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MEETING REPORT

5th RARE DISEASE SOUTH EASTERN EUROPE (SEE) MEETING, SKOPJE, MACEDONIA (NOVEMBER 15th, 2016)

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ABSTRACT

The fifth SEE meeting on rare diseases (RDs) was held in Macedonian Academy of Sciences and Arts (MASA) the November 11th, 2016. Several lectures dealt with mucopolysaccharidosis, glycogen storage diseases and the possibilities for their diagnosis and treatment. Enzyme replacement treatment (ERT), its availability, effects (or the lack of it) on the brain, and further prospects of eventual gene treatment were comprehensively exposed and discussed. Special accent was on Gaucher, Morquio IVA, Hunter and the audience was given new knowledge on the complexities of diagnosis and treatment. A block of lectures on rare renal diseases was also impressive. From renal stones, their molecular and genetic mechanisms to different forms of CAKUT the use of NGS and other molecular methods in diagnosis of RDs. Mitochondrial diseases, the novelties and importance of early discovery were comprehensively exposed. Special lecture was given on the complement system. Endocrine disruptors, microprolactinomas were also the topic of the meeting. A rather reach session of posters was also presented.

Key Word: Rare Diseases, rare renal disease, growth disorders, Gaucher..

Momir Polenakovic (MASA, Macedonia)

has given an update on RDs, first defining RDs as those that affects less than 1/2000 (Europe), 1/1250 in the USA, while in Japan RD is the one that affects less than 1/50,000 patients. It is estimated that 6-8% of European population (27-32 million) suffers from 5-8.000 RD. Impressively, the majority of RDs affect children (75%) and, unfortunately 30% of children die before the fifth birthday.

In renal diseases, over 100 conditions meet the epidemiological criteria to be defined rare: polycystic kidney disorders, Fabry, Alport disease but also less known and rarer conditions. Other organs might involve with the kidney disorder. Early diagnosis of renal RD is important in order to take appropriate therapeutic measures, either siple ones (potassium citrate and large hydration in cystinuria) or expensive as it is enzyme replacement therapy in Fabry disease. Both treatment enables long term renal survival and good quality of life. Progresses in genetics, particularly new technologies of next generation sequencing have opened unprecedented opportunities for the identification of faulty gene(s), novet treatments and personalized medicine

In Macedonia we lack comprehensive registries at the national level. The published articles of Macedonian health professionals on renal RD in PubMed journals present only the tip of the iceberg.

Milosevic Danko (Zagreb, Croatia)

presented the atypical hemolytic syndrome (aHUS) in 5 Croatian Children. Two children affected during infancy were treated with PEX/FFP, CVVHD and Eculizumab. The first described patient at the age of 10 months patient was found to be **heterozygous** for a substitution in exon 27 of the *C3* gene (c.3478G>A); **heterozygous** for the ***CFH*** **H3** haplotype and **homozygous** for the **MCPggaac**

haplotype of the *CD46* gene. A **heterozygous** mutation causing amino acid change (**Q950H**) in scr16 of **complement factor H** and heterozygous for *CFH* c.-331C>T polymorphism was also found, as other siblings with MCP S274I mutation and is **homozygous for the MCPggaac** haplotype. Interestingly, his sister had a novel heterozygous mutation (p.**S274I**) in *CD46*. Siblings were treated with methylprednisolone and PEX/FFP. All affected children have anormal life without physical/mental consequences, but for one child who has mild mental retardation.

Adrijan Sarajlija (Belgrade, Serbia)

gave a talk on glycogen storage diseases (GSDs) in one center. He stressed that the strict distinction among various types is impossible since many of these entities affect multiple organs. GSD type 1 with its two subtypes is considered as the most common GSD. Worldwite there is a much higher prevalence of subtype 1a, while in Serbia approximately 80% of patients affected with subtype 1b with . Most common mutation in in *G6PC* gene causing GSD 1a is c.247C>T. Other GSD in Sebia include types 2, 3, 6 and 9. Treatment of GSDs is nutritional treatment with exception of GSD type 2 (Pompe disease) for which enzyme replacement therapy is available. Gene therapy is still in development.

Mitochondrial diseases – Are they rare or common?

Johannes A. Mayr (Salzburg, Austria)

had a fascinating talk on mitochondral diseases., Mitochondria provide the vast majority of energy (ATP) in oxidizing cells. Mutations in the 37 mitochondrial genes and 250 nuclear genes have been associated with human disease.

Impressively, the clinical presentation of these rare disorders is summarized by the slogan: “Any symptom, in any organ or tissue, at any age and with any mode of inheritance”.

The new sequencing techniques allowed for the discovery of several new and unexpected genes.

