Abstract Book

Илустрација: **Васко Ташковски**

8th Meeting for Rare Diseases in South Eastern Europe

(EAP, UEMS Section of Paediatrics)

Ohrid, Republic of North Macedonia

23rd to 25th September 2022

Macedonian Society
for Rare Diseases

Здружение на педијатрите на Република Македонија

LIFE CHALLENGES
Life is a puzzle, collect it.

РЕТКО Е ДА СИ РЕДОК
RRALLË ËSHTË TË JESH I RRALLË
RARE IS TO BE RARE

Abstract book

8th Meeting for Rare Diseases in South Eastern Europe

(EAP, UEMS Section of Paediatrics)

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Фотографија: **Охрид ноќе**

Organizing Committee:

President
Zoran Gucev, Aspazija Sofijanova, Velibor Tasic

Aleksandra Janchevska, Secretary
Todor Arsov
Elena Shukarova Angelovska
Marina Krstevska Konstantinova
Vesna Aleksovska

International Scientific Committee:

Chair:
Velibor Tasic Skopje, North Macedonia
Zoran Gucev, North Macedonia

Members:

Adrijan Sarajlija, Serbia
Danko Milosevic, Croatia.
Jasmina Comic, Germany
Constantinos Stefanidis, Greece
Maria Gaydarova, Sofia Bulgaria
Nora Abazi Emini, North Macedonia

Dear minister of Health D-r Bekim Sali,
Dear Parents, children, colleagues, friends,
Ladies and gentlemen,

On the behalf of the Organizing Committee of the 8th South East European meeting for rare diseases, we are happy to see you in Ohrid and profoundly thankful to you for attending our and your meeting.
As always those meetings are trailblazers in introducing new therapies (Hunter, Morquio, various LSD...). At the same time the meetings are providing the necessary motivation for the policy leaders not to abandon expensive treatment for children and adult patients alike.
Therefore we kindly ask the minister of Health, The President of The Republic, the officials to help treating those rare diseases which for the each patient are the most important in the world. Our numerous members of the press and media are going to help us spread the message of need and the cry for help of our sick children.
Pediatricians, family medicine doctors, GPs and several patient organizations are with us as they are instrumental in diagnosing those various and tough to diagnose diseases. We are profoundly thankful and great the patient organizations who are with us on this long, arduous and difficult journey.
Thank you for coming in the beautiful city of Ohrid, the cradle of Slavic culture and civilization. We wish you a fruitful work, great news on new treatments, wonderful and unforgettable socializing.

Sincerely Yours,

Zoran Gucev,
Velibor Tasic
Aspasija Sofijanova,
Aleksandra Janchevska
Vesna Aleksovska

SCIENTIFIC PROGRAM

FRIDAY, SEPTEMBER 23, 2022

20.00 Get together, Hotel Silex Ohrid

SATURDAY, SEPTEMBER 24

Rare Diseases in SEE

Moderators: Aspazija Sofijanova, Zoran Gucev

09.00-09.30 **Welcome and opening:**

- **Mr. Bekim Sali, Minister of Health, North Macedonia**
- **Mrs. Aspazija Sofijanova, University Children's Hospital**
- **Ms Vesna Aleksovska, Chair of the rare disease association**

Life with challenges

Session I (Hall A)

Moderators: Zoran Gucev, Klaus Mohnike, Júlio César Rocha

09.30–09.45 **Zoran Gucev, Skopje, North Macedonia**
PIK3CA-Related overgrowth specxtrum (PROS): new treatments

09.45-10.25 **Klaus Mohnike, Magdeburg, Germany**
Experiences in pharmacological treatment of achondroplasia dwarfism with vosoritide

10.25-10.40 **Elena Sukarova Angelovska, Skopje, North Macedonia**
Phenylketonuria (PKU) – Genetic variations and their clinical presentations in PKU

10.40-11.20 **Júlio César Rocha, Lisbon, Portugal**
How to implement basic PKU management practices toward the best standard of care

Discussion
Press Conference

11.40-12.00 **Coffee break**

12.00-12.15 **Aspazija Sofijanova, Skopje, North Macedonia**
Introducing inovative therapy and experince with SMA in North Macedonia, will genetic therapy be final solution?

12.15-12.35 **Dimitrije Nikolić, Belgrade, Serbia**
Neonatal screening for SMA in Serbia – First Results

12.35-12.55 **Tanja Loboda, Ljubljana, Slovenia**
Duchenne muscular dystrophy - from early diagnosis to novel therapies

12.55-13.25 **Constantinos Stefanidis, Athens, Greece**
Epidemiology of hyperoxaluria type 1 (PH1)

13.25-13.55 **Maria Gaydarova, Sofia Bulgari**a
Status of PH1 in Bulgaria and patient cases

13.55-14.15 **Goran Chuturilo, Belgrade, Serbia**
Importance of diagnostic of rare diseases with enzyme and genetic testing

Discussion

14.15-15.15 **Lunch**

Session II (Hall A)

Moderators: Velibor Tasic, Adrijan Sarajlija, Dijana Plaseska Karanfilska

15.15-15.45 **Timothy Cox, Cambridge, UK**
Gaucher Disease Matters

15.45-16.05 **Dijana Plaseska Karanfilska, Skopje, North Macedonia**
Genetics of Gaucher disease

16.05-16.25 **Adrijan Sarajlija, Belgrade, Serbia**
Treatable inherited metabolic diseases

16.25-16.45 **Jasmina Comic, Munich, Germany**
Genetics of Alport syndrome-Munich experience

16.45-17.05 **Aleksandra Janchevska, Skopje, North Macedonia**
The overgrowth syndromes – the story of a patient with Beckwith Wiedemann Syndrome (BWS)

17.05-17.20 **Sonja Bojadzieva, Skopje, North Macedonia**
Wilson's Disease in Children- diagnostic aspects and therapy

17.20-17.35 **Aco Kostovski, Skopje, North Macedonia**
Allagile syndrome – new treatment possibility

Discussion
Conclusion remarks
Zoran Gucev, Velibor Tasic

2nd Balkan Alport Meeting (Hall B)

15.00-15.10 **Gordana Loleska, Skopje, North Macedonia**
Alport Macedonia – Who are we?

15.10-15.25 **Ana Momirovska, Skopje, North Macedonia**
Diagnostics of COL4A diseases in North Macedonia from the very beginning

15.25-15.40 **Nora Abazi Emini, Skopje, North Macedonia**
Type-IV-Collagen-Related nephropathies in North Macedonia

15.40-15.55 **Velibor Tasic, Skopje, North Macedonia**
Extrarenal features of COL4A nephropathies

15.55-16.15 **Jasmina Comic, Munich, Germany**
The Munich Microhematuria Project

16.15-16.30 **Constantinos Stefanidis, Athens, Greece**
COL4A nephropathies in Greek children

16.30-16.45 **Nikola Gjorgjievski, Skopje, North Macedonia**
Alport syndromre-when should one consult nephrologist

16.45-17.00 **Marija Gaydarova Sofia, Bulgaria**
COL4A Nephropathies in Bulgaria

17.00-17.15 **Danko Milosevic, Zagreb, Croatia**
COL4A nephropathies in Croatian Children

17.15-17.30 **Todor Arsov, Skopje, North Macedonia**
Challenges in genetic counselling for Alport syndrome in the age of genomic medicine

17.30-17.45 **All participants**
Round table

SUNDAY, SEPTEMBER 25

POSTER SESSION (Hall B) 9.00-11.00

Language of the Meeting: **English**

Certificates of Attendance will be provided by Prof. V. Tasic

SPEAKERS / PARTICIPANTS / MODERATORS

Vesna Aleksovska,
IGA Projects officer

Zoran Gucev

Klaus Mohnike

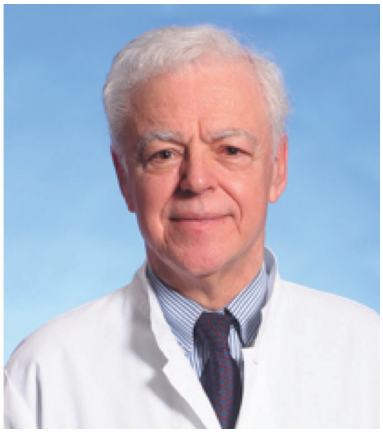
Elena Shukarova

Júlio César Rocha

Aspazija Sofijanova

Dimitrije M. Nikolić

Tanja Loboda



Constantinos J. Stefanidis

Maria Gaydarova

Goran Cuturilo

Timothy M Cox

Dijana Plaseska-Karanfilska

Adrijan Sarajlija

Jasmina Ćomić

Aleksandra Janchevska

Sonja Bojadzieva

Aco Kostovski

Gordana Loleska

Ana Momirovska

Nora
Abazi Emini

Velibor
Tasic

Nikola Gjordjievski

Danko Milosevic

Todor Arsov

PRESENTERS - BIO & ABSTRACT

Vesna Aleksovska, IGA Projects officer

Vesna Aleksovska has a background in journalism, non-government sector, project management and business consulting and 12 years of experience in patient organizations and advocating for patients' rights.

She founded the Association of citizens for rare diseases "LIFE WITH CHALLENGES" – Bitola in 2009. She is a Gaucher patient and patient advocate for rare disease patient in R. Macedonia. Aleksovska is also co – founder and former President of the National Alliance for Rare Diseases of the Republic of North Macedonia from 2014. She is now in the board of NARDM and in the board of the Alliance of Patient Organizations of the Republic of North Macedonia.

In 2013 she become a member of the DITA (Drug Information, Transparency and Access) Task Force EURORDIS (European Organization for Rare Diseases) and since 2014 a director in the board of directors of the International Gaucher Alliance (IGA).

In 2019 she became the Chair of the IGA. She is also EUPATI (European Patients Academy on Therapeutic Innovation) fellow and trainer since 2015.

From December 2021 Vesna is a Projects officer at IGA.

Vesna works in the field of advocacy and lobbying for rights of the rare disease patients in the Republic of North Macedonia, through cooperation and communication with organizations and institutions (government and non-government) on national and international level.

