lobbied for recognition. Politicians, industry and the health care sector have recognized that rare diseases collectively are a major cause of morbidity and disability. Scientists may see rare diseases as a test case for molecular discoveries and for developing innovative treatments, and pharmaceutical companies believe there may be a market for rare diseases therapies as opposed to another new "blockbuster" for common diseases.

SG: There are numerous reasons for the expanding interest in rare diseases research and orphan products development activities in a growing number of countries and this increase has resulted in a global interest. There is an increased understanding that rare diseases are a global public health problem due to the lack of appropriate treatments. Patients and families understand that public awareness and knowledge of their diseases are necessities and this requires participation in the establishment and the activities of patient advocacy groups. Their outreach activities may require personal availability to the public and to the media. As we expand our knowledge of rare diseases and with greater access to patients willing to participate in clinical studies and trials, increased scientific opportunities exist for the research communities. Certainly, increased research budgets of the past 10-15 years have enabled more investigators and especially new and younger investigators to develop a research emphasis on rare diseases. The increase in research interest has led to the discovery of potential new products and increased interactions and licensing agreements with the pharmaceutical industry which may lead to commercialization of these discoveries and newer technologies. There continues to be a growing interest in smaller rare diseases niche markets by the pharmaceutical, biological, and medical device industries. Due to the lack of a large number of patients with rare diseases at any one location, multiple research sites are required for successful completion of clinical studies. An increased number of research investigators, understand how to design and conduct multi-center, international clinical trials of rare diseases and condition with smaller patient populations available for participation. This knowledge must be exported to those considering such studies.

YN: As I described before, my main research area is Social Science. Therefore, I would like to try to bridge among related people and society. I am interested in: 1) collaboration among the appropriate stakeholders in an attempt to speed up the development of new rare diseases treatments and orphan drugs/products; 2) making proposal to national/regional government some concrete plan for this area; 3) practising several workshop and awareness campaign with patient groups; 4) establishing an international communication network with patient groups and providing/exchanging valuable information. I also have conducted the investment activity with professionals for seeking alternative ways to accelerate developments and commercialization of new therapies for rare diseases. Our first target is one of mitochondrial disease.

There are numerous and very different rare diseases issues. Which of them should be globally addressed and which ones should be managed at national/regional level?

HL: Research, especially clinical trials, requires international collaboration. Patient care needs to be organized and accessible at a national or regional level, but it is still important to pay attention to best practice care standards agreed at an international level.

SG: Rare diseases do not recognize global, national, or regional boundaries. With encouragement and opportunities made available at the local, regional or national levels, stronger individual and national program emphases will lead to expanded global approaches. As planning activities and discussions are held for new projects and programs, the rare diseases community should ask how any activity can be made available for patients throughout the world. Personnel and financial resources may be available from national sources to enable the participation of their citizens in the development and access as participants to collaborative clinical research studies and clinical trials, natural history studies, patient registries, collection and distribution of biospecimen samples from patients and family members. There is also increased national and international interest and support for the development of more directed translational research activities leading to the development of interventions and diagnostics. Public-private partnerships will require the utilization of the strengths and resources of the research partners involved in the development activities for rare diseases and orphan products.

YN: At first, Japanese government should carry out effective measures related to NANBYO area. Japan has a long history of measures for NANBYO, which now requires a review. We should reconsider the meaning of "NANBYO", intended diseases in "NANBYO", and equitable support for all "NANBYO". We also have to discuss how to facilitate interactions among other related policies (ex. Common healthcare system, Act on Welfare of Physically Disabled Persons, etc). Besides that, we need the review of orphan drug development supporting system, information sharing/providing among stakeholders, human resource development related to this field.

In your opinion, what the global approach to rare diseases should consist of?

HL: In general, international research collaborations in rare diseases are important to develop new and better diagnosis and treatments. This has been recognized by major institutions and funders like the European Commission and the NIH resulting in a truly global initiative called IRDiRC. The goals of IRDiRC are to diagnose all rare diseases and to develop 200 new therapies by the year 2020. This globally harmonised approach to research funding should help reduce duplication of effort and accelerate research developments. In parallel, policy initiatives such as national plans for rare diseases should provide an impetus for all countries.