Furthermore, defects in the mitochondrial energy metabolism were reported as early as more than 90 years ago by Otto Warburg in solid tumors. Furthermore, an increasing number of underlying biochemical and genetic defects were identified in the last decade, in neurodegenerative diseases and in the aging process.

Velibor Tasic (Skopje, Macedonia)

described the super rare disease of Pitt Hopkins through the personal travails and suffering of a child and his family. Pitt Hopkins syndrome (PTHS) is a neurodevelopmental disorder due to haploinsufficiency of the mutated TCF4 gene. Severe mental retardation, wide mouth, and intermittent overbreathing are the signs of the syndrome.

The prevalence of PTHS is estimated between 1 in 34,000 to 1 in 200,000-300,000.

PTHS is considered an Autism Spectrum Disorder. TCF protein is important for development of the nervous system and the brain, and is also found in patients with schizophrenia (overexpression of the TCF4 protein). There may be overlap with clinical syndromes and patients may be misdiagnosed as Angelmann, Mowat Wilson and Rett syndrome.

The current research approach tries agents that are able to enhance/augment the function of TCF4 activity without directly activating the protein.

Gaucher Disease (GD) was a theme of talks by Zoran Gucev (Skopje, Macedonia) Milan Lakocevic (Belgrade, Serbia) and Zlate Stojanovski (Skopje, Macedonia). GD is an autosomal recessive lysosomal storage disorder caused by deficiency in glucocerebrosidase. Partial deficiencies cause Type 1 GD, largely a disorder of macrophages with the pathologic hallmark the Gaucher cells (an enlarged, often multinucleate macrophage with crumpled cytoplasm). Infiltration by Gaucher cells leads to hepatosplenomegaly, hypersplenism, and displacement of haematopoietic bone marrow. Bony involvement encompases recurrent osteonecrosis, osteoporosis and fractures. More severe enzyme deficiency leads to accumulation of endogenously derived substrate in neuronal cells and a brain disorder: slowly progressive neurodegenerative disease with myoclonic epilepsy (both forms of Type 3 disease), to a rapidly fatal infantile form (Type 2 GD). Since 1991 enzyme replacement therapy (ERT) is available with recombinant technology and most recently by gene activation techniques. ERT has dramatic effects on visceral and bone marrow disease, while the effects on bone are slower and sometimes partial. Both Milan Lakocevic and Zoran Gucev kept our attention on ERT, while Zlate Stojkovski presentet a patient with GD an polycythaemia vera rubra.

Zoran Gucev (Skopje, Macedonia)

took us to a journey of rare diseases with the hallmark of a growth disorder as diagnosed in Mac-

edonia. Growth disorders are a rather diverse and frequent occurrence in childhood. A variety of rare endocrine (LHX4, IGHDII, SHOX hormonal deficiencies…), metabolic diseases (Hunter, Morquio IV A and B, Lesch-Nyhan…), disproportionate short stature (spondilocostal dysplasias, overgrowth syndromes…), dysmorphias (Adams Oliver Syndrome, Wiedeman Steiner, Rubinstein-Tayby…) were describee. The unforeseen usefulness of anomalies in the prenatal diagnosis, in uncovering of novel molecular mechanisms and in discovering novel treatments is comprehensively exposed. Several new genes (*PIK3CA, TBX6* …) discovered in the course of investigation of growth disorders are also presented.

Rossella Parini (Monza, Italy)

gave a talk on mucopolysaccharidoses (MPS). Those genetic progressive diseases cause disabilities, reduced quality of life and early death.

Central nervous system (CNS) damage is seen in the most severe forms of MPS I and MPS II, in the totality of MPS III and in some MPS VII patients, while it is almost absent in MPS IV and VI. Only MPS I had a possible curative treatment which was the bone marrow transplantation.

The enzymatic replacement therapies (ERT) at present are available for MPS I, MPS II, MPS VI and MPS IV. In general ERT improves of some clinical signs and stabilisates others.The major disadvantage is that ERT cannot cross the blood-brain-barrier. ERT efficacy is more evident when patients are treated early. Therefore the neonatal screening is strongly supported.

Joachim Seitz (Hamburg, Germany)

presented all the perils of the endocrine disruption as cause of (rare) diseases. Plastics on land and see reach food and drinking water. At the cellular and molecular level some of those organic substances act like hormones and severely interfere with the physiological hormone cascade, which explains the origins of the term "endocrine disrupting chemicals" (EDCs).

Oliver Bartsch (Meinz, Germany)

Genetic causes of developmental delay (DD) and intellectual disability (ID) have been increasingly found with the application of next-generation sequencing (NGS). In >100 patients with DD/ID and normal findings by karyotyping and microarray analysis NGS was performed. A definite diagnosis was achieved in 25% of families.