She believes that through empowering the patients and raising public awareness about rare diseases the world can become a better place to live in, for patients and families that face life filled with challenges. Being a patient advocate for Vesna, means building future for families with rare diseases.

Zoran Gucev

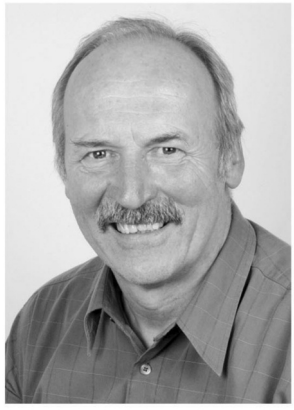
Zoran Gucev was born in 1955 in Skopje, Macedonia. Skopje was the town where he completed his medical education, residency and his studies in classical philosophy. His foreign education included Vienna, Paris, Leipzig, Utrecht, Murcia, Portland (OR), San Francisco (CA). Pediatric endocrinology and genetics are his main fields of interest and subjects of his 9 published books and 132 articles on Pubmed. He also took part in a dozen international projects and was a member, served in several pharmaceutical boards and committees. He enjoys spending his free time with his family as well as reading, writing, hiking and swimming.

PIK3CA-RELATED OVERGROWTH SPECTRUM (PROS): NEW TREATMENTS

Zoran Gucev
Medical faculty Skopje

PIK3CA-related Overgrowth Spectrum (PROS) is a group of dozen overgrowth syndromes with the common cause: PIK3CA-variant which has a gain of function effect. The degree of malformation largely depends on the timing of the embryonic hit and its location. We present two children with malformations from this group of diesease. The first child was diagnosed at the age of 15 days having CLOVE (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Scoliosis/Skeletal/Spinal anomalies). The second child had and marked vergrowth of the left foot, left leg and left labia majora. Whole genome sequencing found the PIK3CA variant in the affected tiussue, demonstrated its gain of function in vitro comparing affected and unaffected tisssue. Further confirmation was done in murine knock out model. The patient already had surgery on the left foot and the mther observed an »apparent« continuation of tissue growth despite the surgical reduction. As an adult patient had to have a leg of 110 kg amputated. Treatment with rapamicin gave mixed results. FDA approved the Alpelisib the 5th of April, a kinase inhibitor which works by inhibiting the PI3K pathway. The medication inhibits the specific overgrowth in affected organs.

Key words: Overgrowth syndromes, PIK3CA, Rapamycin, Alpelisib



Klaus Mohnike

1970-1975 Med. School Humboldt-University of Berlin, GDR
1975-1980 Training as Pediatrician at Dept. Pediatrics at Medical Academy Magdeburg (since 1993 Med. Faculty of OvGUniversity), Germany
1977 Promotion A (MD thesis), Humboldt-University of Berlin, Germany
1980 Board certificate as Pediatrician
2000 Habilitation (PhD)
2001-2018 Head of center for neonatal screening Saxony-Anhalt
2008 Henning-Andersen Award of the European Society for Ped. Endocrinology (ESPE) for Epidemiology research project in congenital hyperinsulinism
2009 Hormone Research Price (ESPE) for `Novel insights´ in congenital hyperinsulinism
2010 Extraordinary Professor at Dept. Pediatrics OvG University

RELEVANT JOB TRAINING

4/ 1986 Research on insulin receptor ontogenesis at Institute Biology (Prof. Csaba) Semmelweis University Budapest/ Hungary
9-11/1988 Fellowship on Hypoglycemia and Congenital Hyperin sulinism at Inst. Child Health, Newcastle/ Tyne, UK (Prof. A. Aynsley-Green)
9/1993-8/1994 Research project at Dept. Pediatrics (Prof. L. Key) and Dept. Cell Anatomy (Prof. S. Frawley), MUSC Charleston, SC

2014-2020	Vice-Chair of German Association for centers of rare diseases
2016-2019	Chair of Saxonian-Thuringian society for Pediatrics and Ped. Surgery (STGKJM)
2017-ongoing	Chair of Central-German Network for rare diseases (MKSE)
Member of	Endo-ERN, Metab-ERN, BOND-ERN (i.e. European certified centers for rare diseases), chair of HCP OvGU.

CONTACT INFORMATION

Official address	Otto-von-Guericke University Magdeburg, Dept. Pediatrics Leipziger Str. 44, 39120 Magdeburg, Germany
Work telephone:	++49-391-6724032; Fax: ++49-391-67290038
Email:	Klaus.mohnike@med.ovgu.de

EXPERIENCES IN PHARMACOLOGICAL TREATMENT OF ACHONDROPLASIA DWARFISM WITH VOSORITIDE

Klaus Mohnike
University Children`s Hospital, Otto-von-Guericke University Magdeburg

Achondroplasia is the most common form of short-stature skeletal dysplasia, with an expected worldwide incidence of 1 per 20,000 to 25,000. Nearly always achondroplasia is caused by one of two pathogenic FGFR3 variants in the transmembrane region at amino acid position 380, constitutively upregulating the receptor. The FGFR3 variant arises de novo in 80% of individuals. This affects endochondral bone formation, leading to characteristic skeletal features and disproportionate short stature. Multisystemic complications, in particular orthopaedic, neurological, and ENT manifestations, as well as psychosocial issues are highly relevant. A coordinated multidisciplinary team approach, starting in the prenatal period, including surgical interventions are necessary to reduce morbidity and mortality, esp. in the first years of life. To target the underlying molecular etiology animal studies had been performed, showing that stimulation of the C-type natriuretic pathway increased long-bone and craniofacial growth. Vosoritide, a modified C-type natriuretic peptide, stimulates endochondral ossification and clinical studies since 2011 proved safety and efficacy for the treatment in individuals with achondroplasia. Furthermore, a phase 3 randomized, double-blind, placebo-controlled trial conducted in 121 children with achondroplasia aged 5 to< 18 years resulted in a mean difference of annualized growth velocity between participants in the vosoritide group and placebo group was 1.57 cm per year in favor of vosoritide and a satisfactory safety profile. Data of a 5 year observation period on the ongoing studies proved additional gain of 9 cm compared to natural history data, without signs of accelerated maturation.

Key words: achondroplasia, dwarfism, treatment, vosoritide

Elena Shukarova

Prof. Dr. Elena Shukarova-Angelovska graduated on 24.1. 1987 at the Faculty of Medicine at the University of St. "Cyril and Methodius" in Skopje, with an average score of 9.76. In 1996, she completed specialization in the field of pediatrics. She completed the second cycle (master's) studies in 1989, with an average grade of 10.0, and then defended her master's thesis on the topic: "Frequency of chromosome associations in parents of children with trisomy 21". She finished her doctoral dissertation on the topic: "The significance of minor malformations in the diagnosis of multimalformative syndromes" on November 14, 2008. Since 2012, she has been elected as an assistant professor at the Department of Human Genetics as a newly established department at the Faculty of Medicine - Skopje. Currently she is a professor at the Cathedrae of Human Genetics of the University. She has been elected as the head of the Cathedrae of Human Genetics since 2012. Also she holds the position of Head of the department for clinical genetics with genetic laboratory at the University pediatric Clinic.

She is a member of rare disease committee at the Ministry of health of North Macedonia since 2009 year and a co-writer of the National program for rare disease for the last decade.

In order to improve her knowledge in the field of clinical genetics, she completed several stays in foreign institutions - Clinical Center Ljubljana, Center for Human Genetics - Louvain, Belgium, dysmorphological schools in Manchester, England, Bertinoro-Italy, etc.

As a co-author of a textbook in the field of human genetics, she won the Goce Delchev award. Author and co-author of 250 publications, of which 60 are full papers. She is the principal investigator in 3, coinvestigator in 8 international projects.

PHENYLKETONURIA – GENETIC VARIATIONS AND CLINICAL PRESENTATION

Sukarova-Angelovska Elena
University Clinic for Pediatric Diseases, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, 1000 Skopje, Republic of North Macedonia

Phenylalanine is an essential α-amino acid with a nonpolar side chain that facilitates hydrophobic interactions. Phenylalanine is a precursor of tyrosine, which has the crucial role in regulating enzymatic activity and signal transduction. Major amount of phenylalanine taken from food has being catalyzed to tyrosine by hydroxylation of the aromatic side chain of phenylalanine.The bottleneck for this metabolic pathway is the activity/function of the enzyme phenylalanine hydroxylase. The enzyme is encoded by the PAH gene, mapped on 12q23.2, consists of 13 exons. More than 1000 variants of the gene were described in the two main PAH databases. Homozygous or compound heterozygous gene alterations in the PAH gene cause phenylketonuria. These variations impair the activity of the enzyme causing increased enzyme instability and aggregation, defective protein folding that produces defective oligomerization. Classification (classic, mild, or undefined PKU) has been made on biochemical level, using as the main criteria of the Phenylalanine level at diagnosis. Variants are predominant into the catalytic part of the gene, -59%, followed by variations in N terminal, and oligomerization part of the gene. It has been noticed that some variants give rise to more severe phenotype than the other. Several studies confirmed that residual activity of the enzyme is responsible for the clinical presentation. Genetic analysis was performed in 10 phenylketonuria patients where variants of the gene were found consistent with classical-severe or pf the disease. Treatment strategies could be planned according biochemical findings and molecular data.