SG: Shared programs with potential partners have proven to be a successful approach to rare diseases on a global basis. We must utilize the proven models for product discovery and development. These models require repurposing of approved and investigational products and establishing working relationships with the staff of regulatory agencies and our industry partners. We see the value of multidisciplinary collaborative research efforts involving research consortia and networks to attain the critical mass of investigators and patients required to increase the likelihood of completing the research projects in a timely fashion. Disease-specific patient advocacy groups have also proven to be reliable research partners and can assist in patient recruitment for clinical trials and linking patients from around the world through their organization. We have the capability of linking the community together electronically and need to consider the strategic alliances required for rare diseases research advances and orphan product development activities. We also are seeing more preclinical and clinical translational research resources becoming available from funding sources such as the NIH in the USA. We have to develop an awareness of these resources and availability for innovative research projects in rare diseases.

YN: It is essential that patient groups adopt a global approach to memberships and activities in order to provide better access to information and interventions to improve quality of life for all patients with rare diseases. Almost all global projects are established under the initiative of the government, however, we should discuss on global level how to provide unbiased information to patients whose home governments don't participate in. As Japanese government, we have to select a person in a position of responsibility as participant in those meetings, and he/she makes efforts to convey to our rich information actively.

Recently, many international projects and consortia have focused on managing undiagnosed cases and developing new therapies. What are the perspectives of these activities?

HL: The –omics revolution will hopefully accelerate therapeutic developments in rare diseases, and international coordination and collaboration through projects and consortia such as IRDiRC are essential to success, as resources are limited. In the long-term, it will be important to make the rare diseases field more attractive to young clinicians and scientists, and to reward collaboration.

SG: The difficulty of obtaining the appropriate diagnosis has resulted in a diagnostic odyssey for many patients. Surveys have shown that nearly 15% of patients have waited for over 5 years to obtain the correct diagnosis. We think diagnostic capabilities will continue to improve, particularly for rare genetic disorders. As we gain additional experience and knowledge, the promise exists for quicker and more accurate diagnoses resulting from interpreting the results of whole genome sequencing for individuals. Costs continue to drop for these tests. A major need is to assure an adequate number of clinicians are available and trained appropriately to interpret the results. It is important for these clinicians to communicate the results back to patients and their families.

We recognize that the immediate goal of most patients is to obtain the diagnosis. It is reassuring to patients and families to have the correct diagnosis regardless if an intervention is available or not. Having the diagnosis enables individuals to expand their knowledgebase about their disease. They will attempt to learn as much as possible about their disease from numerous sources. They will attempt to locate others with the same or related diseases, including established patient advocacy groups, and will seek out those clinicians with a better understanding of their disease or who have established standards of care for their disease.

One of the many benefits of research networks and consortia is the ability to aggregate clinical data from a large number of patients from multiple research sites throughout the world. Utilizing a global approach, patient registries, collection of bio-specimen samples and longitudinal and natural history studies can be opened and prepare the way for clinical trials when interventions become available for evaluation.

YN: These activities are very valuable. Japan country has to participate in, but at the same time, we have to discuss several issues as follows: 1) Defining undiagnosed diseases as a brand new type or a subtype of an existing rare disease to re-build the concept of certain diseases along with constructing a better information system, 2) Coordinating national centers, hospitals, and university hospitals so that patients can be registered and experts can evaluate them with ease, 3) Treatment development for NANBYO diseases needs an effective registry system of patients and patients' lead research bringing global collaboration into view.

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

HL: We are grateful for the support of many people in the RD field, but particular patients and families affected by RD. We encourage patients and families to get involved with efforts such as patient registries that may be available for their disease.

SG: Success is defined as the development of appropriate diagnostics and access to new interventions. For most rare diseases, there are no appropriate treatments available and this measure of success may have to be considered until such time as a treatment becomes available. The recent increased emphasis on translational research programs offers tremendous hope that initiatives will speed up the development of interventions. These interventions may come from new compounds or discoveries of new treatments from the repurposing of products already approved and available for use in other rare diseases. Translational research enables discoveries from industry and academic research centers, government laboratories and clinics, and foundations to be "translated" into interventions. To address this issue, several patients and patient advocacy groups have developed model systems to speed up the development of products for their disease. This model requires careful planning of global research initiatives and attention to the details of the types of preclinical and studies in humans required by regulatory agencies, the resources (funds and personnel) required to conduct these studies. A novel approach just announced by NIH with several grant awards will look to the identification of safer and more useful products by the use of tissue chip technology to speed up the development of potential compounds with an acceptable safety profile.