NGS tremendously increased the diagnostic yield, by 25%. His laboratory is now replacing the MPIMG1-test by whole exome sequencing (WES).

Jan Halbritter (Leipzig, Germany)

gave a lecture on nephrolithiasis (NL). NL is contributing to development of chronic kidney disease (CKD). Ca-based (e.g. Ca-oxalate >> Ca-phosphate) calculi are the most frequent. NGS identified more than 30 monogenic forms of over the last two decades. Distinct pathomechanism are found depending on the physiological function of the defective protein. Modern NL metaphylaxis may include mutation. Zoltan Prohaska (Budapes, Hungary) shed a sharp light on meny dark corners of the complex complement system.

Ljiljana Saranac, Ivana Markovic (Nish, Serbia)

turned the audience's attention on microprolactinoma in childhood and adolescence. The estimated incidence was 0.1 per million children. Galactorrhoea/amenorrhoea syndrome in women and gynecomastia/ hypogonadism in adult men, hyperprolactinaemia in children has different clinical expression influencing growth, puberty and weight gain. The diagnosis is made on the basis of consistently elevated PRL levels (at least 3 measurements) and dynamic tests of all pituitary axes.

A neuroradiological investigation (pituitary MRI) is necessary for adenoma confirmation.

Wheather micro-or macroadenomas, prolactinomas are treated medicaly with dopamine agonists. The medical treatment is able not only to normalize PRL levels, but also to produce a rapid tumor mass shrinkage. Due to senescense phenomenon microprolactinomas never progress to macroprolactinomas.

Stefan Chichevaliev, Vesna Aleksovska (Skopje, Macedonia)

informed about the policies, practice and their impact on the quality of life of patients with RDs.

The investigation on relevant international relevant documents, as well as documents from countries from the region: Bulgaria, Slovenia, Serbia and Croatia following improvements are required:

1) increasing the financial support for procurement of medicines and medical devices (100%); 2) raising awareness among health professionals for RD (81,2%); 3) establishing an international professional collaboration for research, monitoring and promotion of the doctrine and practice for RD (81,2%); and 4) establishing a database and knowledge for RD (90%).

A voluminous sessions with poster presentation followed, given by specialists, residents and students.