Key words: phenylketonuria, PAH gene, oligomerization, classification

Júlio César Rocha

Assistant Professor
NOVA MEDICAL SCHOOL | Faculdade de Ciências Médicas, Universidade Nova de Lisboa, PT

Nutritionist, PhD
Reference Centre of Inherited Metabolic Diseases, Centro Hospitalar Universitário Lisboa Central, PT

Researcher
Center for Health Technology and Services Research, PT

Júlio César Rocha is a Nutritionist (0438N – specialist in Clinical Nutrition), with a post graduate qualification in Clinical Nutrition from the Faculty of Nutrition and Food Sciences – University of Porto (UP) andhe has also a PhD in Metabolism, at the Faculty of Medicine, UP.
He has been working in the field of inborn metabolic diseases since 2003. He is Assistant Professor at NOVA Medical School teaching in the field of Nutrition and Metabolism. He is also member of the multidisciplinary clinical team at the Reference Centre of Inherited Metabolic Diseases at Centro Hospitalar Universitário Lisboa Central and he is a researcher at CINTESIS (Center for Health Technology and Services Research).
He is council member of the SSIEM (Society for the Study of Inborn Errors of Metabolism), Chair of the Dieticians Group of the SSIEM (SSIEM-DG), Chair of the Nutrition Group of the Portuguese Society of Metabolic Disorders (SPDM-GN) and Presi-

dent of the Portuguese Society of Clinical Nutrition and Metabolism (SPNCM).
He is also member of the working group of the European Phenylketonuria Guidelines (EPG 2.0) under the umbrella of the ESPKU (European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria). He has been also member of the PKU European Parliament Cross Party Alliance, a joined group of Members of the European Parliament (MEP), experts and civil society.
He is author of more than 65 international, indexed, scientific publications and he has done more than 100 oral presentations/lectures/conferences in more than 12 different countries.

HOW TO IMPLEMENT BASIC PKU MANAGEMENT PRACTICES TOWARD THE BEST STANDARD OF CARE

Júlio César Rocha
Reference Centre of Inherited Metabolic Diseases, Centro Hospitalar Universitário Lisboa Central, Portugal

Phenylketonuria (PKU) is an inborn error of Phenylalanine (Phe) metabolism caused, in the great majority of the patients, by mutations in the gene that encodes for Phenylalanine Hydroxylase (PAH) enzyme. More than 1200 variants are described, which contributes to the high phenotypic variability. Untreated PKU patients manifest increased blood and brain Phe concentrations, resulting in severe neurological impairment. Even though it was demonstrated in 1953 the use of the Phe restricted diet as a treatment for these patients, an important milestone in the PKU journey was achieved by the discovery of the Guthrie test in 1963. This test allowed patients to be diagnosed in the neonatal period, preventing neurological sequelae. Every country should have nowadays implemented a newborn screening program, allowing early detection and prompt treatment of every patient with PKU.
In PKU patients, a Phe restricted diet should be immediately started after diagnosis. The Phe and natural protein restriction should be complemented with a protein substitute prescription, usually,but not exclusively, a Phe-free L-amino acid mixture. From weaning onwards, special low protein foods can also be used as an energy source, allowing a more anabolic environment. Beyond diet therapy, pharmacological treatments are now available to be used in several countries and much more are under development at this moment.
It is nowadays very important that all treatment strategies are available in different countries allowing metabolic teams to decide the best treatment for each patient at the right time. This is of highest value since it should be standard of care to keep all patients

under follow-up, adjusting treatment strategies according to their needs throughout paediatric age and in the adulthood. Treatment centres should be prepared for the challenges of the transition of care from paediatric to adult teams, also allowing an adequate care before, during and after pregnancy.

Keywords: Phenylketonuria, phenylalanine, newborn screening, amino acid, transition

Aspazija Sofijanova

1991-present

Name and address of employer	University Children's Hospital in Skopje, Republic of North Macedonia Vodnjanska 17, 1000 Skopje / North Macedonia
Type of business or sector	Health care and education
Occupation or position held	pediatrician
Main activities and responsibilities	Providing tertiary health care service for children Transport of critically ill children and neonates Conducting practice for educational purposes and lectures for university students Lectures on national and international congresses Executive of various projects including perinatal and neonatal morbidity and mortality Educator for mechanical ventilation in the NICU in all country. Also educator for cooling and bubble c pap in the NICU. Special emphasis is put on the neonatal transport service that provides saving lives of all critically ill children all over the country and as a regional center in the countries abroad. It is into the system for flying in other countries for extra medical support and additional medical services. International course of Management of health in Japan International course of Management of health Services in Times of Crisis Haifa Izrael. International course of Neurology, Slovenia Fifteen years experience in giving additional medical practice and lectures for students studying medical faculty and dentistry.

Education and training

Dates	1984-2003
Name and type of organisation providing education and training	Medical Faculty in Skopje, Republic of North Macedonia University Children's Hospital in Graz(LKH), Austria University Prince Alfred Hospital in Sydney,Australia University of George Washington, Washington DC, USA
Principal subjects/occupational skills covered	1990 general practice 1997 specialization in pediatrics 2004 Master degree(neonatology and intensive care) 2012-2017 Medical director PHI Clinic of Pediatrics-Skopje
Title and qualification awarded	2012 Doctoral degree PhD M 2014 National coordinator of transplantation 2015 President of the Association of Paediatrics 2020- Medical director PHI Clinic of Pediatrics-Skopje

Personal skills and competences

Mother tongue	Macedonian-romanian
Other languages	English
Organisational skills and competences	Management and coordination of human resources, networking between different scientific groups of various scientific background (medicine, psychology, defectology) risk assessment,
Coordination and administration of people, projects and budgets, at work, in voluntary work	project management and coordination, publishing various texts in the field of medicine and ctr. Experience in scientific and financial management

INTRODUCING INNOVATIVE THERAPY AND EXPERIENCE WITH SMA IN NORTH MACEDONIA, WILL GENETIC THERAPY BE FINAL SOLUTION?

Sofijanova A. Bojadzieva S. Jordanova O.
University Clinic for Pediatric Diseases, 1000 Skopje, Republic of North Macedonia,Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, 1000 Skopje, Republic of North Macedonia

Spinal muscular atrophy (SMA) is a rare, inherited, progressively debilitating neurodegenerative disease. It is an autosomal recessive disease, caused by a deletion or loss-of-function mutationsof motor neuron 1 gene. It results with reduction in SMN protein levels that leads to motor neuron death and progressive muscle atrophy and weakness, which affects the muscles used for activities such as breathing, swallowing, crawling, and walking.SMN protein is found throughout the body and increasing evidence suggests SMA is a multi-system disorder and the loss of SMN protein may affect many tissues and cells, which can stop the body from functioning.SMA is the most common genetic cause of infant mortality and one of the most common rare diseases, affecting approximately one in 6,000 - 11,000 live births worldwide. SMA leads to the progressive loss of nerve cells in the spinal cord that control muscle movement. SMA is categorized into five subtypes, which are defined according to the maximum motor milestone attained and the age of symptom onset.The Macedonian Agency for Medicines and Medical Equipment in 2021 has approved two medicines for SMA: nusinersen, and risdiplam.Each of these two medicines has led to improvements in survival and motor function in patients with SMA. Nusinersen is SMN2-targeting antisense oligonucleotide therapy indicated for treatment of adults and children.In many SMA patients, when compared to placebo or no treatment, nusinersen has been shown to increase the availability of SMN protein, leading to clinically meaningful improvements in muscle function. Risdiplam is a systemically distributed small molecule, administered once daily orally in liquid form, that mod-

ifies SMN2 pre–messenger RNA splicing. Our local clinical experience in broad spectrum of SMA patients and data from clinical trials are showing that treatment with risdiplam resulted in a significant improvement in overall survival and motor function in patients with SMA.

Keywords: Spinal muscular atrophy, innovative therapy

Dimitrije M. Nikolić

UNIVERSITY EDUCATION AND CAREER

1988-1994	Medical Studies at Belgrade University School of Medicine, graduated in February 1994 with average mark 9,84/10,00.
1990-1994	Teaching assistant on Medical Chemistry and Histology with embriology
1994-1995	GP medical residency as a resident of Belgrade University School of Medicine
1994-1996	Scholarship holder of Republic Ministry for Science and Technology of Serbia; Post graduate studies
1995-1999	Residence training in pediatrics at the University Children's Hospital Belgrade
1999 -	Full time specialist of pediatrics at the Neurology department at the University Children's Hospital. Consultant on Intensive care unit (pediatric and surgical) and neonatology
1999.	Master of science degree at the Belgrade University School of Medicine with Master thesis: Evaluation of staturo - ponderal and psychomotor development of children with con genital hearth defects
2009.	PhD degree at Belgrade University School of Medicine in pediatric neurology/epileptology with PhD thesis: West Syndrome of different etiology: correlation of neurological, neurophysiological and neuroradiological findings
2000-2010.	Assistant professor of pediatrics at the Belgrade University School of Medicine
2011-2016	Associate professor of pediatrics at the Belgrade University School of Medicine
2017-	Professor of pediatrics at the Belgrade University School of Medicine
2011-	Consultant for pediatric neurology at the Institute for Neonatology, Belgrade

NEONATAL SCREENING (NBS) FOR SPINAL MUSCULAR ATROPHY (SMA) IN SERBIA – FIRST RESULTS

Dimitrije Nikolić, Kristina Jovanović
University Children's Hospital Belgrade

Dimitrije Nikolić
Belgrade University Medical Faculty

Miloš Brkušanin, Jelena Karanović, Dušanka Savić-Pavićević, Nemanja Garai
Centre for Human Molecular Genetics, University of Belgrade-Faculty of Biology, Belgrade, Serbia

Tamara Šljivančanin Jakovljević
Clinic for Gynecology and Obstetrics "Narodni Front"

Introduction: SMA is rare, monogenic autosomal-recessive neuromuscular disorder characterized by progressive muscular weakness and atrophy.There are 4 types of disease, regarding on age of onset, clinical presentation, number of SMN2 copies. Until recently, SMA type 1 was recognized as a leading cause of genetic mortality in infancy. In other types severe permanent invalidity and shortened life expectancy is present as well as impaired quality of life.

Thanks to new therapeutic options, clinical course of treated patients is signifficantly changed. Nowadays, there are three avalilable therapies that can „modify" natural course of disease, descreasing level of invalidity and improving of overall life quality. It is well known that over 90% of alpha motoneurons loss their function within first few months upon birth, if not treated. This is usually the time when symptoms became more obvious, but unfortunately neuronal damage is permanent. That's why, starting the treatment is needed before first symptoms occur in order to have an adequate achieving of motor milestones (results from Nurture, Rainbowfish and SPR1NT studies).

Having in mind all those facts, NBS is found to be very useful in diagnosing those patients in presymptomatic phase.
NBS (pilot project) started in April 2022. (2834 pts tested, 2 diagnosed; then older brother of 1st patient as a third asyptomatic; 4 copies for siblings, 3 copies for the other one).
Concluision: Diagnosing presymptomatic patients and immediate start of therapy in presymptomatic phase of disease could give an excellent perspective for those patients in all aspects of their lives.