Since resources will be required from various sources, it is important to develop collaborative partnerships based on trust and commitment to develop diagnostics and treatments. This shared trust is built upon personal collaboration established with continued communication among all partners. Strong leadership at the patient advocacy group level is the defining factor in the successful approaches to rare diseases research and orphan products development. We are unable to meet the treatment needs for everyone with a specific rare disease but with technology available today, it is essential that the rare diseases community - patients, families, patient advocacy groups, researchers, research and regulatory agencies, and industry partners - maintain constant contact. Partnerships can assist in developing the very best information about a disease, establishing standards of care, how best to live and cope with a rare disease throughout their lifetime. Continued support for the leadership of PAGs is essential to encourage the development of information to inform clinicians, legislative bodies in individual countries, and the media and the public. Support for these activities that can be initiated at local, regional, national, and global levels is essential. We come full circle starting with patients in need of diagnostics and treatments and ending with patients who have been active participants and the leaders to accomplish these goals. Patients and their families will touch all partners in the rare diseases community dedicated to developing these interventions. Our task is to remove the barriers and facilitate the steps for the rare disease community to move forward as quickly as possible.

YN: I am sure that I don't have rich empirical value of these fields. However, I have many talented people behind me and a strong network. I strongly believe all of them support to our activities, because they also need them. My standing point is very unique, but I believe strongly in the value of my type, as a spokesman to the society. My message is very simple: Connection + Collaboration = Creation! We can connect with, collaborate with, and then, create something valuable for the society. I would like to connect with your "wish to connect".

SPINA BIFIDA

Definition and prevalence

Spina bifida is an inborn anomaly of the spinal column, which consists of incomplete closure of the posterior wall of the spinal column, most frequently in the lumbo-sacral region. However, it can occur anywhere along the spinal axis. As a result the dura, and/or the arachnoid and/or the spinal cord may protrude out of the bony defect of the vertebral arch. If the defect is open it is called spina bifida aperta, and if it is covered by skin the term is spina bifida oculta. This is one of the most common birth defects with an average prevalence worldwide of 1-2 cases per 1000 births.

Etiology

A multifactorial inheritance has been proposed to be responsible, coupled with environmental factors, of which nutrition and folic acid are most important. Cytoplasmic factors, polygenic inheritance, chromosomal aberrations, and environmental influences (eg, teratogens) have been considered as possible causes. Fetus with an open neural tube defect has an elevation of alpha-fetoprotein in the amniotic fluid. Ultrasound confirmation with amniocentesis generally is possible at 15-18 weeks to rule out a spina bifida.

Prevention

There is neither a single cause of spina bifida nor any known way to prevent it entirely. However, dietary supplementation with folic acid has been shown to be helpful in reducing the incidence of spina bifida. Sources of folic acid include whole grains, fortified breakfast cereals, dried beans, leaf vegetables and fruits. Folate fortification of enriched grain products has been mandatory in the United States since 1998. The US Food and Drug Administration, Public Health Agency of Canada and UK recommended amount of folic acid for women of childbearing age and women planning to become pregnant is at least 0.4 mg/day of folic acid from at least three months before conception, and continued for the first 12 weeks of pregnancy.

Clinical picture

Patients with spina bifida have variable neurologic deficits. Examination of neurologic deficit helps determine the functional level at which the spina bifida cystica lesion has interrupted function. Patients are categorized into general groups according to the level of deficit. Generally, the neurological level is grouped as thoracic, upper lumbar (L1, L2, L3), lower lumbar (L4, L5), or sacral. The neurologic deficits characteristically cause deformity by muscle imbalance forces. Unopposed muscle pull can cause spinal deformity, progressive lower extremity contractures, hip dislocations, and, less commonly, dislocations in other joints (foot and ankle). 22% of patients have a significant fracture in their lifetime and may have a fracture associated with a significant surgical procedure, such as reduction of the hip or spine surgery. Osteoporosis is a frequent finding, complicating their already present osteopenia. Ulcers from bracing are prominent in the lower extremities in the pelvis and, particularly, over the bony prominences as a result of sitting. Infection is common, particularly with a neurogenic bladder.