- Daniela Chaparoska. NEUROLEPTIC MALIGNANT SYNDRONE: CASE REPORT
- Gordana Kiteva-Trenchevska. REFRACTORY EPILEPSY IN TOUBEROS SCLEROSIS COMPLEX
- S. Nikolovska, V. Grivcheva-Panovska, K. Damevska, D. Chaparoska , N. Baneva. KLIPPEL-TRENAUNAY SYNDROME – CLINICAL EXPERIENCE
- Nada Petrova. TUBEROUS SCLEROSIS COMPLEX - A CASE REPORT
- Irena Rambabova Bushljetik, Gjulsen Selim, Igor Kuzmanovski, Menka Lazarevska, Milan Risteski, Jelka Masin-Spasovska, Olivera Stojceva Taneva, Ladislava Grcevska, Goce Spasovski. USE OF mTOR INHIBITOR – EVEROLIMUS IN PATIENT WITH BILATERAL ANGIOMYOLIPOMA AND SUBEPENDIMAL ASTROCYTOMA ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX
- Vesna Dichoska, Ana Stamatova, Emilija Sahpazova, Velibor Tasic, Dorottya Csuka, Zoltán Prohászka. ATYPICAL HEMOLYTIC UREMIC SYNDROME
- Nikolina Zdraveska, Anet Papazovska Cherepnalkovski, Natasa Aluloska, Jana Jovanovska, Katica Piperkova. SYSTEMIC MASTOCYTOSIS - REPORT OF A RARE CONDITION IN NEWBORN
- L. Milenkova, A. Papazovska, N. Aluloska, N. Zdraveska. FAMILIAL OCCURRENCE OF MULTICYSTIC DYSPLASTIC KIDNEY
- Kreshnik Pollozhani, Hana Starova, Kristijan Bundovski, Emilija Sahpazova. ATYPICAL HEMOLYTIC-UREMIC SYNDROME-A CASE REPORT
- Ana Stamatova, Meri Miholova , Velibor Tasic. UROFACIAL OR OCHOA SYNDROME
- A. Janchevska, K. Kuzevska - Maneva, L. Tasevska Rmush, A. Sofijanova, O. Jordanova, A. Ugrinska. UNUSUAL PRESENTATION OF HASHIMOTO'S DISEASE WITH THYROID-ASSOCIATED OPHTALMOPATHY IN A 12.5 YEAR OLD GIRL
- Marija Dimishkovska, Zoran Gucev, Svetlana Kocheva, Vjosa Kotori, Momir Polenakovic, Dijana Plaseska-Karanfilska. NOVEL MUTATION IN FANCA GENE (c.3446_3449dupCCCT) IN TWO UNRELATED PATIENTS FROM MACEDONIA AND KOSOVO
- V. Jovanovska, R. Kacarska, K. Kuzevska Maneva, B. Gjurkova Angelovska , M. Neskovska Shumenkovska, E.Shukarova Angelovska. WILLIAMS-BEUREN SYNDROME WITH SUPRAVALVULAR AORTIC STENOSIS. CASE REPORT
- Salihu S, Tosevska K, Cekovska S. SDS PAG ELECTROPHORESIS IS A RELIABLE SCREENING TOOL IN PATIENTS WITH OCRL MUTATIONS
- Milan Velkov, Aleksandar Petlickovski, Momir Polenakovic, Zoran Gucev. SYNDROME NIJMEGEN BREAKAGE AND A DIFFUSE LARGE B CELL LYMPHOMA
- Katarina Abraseva, Marko Kostovski, Marina Krstevska-Konstantinova. RUBINSTEIN-TAYBI SYNDROME WITHOUT *CREBBR* AND *EP300* GENE ALTERATIONS
- Eva Markovska, Natasa Petrovska, Zoran Gucev. UNBALANCED TRANSLOCATION 8;13 IN A 13 YEAR OLD BOY WITH FACIAL DYSMORPHIA AND MENTAL RETARDATION
- Ana Stamatova, Zoran Bozinovski, Aleksandar Solev, Sanja Ivanovska, Dijana Plasevska Karanfilska, Momir Polenakovic, Zoran Gucev. A VARIANT OF FIBRODYSPLASIA OSSIFICANS PROGRESSIVA CAUSED BY THE *G328E* (c.9836>A) MUTATION OF THE *ACVR1* GENE
- Teodora Stojanovska, Kristijan Bundovski, Gjorgji Bozhinovski, Velibor Tasic. ISOLATED CONGENITAL ANOMALY OF THE KIDNEY AND URINARY TRACT IN A CHILD WITH 22q11.2 MICRODELETION SYNDROME
- V. Ambarkova, N. Stavreva. DENTAL ASPECTS OF YOUNG PATIENTS WITH ECTODERMAL DYSPLASIA SYNDROME
- Kristijan Bundovski, Teodora Stojanovska, Gjorgji Damjanovski, Velibor Tasic. NUTCRACKER PNENOMENON IN A PATIENT WITH RECURRENT GROSS HEMATURIA

- S. Fustik, A.Stamatova,_T. Jakovska, L. Spirevska. EARLY VERSUS LATE DIAGNOSIS OF CYSTIC FIBROSIS: A NEED FOR IMPLEMENTATION OF NEONATAL SCREENING
- Sanja Ivanovska, Snezana Jancevska , Marina Krstevska Konstantinova. WIEDEMANN-STEINER SYNDROME IN A PATIENT WITH NORMAL HEIGHT AND NO ALTERATION IN *KMT2* GENE

Резиме

ПЕТТИ СОСТАНОК ЗА РЕТКИ БОЛЕСТИ НА ЈУГОИСТОЧНА ЕВРОПА, СКОПЈЕ, МАКЕДОНИЈА, 15 НОЕМВРИ 2016 ГОДИНА

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Апстракт

Петти состанок за ретки болести на југоисточна Европа се одржа во МАНУ на 11 ноември 2016 година. Повеќе предавања се занимаваа со мукополисахаридози, болести на гликогенските депоа и можностите за нивна дијагноза и третман. Ензимската заместителна терапија, нејзината достапност, ефектите (или нивниот недостаток) на мозокот), и идните изгледи за евентуална генетска терапија беа сеопфатно изложени и дискутирани. Посебен акцент беше ставен на Гоше, Morquio IVA, Хантер I и публиката стекна нови знаења за комплексноста на дијагнозата и третман. Групата предавања за ретките бубрежни заболувања исто така беше импресивна. Од бубрежни камења, нивните молекуларни и генетски механизми до различните форми на CAKUT употребата на NGS и други молекуларни методи во дијагнозата на RDS. Митохондриските болести, новините и значењето на раното откривање беа сеопфатно изложени. Специјално предавање беше одржано за комплементниот систем. Ендокрините нарушувачи и микропролактиномите исто така беа тема на состанокот. Исто така, беше презентирана прилично богата постер сесија.

Клучни зборови: ретки болести, ретки бубрежни болести, нарушување на растот, Гоше.