Key words: Neonatal screening, spinal muscular atrophy, Serbia, pilot project

Tanja Loboda

After finishing Medical faculty in Ljubljana and postgraduate medical training in pediatrics, she first worked as a pediatrician in primary health care. Since 2017 she is employed in Children's Hospital Ljubljana at the Department for child, adolescent and developmental neurology. Her special interest are children with neuromuscular diseases, developmental delay and neurofibromatosis. She is a member of Medical Chamber of Slovenia, Slovenian society for health care and European Pediatric Neurology Society.

DUCHENNE MUECULAR DYSTROPHY – FROM EARLY DIAGNOSIS TO NOVEL TREATMENTS

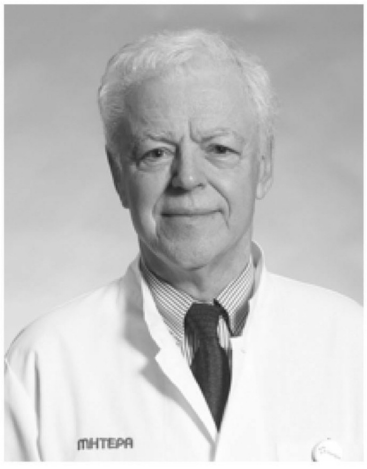
Tanja Loboda
University Children's Hospital, Ljubljana, R. Slovenia.

Duchenne muscular dystrophy (DMD) is the most common neuromuscular disease in childhood. It is an X-linked recessive disesase, caused by mutations in the dystrophin gene, primary resulting in skeletal and heart muscle abnormalities. It occurs in one in 3000-5000 male births. In most boys the first signs of the disease appear as progressive muscle weakness between the ages of 3 and 5 years. Muscle weakness is more pronounced in proximal muscles of the lower limbs and most children become wheelchair-dependent between the age of 11-12 years. The progressive respiratory muscle failure results in chronic respiratory insufficiency and the patients require ventilatory support.By the end of the second decade, most children develop cardiomyopathy.

There is no cure for the disease, but treatment with corticosteroids prolongs ambulation, reduces incidence in severe scoliosis and tempers pulmonary and cardiac decline. Several drugs are being developed, including exon-skipping treatment and novel genetic therapies. Patients with nonsense mutation in the dystrophin gene can be treated with ataluren, a small molecule compound.

The treatment of DMD patients requires a multidisciplinary approach, which coupled with steroid treatment, physical therapy, supportive treatment and specific aids, has led to increased longevity and the improvement of quality of life in these patients.

Key words: muscular dystrophy, dystrophin gene,
novel therapies



Constantinos J. Stefanidis

Current position: Head of Pediatric Nephrology, “Mitera” Children’s Hospital. Athens, Greece.

Research interests: Pediatric dialysis, nutritional and bone disorders management of children with Chronic Kidney Disease, Acute Kidney Injury in children

Interesting facts:

1973	Medical Degree (Magna Cum Laude), valedictorian of the class. University of Athens, Greece.
1978	Certified Pediatrician (Greece).
1978	Certified by the College of Physicians and Surgeons of Ontario Canada.
1982	American board of pediatrics eligibility.
1984	PhD (Magna Cum Laude), University of Athens, Greece.
2021	Fellow of the European Society of Pediatric Nephrology.
1974-78	Resident in Pediatrics, University of Athens, Greece.
1978-82	Resident in Pediatrics and Fellow Western University and University of Toronto.
1982-04	Consultant Pediatric Nephrologist, “A. and P. Kyriakou” Children's Hospital, Athens, Greece.

2004-18	Head of Pediatric Nephrologist, “A. and P. Kyriakou” Children's Hospital, Athens, Greece.
2018-	Head of Pediatric Nephrology, “Mitera” Children’s Hospital. Athens, Greece.
1997	President of the 31st Meeting of European Society of Pediatric Nephrology(ESPN)
1999-02	Councilor of ESPN
2007-11	Chair of the Tertiary Group of European Academy of Pediatrics.
2009-	Editor of the journal "Pediatric Nephrology" of the International Pediatric Nephrology Association(IPNA)
2010	Chair of the Organizing Committee of the 3rd Congress of the European Academy of Pediatric Societies, Copenhagen 2010.
2012-19	ESPN-ERA Registry representative.
2013-21	Board member of the Dialysis Working Group of ESPN.
2020-	Associate Editor of the journal Frontiers in Pediatrics - Pediatric Nephrology.

104 publications in peer-reviewed medical journals

3056 Citations (August 2022), h-index: 31, i10-index: 68

EPIDEMIOLOGY OF HYPEROXALURIA TYPE 1 (PH1)

Constantinos J Stefanidis
"Mitera" Children's Hospital, Athens, Greece.

PH1 has a prevalence ranging from one to three patients per million population. The incidence rate of PH1 is ~1:100 000 live births per year in Europe.This rate is possibly underestimated since PH1 is reported as~1% of pediatric end-stage kidney disease (ESKD) in registries from Europe and US. In addition, an overall PH carrier frequency of 1:71 is reported with a predicted prevalence of 1:58,243 as recently calculated from the 22 known mutant alleles. Obviously, PH1 is still underdiagnosed. Underdiagnosis possibly occurs because of the phenotypic heterogeneity, ranging from infantile nephrocalcinosis with kidney failure to only occasional stone formation (similar to idiopathic stone disease), and unfamiliarity with this rare monogenic disorder.
Children with earlystage PH1 usually have recurrent kidney stones and nephrocalcinosis. Progressive decline in kidney function occurs in a later stage.
The deposition of oxalate in patients with PH1 is responsible for systemic manifestations as bone pain, pathologic fractures, joint involvement, chondrocalcinosis,vascular problems(nonhealing ulcers), heart manifestations (conduction defects, heart blocks, and cardiomyopathy), nervous system and hematologic involvement.
To diagnose PH1 a 24-h urine collection for oxalate, creatinine and glycolate is required. However, plasma oxalate (POx) should be measured when GFR is <60 mL/min/1.73m 2
Genetic testing is required in children with clinical and biochemicalfindings of PH1
Early medical treatment of PH1 is essential to decrease the oxalate level and prevent deterioration of renal function.

Key words: primary hyperoxaluria, epidemiology,
kidney stones, nephrocalcinosis

COL4A NEPHROPATHIES IN GREEK CHILDREN

Constantinos J Stefanidis
"Mitera" Children's Hospital. Athens, Greece.

Familial microscopic haematuria (FMH) of glomerular origin occurs relatively frequently in Greece. It is well documented internationally that estimated population prevalence is ~1%.
What we learned during the last years is that 40–50% of cases with persistent or recurrentFMH is caused by defective synthesis of collagen type IV due to heterozygous mutations in the COL4A3 or COL4A4 genes. The majority of these children have a normalkidney function, and minimal or no proteinuriaduring the diagnosis of the disease. However, they might deteriorate in the future. In contrast, Alport syndrome (AS) is a severe hereditary nephritis. 85% of cases have X-linked AS (XLAS) caused by mutations in COL4A5.14% of cases have autosomal recessive Alport syndrome (ARAS), due to homozygous or compound heterozygous mutations in COL4A3 or COL4A4. Finally, ~ 1% of patients have an autosomal dominant AS (ADAS), carrying heterozygous COL4A3/A4 mutations.Some of these patients have rearing impairment and/or ocular lesions. Unfortunately, the majority of these children progressively develop severe kidney failure, frequently associated with focal and segmental glomerulosclerosis (Matthaiou A et al.2020 https://doi.org/10.1093/ckj/sfz176).
In Greece there are teAms of experts (clinicians, pathologists, geneticists) managing children with COL4A nephropathies. Children with persistent or recurrent FMH have a whole exome sequencing study to document a possiblemutation in the COL4A3 or COL4A4 genes. These patients are managed by Pediatric Nephrologists usually in Pediatric Hospitals
All these patients have ear (audiology) and eye(ophthalmology) investigation. Renal biopsy with EM is also available. Kidney transplantation for children is also performed in Greece. It will be important to conduct clinical trials to document the local epidemiological features.

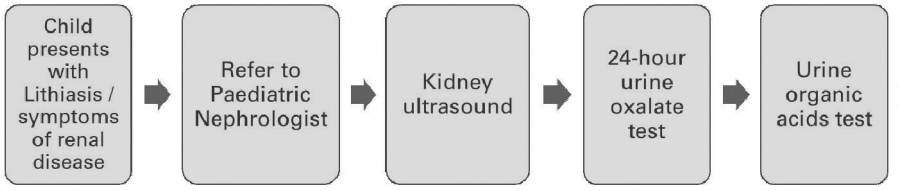
Key words: Alport syndrome, hematuria, children

Maria Gaydarova

Current position: Head of Paediatric Nephrology and Dialysis Clinic, at the University Paediatric Hospital “Ivan Mitov”, Sofia, Bulgaria.

Research interests: Assoc. Prof. Dr. Maria Gaydarova has a specialty in Paediatric and subspecialty in Paediatric Nephrology. She has a special interest and focus on Intensive care of children on hemo- and peritoneal dialysis, Management of infectious renal diseases in children, Screening for renal anomalies, Management of end-stage renal failure, Preparing children for renal transplantation. She has published a total of over 60 scientific papers and publications in national and international journals.

Memberships: Assoc. Prof. Dr. Maria Gaydarova, MD is a member of the Rare Disease commission in University Paediatric Hospital “Ivan Mitov”, Sofia, Bulgaria. She is also a member of the Bulgarian Society of Nephrology, Bulgarian Paediatric Society. She obtains educational course at European Society of Pediatric Gastroenterology Hepatology and Nutrition(ESPGHAN) and is a member at European Society for Paediatric Nephrology.



STATUS OF PH1 IN BULGARIA AND PATIENT CASES

Maria Gaydarova
Pediatric Department "Nephrology and dialysis", Specialized Children's Hospital "Prof. Dr. Ivan Mitev", Sofia, Bulgaria.