Treatment

A child born with myelomeningocele is transferred to a center, where neonatal surgery and closure can be performed. Surgery involves freeing lateral muscles and skin for coverage and attempting to form a closure of the neural elements with minimal scarring as late complication of a tethered cord has frequent and severe consequences. Further follow-up is carried out by a multidisciplinary team. Neonatal neurosurgery is followed by serial examination of muscle strength and joint range of motion, orthopedic evaluation to detect any early changes that may require intervention. Patients are followed-up for appropriate development and provided with prolonged physical therapy and adaptive training while in school. Neurosurgical follow-up is required to recognise the complications of hydrocephalus or a possible tethered cord and to monitor any potential causes of seizure activity.

Urologic evaluation is necessary to establish a bladder regimen to prevent frequent urologic infections and to recognize and treat early potential hydronephrosis or other causes of renal damage that can limit life expectancy. Pediatric evaluation is appropriate for any child and, specifically, should include efforts to maintain a reasonable weight, as children without ambulation tend to gain excessive weight and develop associated morbidity. Endocrinologically, a growth hormone deficiency may be present, which could cause patients to be about a foot shorter than their peers.

Rehabilitation and follow-up care

Rehabilitation in children with spina bifida varies according to age and degree of sensory-motor impairment due to malformations. If spinal cord is not directly affected (as in the case of spina bifida occulta), there is normal motor development of the patient. However, there is a tendency these patients to develop chronic lower back pain. Rehabilitation for spina bifida includes physical therapy, occupational therapy, and recreational therapy. Speech therapy may be indicated for patients with speech and/or swallowing difficulties.

In managing the cases of newborns with myelomeningocele, the physical therapist establishes a baseline of muscle function. As the child develops, the physical therapist monitors joint alignment, muscle imbalances, contractures, posture, and signs of progressive neurologic dysfunction. The physical therapist also provides caregivers with instruction in handling and positioning techniques and recommends orthotic positioning devices to prevent soft tissue contractures. Near the end of the first year of life, it is recommended to provide the child with an effective means of independent mobility in conjunction with therapeutic exercises that promote trunk control and balance. Children with spina bifida often have impairment in fine motor skills and conducting activities of daily living. Early training is expected to compensate for these deficits and it should progress along the developmental sequence as closely as possible. For the school-aged child, recreational therapy provides opportunities for participation in adapted sports and exercise programs, which can result in long-term interest in personal fitness and health.

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UPCOMING RARE DISEASES CONFERENCES, WORKSHOPS AND INITIATIVES

- **10-11 September 2012 – Inception workshop on national planning for rare diseases, Rome (http://www.europlanproject.eu/_newsite_986987/events1.html)**
- **14-15 September 2012 – 3rd Bulgarian national conference for rare diseases and orphan drugs, Plovdiv (www.conf2012.raredis.org)**
- **28-29 September 2012 – 2nd European lymphangioleiomyomatosis (LAM) conference, Barcelona http://www.europelamfederation.org/**
- **8-9 October 2012 – International Workshop "Rare Diseases and Orphan Drug Registries", Rome (http://www.epirare.eu/_meet/20121008.html)**
- **16-17 October 2012 – Conference on Childhood Immunisation, Luxembourg http://ec.europa.eu/health/vaccination/events/ev_20121016_en.htm**
- **17-18 October 2012 – 2nd Annual orphan drug congress, Barcelona (www.pharma.flemingeurope.com/orphan-drug-congress/category/home)**
- **18 October 2012 – Building a Framework for Societal Benefits Approach to Health Technology Assessment, Brussels http://www.epposi.org/index.php/events/details/17-AIP-HTA-Building-a-Framework-for-Societal-Benefits-Approach-to-Health-Technology-Assessment**
- **24-26 October 2012 – 3rd Pan-European Conference on Haemoglobinopathies and Rare Anaemias, Limassol http://www.thalassaemia.org.cy/pan_euro_3rd.html**
- **5 December 2012 – An Optimal European Chronic Care Model: Towards Implementation and Benchmarking, Brussels http://www.epposi.org/index.php/events/details/14-aip-ccm-all-stakeholder-workshop**

SPINA BIFIDA AND HYDROCEPHALUS BULGARIA PATIENT ORGANISATION

A new patient organisation, "Spina Bifida and Hydrocephalus Bulgaria" (SBHB) has been recently established. SBHB is an association formed by parents of children with spina bifida and hydrocephalus. SBHB is a natural, modern and adequate way to meet the growing needs of the patient community in terms of support and assistance, access to information, exchange of experience and ideas, protection of common interests before state institutions.

You can find further information about SBHB on the organisation's website.
http://www.sbhb.org/

Editorial Box

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