There is no register for PH1 incidence in Bulgaria. For the last 30 years in Department of nephrology and dialysis in University Paediatric hospital in Sofia, 5 children with PH1 were diagnosed which gives prevalence of < 1 case per million population.
PH1 diagnostic journey in Bulgaria:

- Investigation is typically triggered by symptoms of kidney stones or impaired renal function
- Patients are often sent to specialised paediatric centres for further testing
- Genetic testing is generally undertaken for all patients with high oxalate levels
- PH1 patients being managed are largely diagnosed by the treating Paediatric Nephrologists

Bulgarian PH1 Clinical cases
Clinical case 1: girl, now 6 years old, first symptoms of PH1:
6 months of age: failure to thrive - severe anemia – chronic kidney disease, Bell's palsy at 3 years of age, eGFR:14/ml/min / 1,73m2 (Shwartz). Renal echo: diffuse nephrocalcinosis, Kidney biopsy - Collapsing variant of FSGS.
Genetic testing NGS: two heterogenous pathogenic variants of AGXT, c.534C>G(p.Cys178Trp) c.731T>C (p.Ile244Thr) –sensitive to pyridoxine treatment. Treatment: NaHCO3, Pyridoxine, Calcitriol,Erythropoietin,Fe.

Presenting symptoms – at age of 6 months - CKD of unknown etiology; at age of 2 years - Genetic diagnosis: PH 1;at age of 6 years - Uox - 587 U/mmolCr (0-352), Pox: 49µmol/l (3-11), Uglycolate - 144 U/mmolCr (0-92), Oxalosis – bone, eyes and ESKD. Start treatment with lumasiran – 04.2022

Clinical case 2 - infant, boy, now 3 years old: First symptoms of PH1: 6 months of age: failure to thrive - severe anaemia – ESKD, Bell's palsy at 2 years of age. eGFR: 4/ml/min /1,73m2 (Shwartz). Renal echo: diffuse nephrocalcinosis.

Genetic testing NGS: two heterogenous pathogenic variants of AGXT - c.33 dup (p.Lys12Glnfs*156); c.969_970TG[1])Val324Glyfs*7.

Treatment: PDPresenting symptoms: ESKD of unknown etiology,at age of 6 months;at age of 1 year - Uox - 772 U/mmolCr (0-352), Uglycolate - 241 U/mmolCr (0-92); At age of 2 years: Oxalosis – bone, eyes; ESKD.Start treatment with lumasiran

Clinical case 3 : boy, now 9 years old. First symptoms of PH1: 2 years of age: collapse, gross hematuria, flank pain, at 6 years of age same symptoms, at 8 years of age – hydronephrosis – JJ stent, normal renal function. Renal echo: nephrolithiasis, nephrocalcinosis. Genetic testing NGS: homozygous pathogenic variant of AGXT - c.331C>T (p.Arg111*) AGXT . Treatment: NaHCO3, Magnesium citrate,Calcitriol, Erythropoietin, Fe, Hyperhydration

Presenting symptoms: at age of 2 years -normal renal function,
Uox - 941 U/mmolCr (0-352), Uglycolate - 466 U/mmolCr (0-92));at age of 7 years old - Genetic testing - PH1; at age of 9 years - Oxalosis – not detected, chronic kidney disease, eGFR: 20/ml/min /1,73m2 (Shwartz). Start treatment with Lumasiran in AUG 2022

PH is a rare disorder of glyoxylate metabolism characterized by overproduction of oxalate. There are 3 types of PH, classified by the enzyme affected; PH1 is the most common (70–80% of PH cases) and most severe. Delays in diagnosis are common because the primary clinical manifestations are heterogeneous and unspecific. There is a significant unmet medical need for additional management options for patients with PH1

СИНДРОМ НА АЛПОРТ В БЪЛГАРИЯ

Доц. М. Гайдарова
Клиника по детска нефрология и диализа, СБАЛ по детски болести „Проф. Иван Митев“, София, България, Катедра педиатрия, МУ-София,

Синдромът на Алпорт представлява най-честата наследствена нефропатия причинена от мутации в гени отговорни за биосинтеза на колаген тип IV, водещи до промени в структурата и функцията на гломерулнатабазална мембрана (ГБМ). Унаследяването може да бъде Х-свързано със засягане на мъжкия пол, автозомно – рецесивно (АР) и автозомно - доминантно (АД). Клиничното протичане е основно с бъбречна изява, с данни за микроскопска хематурия и в последствие протеинурия и артериална хипертония. Екстраренални прояви са невросензорна загуба на слуха и различни очни аномалии. Диагнозата се поставя на базата на щателна фамилна анамнеза, лабораторни данни за хематурия и бъбречно засягане, бъбречна биопсия с електронна микроскопия и генетично изследване. Лечението се състои в намаляване прогресията до краен стадий на бъбречно заболяване. Пациенти от мъжки пол с Х-св. унаследяване и пациенти от двата пола с АР унаследяване неизбежно прогресират до краен стадий на бъбречно заболяване преди 40 годишна възраст, също така повечето развиват сензоневрална глухота.
В България децата с Алпорт синдром се диагностицират и проследяват в единствената за страната Клиника по детска нефрология и диализа на СБАЛ по детски болести „Проф. Иван Митев“ гр. София.За момента в клиниката се проследяват около 10 деца с Алпорт синдром. Заболяването е заложено в учебния план както в обучението по медицина, така и в следдипломните квалификации по педиатрия и детска нефрология. За съжаление вмомента в България не се извършва бъбречна трансплантация при деца.

Goran Cuturilo

University Children's Hospital,
University of Belgrade, Serbia

Goran Cuturilo received his M.D. degree from the Medical Faculty, University of Belgrade in Serbia (9,46/10). He took his residency in Pediatrics and fellowship in Clinical Genetics at the University Children's Hospital in Belgrade. He was also trained in Molecular Genetics at the University of Belgrade, Faculty of Biology, Department of Molecular Biology where he received his Ph.D. degree. He is Associate Professor of Pediatrics and Clinical Genetics and Head of Department of Medical Genetics at the University Children's Hospital. Dr. Goran Cuturilo has been working in the field of Clinical Genetics for 17 years, including neurogenetics, inborn errors of metabolism, dysmorphology, cardiogenetics, cancer genetics, and other. He's been providing outpatient and inpatient genetic consultations for large number of children and adult patients, and has significant experience in genomic test application and interpretation (WES, WGS, array, etc.). He is also involved in enzyme replacement therapy application.
He has published more then 100 scientific reports, and the most prominent are available at
https://pubmed.ncbi.nlm.nih.gov/?term=cuturilo&sort=date

IMPORTANCE OF DIAGNOSTIC OF RARE DISEASES USING ENZYME AND GENETIC TESTING

Goran Cuturilo
University Children's Hospital, Belgrade, Serbia

The lysosomal storage diseases (LSD) are a group of inherited metabolic disorders caused by enzyme deficiencies within the lysosome metabolism resulting in accumulation of undegraded substrate. This usually leads to a broad spectrum of clinical manifestations. Examples of LSD include the mucopolysaccharidoses, Pompe disease, Gaucher disease, Fabry disease, Niemann-Pick disorders, neuronal ceroid lipofuscinoses.
To diagnose LSD blood sample should be sent for enzyme activity, and decreased enzyme activity confirms the diagnosis.
Enzyme activity could be measured for a single LSD, or simultaneously for different LSD enzymes (panel enzyme testing) when features of a patient do not allow for a specific diagnosis.
Molecular genetic testing should also be performed for purposes of genotype-phenotype correlation, family planning and other genetic counselling considerations. More and more frequently we use exome sequencing covering wide variety of LSD and other metabolic genes. Increasing number of LSD patients have been diagnosed using exome sequencing.
Current protocols for LSD-patient follow up also involve more and more blood markers which can be routinely used in patient management reflecting disease severity and therapeutic outcome.

Key words: rare disease, diagnostics, enzyme activity

Timothy M Cox

Timothy Cox is Professor of Medicine Emeritus at the University of Cambridge, Life Fellow of Sidney Sussex College and Honorary Consultant Metabolic Physician at Addenbrooke's Hospital in Cambridge. A founding Fellow of the UK Academy of Medical Sciences, he is a Member of Academia Europaea.

Graduating from the London Hospital Medical College and internships, he took up a two-year post in Pathology, later to return to clinical training in London and Oxford and scientific training at Chelsea college, University of London, the Royal Postgraduate Medical School (now Imperial College London), Sir William Dunn School, Oxford and the Massachusetts Institute of Technology USA. He has held senior positions internal medicine, gastroenterology and hematology. After taking up the chair in Medicine at the University of Cambridge in 1989, he founded and directed the first MB/PhD programme in the UK. With a specialist clinical interest in inherited metabolic diseases, including lysosomal disorders, his current research involves the pathogenesis of sphingolipid diseases and advanced therapies including gene transfer – with the ultimate aim of targeting the CNS manifestations in sphingolipidoses, he conducted several pivotal trials of substrate reduction therapy. Supported by the UK Medical Research Council, Wellcome Trust, the National Institute for Health Research and several charities.

Professor Cox has published more than 300 original research articles and with John Firth and Sir David Warrell (latterly Christopher Conlon), he edits the Oxford Textbook of Medicine (6Th Edition, Oxford University Press, 2020).

GAUCHER DISEASE MATTERS

Timothy M Cox,
Department of Medicine, University of Cambridge, UK

Special legislation across the world has recognized that rare diseases merit serious attention. Not only are there financial incentives, rare diseases with a strong genetic cause offer a concrete opportunity to find new and effective drugs. This 'big effect-size' relates to the modern scientific interest in identifying mutations in human DNA: pretty gems remain attractive even after we find them and the jewellery in which glittering diamonds and other jewels are set can be almost equally precious...

Beyond the potential for commercial success, there is great richness in each rare disease. For hundreds of years, physicians have realized that intensive knowledge of rare diseases is worthwhile – not only because of the creative revelations they provide but because of the humanitarian value of this activity. Advances in genetics and molecular cell biology of rare conditions often provide insights into the complexities of whole families of diseases that are apparently unrelated but share common underlying processes. Above all, there are opportunities for better holistic care of patients beyond the simple magic of targeted therapy - from small beginnings, huge scientific and political advances can, and have been be made for the general good.

So it is in the orphan field of lysosomal diseases: biopharmaceutical inventions for Gaucher disease have been multi-faceted and the portfolio is rich. There are thousands of rare disorders but today Gaucher disease stands with cystic fibrosis and haemophilia A and B as the most exceptionally endowed for treatment. Formerly treated by haematopoietic stem-cell transplantation, there are now five drugs approved globally with three distinct modes of

action. Not only have patients gained clear therapeutic benefit but general investment in the field of lysosomal disease has been secured with improved services and guidelines for clinical practice. The drugs are expensive but the gains for health are exceptional and clear – tireless efforts by advocacy groups, politicians and physicians have enabled treatment to be available for patients in many regions, including modern Balkan countries.

Gaucher disease is characterized by diverse clinical and pathological expression. In 1882, Dr Gaucher was unaware of the skeletal and neurological manifestations of the eponymous condition by which he is remembered; only now, is the dynamic significance of sphingolipids fully recognized. However, as a multisystem disorder involving complex biochemical and immunological changes, much of its pathogenesis remains elusive. The protean systemic manifestations of Gaucher disease are increasingly apparent in the therapeutic era. Long-term follow-up and therapeutic monitoring of patients in expert centers has provided unprecedented opportunities for clinical research. When it is established, the disease has diverse effects: on energy supply and metabolic rate; bile composition; the skeleton and immune system. There is an increased cancer risk (especially lymphoma and multiple myeloma), as well as pulmonary and neurological manifestations that occur at varying ages. For the public health, there is an ill-understood genetic relationship between Lewy body and Parkinson disease – this phenomenon extends across other lysosomal diseases but in most populations, the linkage to otherwise healthy heterozygotes who carry one mutant disease allele, is the strongest. Our aim in this presentation is to survey Gaucher disease in children and adults as seen in different populations. We will discuss disease frequency; the course of the disease; how it is suspected – and how best diagnosed. Effective, disease-modifying treatment is available and so the opportunity to intervene with specific and prompt treatment, places high

expectations on modern doctors. Patients benefit from timely intervention: should therapy be delayed, clinical deterioration is inevitable.
Finally, a look to the future... Scientific developments and fascinating therapeutic research continue to expand knowledge of this disease and sustain the hope of further clinically articulate advances.

Key words: Gaucher disease, timely diagnosis, genetics, research, cancer risk

Dijana Plaseska-Karanfilska

Dijana Plaseska-Karanfilska is employed at the Research Centre for Genetic Engineering and Biotechnology "Georgi D Efremov", Macedonian Academy of Sciences and Arts, Skopje, Macedonia where she holds a position of Full Professor and Head of laboratories for Genomics and Molecular diagnostics. She is also involved in undergraduate, master and PhD studies at the University “St. Cyril and Methodius” in Skopje. Since 2021 she is a member of Academia Europaea and since 2022 a Corresponding member of the Macedonian Academy of Sciences and Arts. She has been engaged in the molecular diagnostics of inherited, malignant and infectious diseases and has contributed to the molecular characterization of different monogenic diseases in the Republic of Macedonia and translation of a number of molecular genetic tests to clinical practice. She has coordinated an infrastructural project that has strengthened the national research capacities in the fields of genomics and proteomics.

She has published more than 150 papers in peer-reviewed journals, and has participated with more than 200 presentations on different scientific events. She is editor of the Balkan Journal of Medical Genetics, and president of the Macedonian Society of Medical Genetics. Her recent research interest focuses in reproductive genetics, breast cancer and rare diseases.

GENETICS OF GAUCHER DISEASE

Dijana Plaseska-Karanfilska
Research Centre for Genetic Engineering and Biotechnology "Georgi D. Efremov", Macedonian Academy of Sciences and Arts, Skopje

Gaucher disease (GD) is caused by deficient activity of β-glucocerebrosidase due to homozygous or double heterozygous pathogenic variants in the GBA gene. In addition, heterozygous GBA pathogenic variants represent the most common genetic risk factor for Parkinson's disease.
This study was initiated with an aimed to determine the GBA mutational spectrum among GD patients and the frequency of GBA pathogenic variants among the general population from RN Macedonia.
A total of 18 GD Type 1 patients, from 13 different families of Albanian (9), Macedonian (3) and Bosnian (1) ethnic origin were studied using several different methods: direct DNA sequencing of GBA exons, Multiplex Ligation Probe-Dependent Amplification (MLPA), and next-generation sequencing (NGS) on MiSeq using Illumina TruSight Inherited panel. The GBA carrier frequency was evaluated among patients with rare diseases that have undergone WES analyses. Allele-specific amplification was also designed to screen for five common GBA mutations among the general population.
A total of eight different GBA pathogenic variants were detected. The most common variant was c.1226A>G (N370S), representing60% of GBA alleles, followed by c.882T>G;1342G>C double allele (H255Q;D409H). The H255Q;D409Hwas present exclusively among patients of Albanian ethnic origin. One novel GBA variant (c.392A>G) was detected in one GD patient as a de novo event. A total of 16 carriers of pathogenic GBA variant were detected among 500 non-Gaucher patients with rare diseases.
In conclusion, in RN Macedonia, GD is present predominantly among Albanian population. One in 32 individuals from the gen-

eral population in our country carries a pathogenic GBA variant. The high GBA carrier frequency suggests that there are asymptomatic and/or undiagnosed GD patients. The knowledge of GBA mutational spectrum will facilitate the genetic testing among GD patients and will allow for carrier screening among patients with Parkinson's disease and other at risk individuals.

Key words: Gaucher disease, genetics, mutation, β-glucocerebrosidase

Adrijan Sarajlija

AdrijanSarajlija is a paediatrician and clinical geneticst based in Belgrade, Serbia. He graduated in 2001 at the University of Belgrade, School of Medicine, in 2009 completed specialization in pediatrics and later subspecialized in clinical genetics. His PhD degree was earned in the area of neuroepidemiology at the University of Belgrade. Dr Sarajlija has extensive experience in diagnosing and treating a whole spectrum of genetic disorders, with emphasis on lysosomal storage disorders, glycogen storage diseases, mitochondrial disorders, hereditary bone disorders and neurodevelopmental disorders. International scholar experiences include observerships at Duke University and Heidelberg University and numerous courses in inborn errors of metabolism across Europe. Dr Sarajlija authored a significant number of articles on diverse genetic disorders for renowned scientific journals. He teaches pediatrics at the University of Belgrade School of Medicine.

TREATABLE INHERITED METABOLIC DISEASES

Adrijan Sarajlija
Mother and Child Health Care Institute of Serbia, University of Belgrade School of Medicine

During recent decades we have witnessed the expansion of treatment possibilities for inborn errors of metabolism (IEM). Very different modes of management have been employed in an effort to improve survival and quality of life of IEM patients. Enzyme replacement therapy (ERT) emerged as primary treatment modality for lysosomal storage diseases (LSDs), gaining worldwide recognition for its success in Gaucher disease patients. This success paved the road for the development of ERT for the whole spectrum of LSDs, with different modes of application. Specific oral drugs for LSDs have been designed to reduce the substrate production, and this approach could be used solely or concomitantly with ERT. Pharmacologic management of IEMs includes also chaperone drugs, cofactors, but also drugs repurposed for use in rare metabolic disorders (e.g. successful use of antidiabetic drug empagliflozin in treatment of neutropenia associated with glycogen storage disease type 1b). Organ transplantation is applied in treatment of heterogeneous IEM (e.g. bone marrow transplantation in mucopolysaccharidosis type 1, liver and renal transplantation in glycogen storage diseases and organic acidemias etc.). Efforts have been made to administer liver stem cells in patients with urea cycle disorders. Introduction of CRISPR/Cas9 technology to clinical practice promises further advancement and broadening of IEM treatment in years to come. Rarity of specific disorders remain the main obstacle for creating larger clinical trials. Therefore, creating international registries and expert networks, newborn screening expansion and raising awareness of the importance of early diagnosis and treatment of IEM should be of the highest priority.

Jasmina Ćomić

WORK EXPERIENCE

01/03/2020 – Current Scientific Associate Institute of Human Genetics at the Klinikumrechts der Isar, Technical University of Munich

Main activities and responsibilities:

- The scientific focus of the work is the molecular genetic analysis, mapping of new genes and identification of previously unknown modes of inheritance in genetically caused kidney diseases

EDUCATION AND TRAINING

02/2019 – 03/2019 Internship
Clinical Center of the University of Sarajevo
Department of Clinical Pathology, Cytology and Human

Main subject / occupational skills covered:

- Histological specimens made from human cells and analyzed
- Laboratory processes in genetic analysis carried out (leukocytes differentiated and their lysis)
- Operated with laboratory instruments

02/10/2017 – 03/10/2018 Master of Science (MSc) in Biology – Genetics Faculty of Mathematics and Natural Sciences Sarajevo
Main subject / occupational skills covered:

- Topic of the master thesis: "Investigation of the influence of gender on the frequency of the A1298C mutation in the Bosnian and Herzegovinian population".

07/10/2013 – 13/07/2017 Bachelor of Science (BSc) in Biology – GeneticsFaculty ofMathematicsand Natural Sciences Sarajevo
Main subject / occupational skills covered:

- Topic of my Bachelor thesis: "Population genetic and genealogical analysis of tongue rolling ability in the student population".

CONFERENCES AND SEMINARS

16/03/2022 – 18/03/2022 32nd Annual Meeting of the German Society for Human Genetics - 32. Jahrestagung der Deutschen Gesellschaft für Humangenetik (GfH)

- Congress Center Würzburg, On Site Poster Presenter

30/09/2021 – 02/10/2021 52 Annual Meeting of the Society for Pediatric Nephrology

- Online Online Poster Presenter

16/09/2021 – 19/09/2021 53rd Annual Scientific Meeting of European Society ForPaediatric Nephrology" Amsterdam, Netherlands

- Pitch Poster Presenter

22/06/2022 – 25/06/2022 54th Annual Scientific Meeting of European Society For Paediatric Nephrology Ljubljana, Slovenia

- Poster Presenter

HONOURS AND AWARDS

19/09/2021
In recognition of the best scored oral pitch abstract authorship
Awarding institution: European society for paediatric nephrology.

PUBLICATIONS

2022
Ćomić J, Riedhammer KM, Günthner R, Schaaf CW, Richthammer P, Simmendinger H, Kieffer D, Berutti R, Tasic V, Abazi-Emini N, Nushi-Stavileci V, Putnik J, Stajic N, Lungu A, Gross O, Renders L, Heemann U, Braunisch MC, Meitinger T and Hoefele J

2022
The multifaceted phenotypic and genotypic spectrum of type-IV-collagen-related nephropathy—A human genetics department experience. Front. Med. 9:957733. doi: 10.3389/fmed.2022.957733

GENETICS OF ALPORT SYNDROME – MUNICH EXPERIENCE

Jasmina Ćomić,Korbinian M. Riedhammer,Julia Hoefele
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Disease-causing [(likely) pathogenic and pathogenic] variants in COL4A3-5 are associated with type IV collagen-related nephropathy, which includes Alport syndrome (AS) and thin basement membrane nephropathy (TBMN). The first symptoms of individuals with AS are microscopic hematuria (MH) followed by proteinuria leading to renal failure (90% require dialysis by age <40 years). In addition, sensorineural hearing impairment and ocular abnormalities may be observed. In contrast, individuals with TBMN, an outdated histology-derived term, present with MH, only some of them develop kidney failure (> 50 years of age).Early diagnosis of type IV collagen-associated nephropathy is essential for optimized therapy and slowing of the disease.
Our studies on type IV-collagen-related nephropathy within the last couple of years could show that affected individuals have a complex clinical and genetic picture and implicates that refined nomenclature and interdisciplinary collaboration between clinicians and geneticists are key to optimizing patient care. Furthermore, in female individuals with AS a correlation between the clinical phenotype and X-inactivation could not be observed suspecting other genetic modifiers shaping their phenotype.

Key words: Alport syndrome, COL4A3-5, genetics, X-inactivation

The Munich Microscopic Hematuria Project

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Hematuria is characterized by the presence of blood in the urine. Two forms can be differentiated, i) microscopic hematuria (at least three red blood cells per high-power field on urinalysis) and ii) macroscopic hematuria (visible blood in urine). There are several known causes that can lead to hematuria, including Alport syndrome (AS), thin basement membrane nephropathy (TBMN), IgA nephropathy, menstruation, febrile illness, nephrolithiasis, and malignancies. Although both disorders, AS and TBMN, are characterized by a defective GBM, TBMN needs to be distinguished from Alport syndrome. Genetic data on TBMN comes from analysis of the genes COL4A3/COL4A4 and sequencing of specific single-nucleotide polymorphisms in large multigenerational TBMN pedigrees and not from unbiased exome- or genome-wide rare variant burden analyses
It was our aim to perform exome sequencingin 300 individuals with clinically-ascertained TBMN in order to conduct an exome-wide burden analysis of rare variants compared to control exomes (Munich Exome Server, > 26,000 exomes).DNA of all 300 individuals

with hematuria as well as of all controls have already been collected and sequenced.
This study will provide answers to the question in which genes rare coding variants are enriched in TBMN along with odds ratio calculations of rare variant burden (non-synonymous variants). This data is important for genetic counselling and clinical management of individuals with TBMN and may give further insights in the genetic architecture of TBMN and hematuric glomerular disease in general. The study will be the first of its kind in TBMN research, a disorder common in the general population with a high economic impact.
The calculation of the burden is ongoing, therefore final data cannot present so far. A large follow-up study is planned and therefore further affected individuals and families can be further included.

Aleksandra Janchevska

Aleksandra Janchevska is born in Skopje. After graduating from the Medical Faculty she continued her education in the field of children's diseases.
She completed pediatric training and master's studies in pediatrics with a thesis on new protocols for the treatment of children with lymphoblastic leukemia.
Since 2006 Aleksandra works at the Department of Endocrinology and genetics at the University Children's Hospital in Skopje. She developed her professional skills in pediatric endocrinology during numerous educational and clinical fellowships and seminars (ESPE-Great Ormond Street Hospital, EASD, EASO etc.).
She has had a PhD since 2018.
She actively participated as a co-investigator in 6 multicentre - randomised research studies with diabetic patients, patients with growth hormone deficiency (GHD) and patients with craniopharyngioma and 2 national national research studies with obese patients (children and adolescents) and children with anemia.
Aleksandra is a member of the European Society of Pediatric Endocrinology (ESPE) Obesity Working Group, European Academy of Pediatrics (EAP), National and European Association of Studies in Obesity (EASO), and World Obesity Federation (WOF).
Currently, Aleksandra is an assistant professor at the Medical Faculty in Skopje and a pediatric endocrinologist in UCH, Skopje.

THE OVERGROWTH SYNDROMES – THE STORY OF A PATIENT WITH BECKWITH WIEDEMANN SYNDROME (BWS)

Aleksandra Janchevska
University Children's Hospital, Medical Faculty, Skopje, North Macedonia

BWS is an overgrowth syndrome with predisposition for embryonal tumors and with an overall risk estimated at 7.5%. The prevalence of tumors in these children is greatest in the first 8 years of life. The tumor predisposition in patients with BWS, especially for Wilms tumor, is strongly related with an imprinting status of the H19-DMR (H19-differentially methylated region) and KvDMR1 on chromosome 11p15.5.
An 8.5-year-old boy with clinical presentation of BWS has been regularly followed up every 3 months since the age of 2 months. The molecular analysis has been performed with MLPA (multiplex ligation-dependent probe amplification) in the Center for Human Genetics, Bioscientia Institute for Medical Diagnostics Ingelheim, Germany*. The three monthly monitorings included biochemical analyses, especially serum glycemia and alfa-fetoprotein concentration, followed by an ultrasound scan survey.
At the age of 5-years he had (+2.5 SDS) height and (+2.57 SDS) weight, an adequate intellectual development for his age and normal values of serum glycemia and alfa-fetoprotein concentration at the last follow-up. The performed abdominal ultrasound revealed a presence of a tumor mass with a diameter of 68mm in the left kidney although the MLPA detected a normal methylation pattern for H19-DMR and hypomethylation of KvDRM1 (LIT1) in the chromosome 11p15.5 region with an estimated tumor risk of 1-5%. The abdominal CT scan confirmed the presence of a solitary tumor mass in the left kidney, 80x65x87mm, very suggestive for a nephroblastoma. The left nephrectomy followed by chemotherapy have been done successfully. Now, at the age of 8.5-years he is the best mathematician in his class with (+ 2.9 SDS) height and (+ 5.0 SDS) weight.

The aim of our study is to present a patient with BWS who developed Wilms tumor at the age of 5 years, detected at his usual 3-monthly clinical monitoring. It is unexpected in a child with hypomethylation of KvDRM1 (LIT1) in the chromosome 11p15.5 region and with a low tumor risk of 1-5%. The regular and adequate monitoring in patients with BWS is not only necessary but also lifesaving.

Acknowledgement:
We would like to express our enormous gratitude to Prof. Carsten Bergmann and Dr. Nadine Bachmann from the Center for Human Genetics, Bioscientia Institute for Medical Diagnostics Ingelheim, Germany for their continued and generous collaboration during the research study.

Key words: Beckwith Wiedemann syndrome, overgrowth, hypomethylation, tumor risk

Sonja Bojadzieva

Dr Sonja Bojadzieva is a Professor of Paediatrics at the University Children's Hospital, at the Medical Faculty, Skopje. She was born and grew up in Skopje, where she has finished medical Faculty. In 2021 she was elected as the head of the Department of Pediatrics, Faculty of Medicine, UKIM, Skopje. She is the current Head of Department of Gastroenterology. In 2013 finished doctorate PhD "Correlation between genotypic, phenotypic and immunological characteristics of inflammatory bowel disease", and in 2019 was elected a professor at the Faculty of Medicine. Her postgraduate studies MSc "Significance of quantitative determination of albumin and IgG in the liquor in differentiation of various conditions in the central nervous system", she finished in 2003. She has professional residence and trainings in the field of paediatrics gastroenterology in very important hospitals abroad such as Austria, Germany, Poland, Italy and others. Her special interest is Inflamatory bowel diseases in children. She is very active participant in several national and international congresses. Author and co-author of more than 300 scientific research papers and actively involved in scientific research projects. As a General Secretary of the Paediatric Association of Macedonia she put very high input in the paediatrics education and promotion.

She is also full member of The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN). She has organizational capabilities, exceptional teamwork ability, communicativeness and ambition. She is very dedicated to work and has the ability to work under time pressure and responsibility and is particulary conscientious in performing work tasks. Dr Bojadzieva enjoys reading books, traveling and painting.

WILSON'S DISEASE IN CHILDREN - DIAGNOSTIC ASPECTS AND THERAPY

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Wilson disease (WD) is an autosomal recessive disordercaused by mutations of the ATP7B gene, with a prevalence of 1:30,000–50,000.The common mutations of the ATP7B gene located on chromosome 13 are missense and nonsense and can be either homozygous for one mutation or compound heterozygous.WD characterized by decreased biliary copper excretion and reduced incorporation into ceruloplasmin, leading to excessive copper accumulation in many organs, predominantly the liver, brain and cornea. The diagnosis is based on a combination of clinical, biochemical and genetic tests. Clinical presentations of WD in childhood ranges from asymptomatic liver diseases to cirrhosis or acute liver failure. Neurological and psychiatric symptoms in childhood are rare. Hepatic failure is common feature of WD, predominantly in females 75% versus 25% in males. The fulminant presentation of WD is defined as acute liver disease with encephalopathy and have high mortality in the absence of transplantation.Diagnosis could be established using anamnesis, biochemical tests assessing cooper metabolism and molecular analysis of mutation in the ATP7B gene. Diagnostic approach includes serum ceruloplasmin and 24 hours urinary cooper excretion.Liver biopsy and hepatic parenchymal cooper concentration is very important for diagnosis, and increased concentrations of dry weight remains is the best biochemical evidence for WD.
Therapy is based in using medicine for removal cooper excess, as D-Penicillamine, trientine or medicine for inhibition of intestinal

cooper absorption.Liver transplantationis indicated for children with rapid development of severe hepatic insufficiency, with progression of liver dysfunction to liver failure despite drug therapy. Early diagnosis and therapy of the disease could avoid dramatic disease progression and children's survival.

Key words: ceruloplasmin, Wilson’s disease, children.

Aco Kostovski

Full Professor of Pediatrics, MD PhD
Chief of the Department for Hepatology, University Children's Hospital,
Faculty of Medicine, Ss Cyril and Methodius University, Skopje, North Macedonia.
Visiting Professor of Pediatrics Medical Faculty, Osijek, Croatia.

Graduated at Medical faculty Ss."Cyril and Methodius" Skopje, Macedonia in 1980. The same year employed University Children Hospital. Specialization of Pediatrics, in the period 1983-1987. In 1991 realized clinical Fellowship in pediatric Gastoenterohepatology, University Central Hospital, Tampere, Finland under mentorship of prof. Jarmo Visacorpi and prof. Markku Maki. Master degree of Medicine received in 1994 and PhD in 1998. Subspecialist of pediatric gastroenterohepatology. Medical director of University Children Hospital in Skopje in the periods 2000-2002 and 2007-2012.

Invited lecturer for different topics in the field of pediatric gastroenterohepatology.

Involved as a main investigator and national coordinator in several internationally (ESPGHAN) funded scientific projects. Member of ESPGHAN since 2005.

Author and co-author of more than 200 scientific papers published in national and international journals, and presented on congresses or scientific meetings.

Short term professional clinical stay at several centers for different diagnostic and treatment methods in the field of pediatric gastroenterology and hepatology (Munich, Gothenburg, Houston, Paris, Boston, London, Barcelona, Brussels, Salzburg, Amsterdam) and their introduction at University Children's Hospital, Skopje, Macedonia : computed 24 hour pH monitoring for GERD, upper endoscopy and colonoscopy, liver biopsy, ultrasound of abdomen, combined 24 hour pH monitoring and impedance for GERD, esophageal and rectal manometry with EGG, capsule endoscopy, rectal biopsy, H-breath test.

Professional collaboration with the Gastroenterohepatology and metabolic departments in University Children's Hospital in Heidelberg for diagnosis, and managing the patients with rare diseases.

ALAGILE SYNDROME – NEW TREATMENT POSSIBILITY

Aco Kostovski
University Children's Hospital, Skopje, North Macedonia

Alagille Syndrome (ALGS) is a rare genetic multisystem disease (incidence 1:30-50.000 live births) that affects the liver, heart, eyes, bones and other organs. It is caused by mutations or deletions of the Jagged 1, a ligand in the Notch signaling pathway. Refractory pruritus and cholestatic liver disease progression are frequent indications for liver transplantation with patients with ALGS. Cholestatic pruritus and xanthomas present a significant unaddressed burden of the disease leading to greatly diminished quality of life. New treatment with illeal bile acid transport (IBAT) inhibitor was approved by FDA in 2021 aimed to delay the cholestatic progression.

Eight children with ALGS were diagnosed and followed-up in a single center and University Children Hospital in Skopje in past 10 years. The clinical phenotype varies from subclinical and mild cholestasis (n=3) to severe liver failure requiring liver transplantation. Diagnosis was based on the clinical, hystologic or molecular analysis.

IBAT inhibitor (Maralixibat) interrupts enterohepatic circulation and increases fecal bile acid secretion. Results from three clinical trials of maralixibat treatment over the 6-year period of time showed clear patient benefit including: improvement of pruritus, reduction of serum bile acids concentration and prolonged transplant free survival.

In conclusion, availability of IBAT inhibitor for cholestatic liver disease presents a new era in the treatment of ALGS that will lead to avoid liver transplantation and improve the quality of life.

Key words: Alagile syndrome, new treatment, IBAT inhibitor, Maralixibat

Gordana Loleska

My name is Gordana Loleska and I live in Ohrid, Republic of North Macedonia. I am a single mother of 3 kids, I have 1 girl and 2 male twins. After a 14 year struggle finding out what's the problem with my son's hearing and kidneys, 7 years ago my son was officially diagnosticated with Alport Syndrome. From that day I started doing everything in my power to help people who are struggling with a rare disease and spread awarness among citizents in Republic of Macedonia to help and donate to the Rare Diseases Fund.
As a single mother and a mother of a kid with a rare disease,
I am strongly motivated to continue helping people with rare disease, and I will do everything in my power to teach others to become more aware and give the support to the people who live with a rare disease.

Macedonian post office — Ohrid, Macedonia
As an employee in the Macedonian post office more than 20 years, I came up with the idea of printing a postal stamp dedicated to the children with rare diseases and all the funds from that postal stamp will go to the Rare Diseases Fund. The stamp was published in 2017 and had promotion at the Macedonian Academy of Sciences and arts.

INTERESTS
To spread awarness among people to be more educated and help people who live with rare diseases and help raising funds with any kinds of volonteering activities.

I am one of the initiators and organizers of the First Balkan Meeting for Alport Syndrome, Ohrid, Macedonia 31aug-2sept 2018
2 Years ago I formed an Association for people with Rare Diseases - Alport Syndrome (Rare is to be Rare)
Over the years I have been trying to give more support to patients and families with Alport syndrome knowing that you are not alone in this fight is always easier.
I am very sorry for the stigma that exists among parents and patients, I hope that in time we will overcome these problems.

M**Y WORK SO FAR**

You can find something more about more work in the links bellow:

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Ana Momirovska

Date and place of birth:	15.12.1965, Skopje, Macedonia
Nationality:	Macedonian
Education:	Faculty of Medicine, Sts Cyril and Methodius University, Skopje, Macedonia,
Diploma:	1992
Medical Licence obtained:	1994
	Faculty of Medicine, Sts Cyril and Methodius University, Skopje, Macedonia
Postgraduate studies:	In the field of paediatrics and molecular biology
Master of Science degree:	2002
Thesis:	Molecular basis of fragile X syndrome in Republic of Macedonia
	Faculty of Medicine, Sts Cyril and Methodius University, Skopje, Macedonia,
Postgraduate studies:	In the field of laboratory medicine (medical biochemistry and clinical chemistry), (2009-2015)
Degree:	Specialist in medical biochemistry
Language skills:	Former Yugoslavia languages, German and English

Present employment / position:
CMO and Quality Manager of Synlab Macedonia, Responsible for QM according ISO 15189, Medical Department for “Special tests” including Rare Disease testing, networking with professionals in different specialities abroad and genetic counselling

Former employments / positions:
Assistant in the Research Centre for genetic Engineering and Biotechnology, Macedonian Academy of Sciences and Arts (RCGEB, MASA)

Professional Experience:

- Research fellow from 1994-1999 in the field of protein chemistry and in the field of molecular biology for identification of hemoglobinopathies, fragile X syndrome and detection of viruses with molecular methods.
- From 2003 work in the field of medical laboratory diagnostic as laboratory doctor in clinical pathology.

Participation in Slovenian / Macedonian project for Alport syndrome, in December 2007, Ljubljana, Faculty of Medicine, Institute for Pathology.

- Since beginning of 2006 - research fellow in the RCGEB, MASA: Molecular characterisation of the inherited deafness in Macedonia (external cooperation).
- In 2007 involved in QM management of synlab laboratories in Macedonia.
- Since 2016 cooperation with Faculty of Medicine Ljubljana, Institute for Pathology, on project: Genetic pull of Galicnik village population (maternal and paternal perspective and relations with other populations).
- Since 2016 involved in Medical Management of Synlab Macedonia as Chief Medical Officer.
- Participate at international and local meetings, congresses, seminars and projects in the field of clinical chemistry, microbiology, human genetics, general medical practice and quality management with over 50 oral and poster presentations and written papers.

DIAGNOSTICS OF COL4A DISEASES IN NORTH MACEDONIA FROM THE VERY BEGINNING

Ana Momirovska
SYNLAB Macedonia

Alport syndrome (AS) is an inherited collagen (COL4) disease caused by mutations in a few collagen genes, namely COL4A5, COL4A4 and COL4A3. COL4A5 is X linked and COL4A4 and COL4A3 are autosomal genes.
Clinical features of AS are: progressive nephritis with defect of glomerular basal membrane in kidneys, affected glomerular filtration with hematuria, but also hearing loss, ocular symptoms. Another condition related to COL4 mutations is Thin Membrane Disease (TMB). It is caused by mutations in COL4A4 and COL4A3 (mostly - heterozygous constellation). TMB is characterized by constant hematuria, minimal proteinuria, however with normal kidney function.
Diagnostic approaches have changed during the last decades. First, patients were diagnosed using clinical examination, anamnestic familial data, Ultrasound and urine test (biochemistry and microscopic examination of urine). Laboratory method practiced that followed was biopsy and immunohistochemistry. Biopsy and immunohistochemistry were performed upon request of clinical doctors.
Molecular methods were performed first on Macedonian patients included in the project for AS, a project between the Institute of Pathology, Medical Faculty, Univerza Ljubljana, Slovenia, and the Institute of Pathology, Medical Faculty Skopje, UniverzitetSv. KiriliMetodij, Macedonia, 2004-2006. A group of 60 patients from Macedonia were examined, in Macedonia tested using biopsy and immunohistochemistry, and in Slovenia tested with molecular methods: PCR, followed by SSCA and Sanger sequencing.
Lately most of the samples from Macedonian patients are sent for molecular testing in the Institute for Human Genetics, Technische Universität München,. Rarely samples are still sent to

Slovenia, and some via private labs like SYNLAB to the big diagnostic centers. Recent approaches are Next Generation Sequencing (panel tests) and Sanger Sequencing for unknown mutations and PCR for known mutations.
In our country a stable molecular method for diagnostic purposes is still not established, even though there were few initiatives to introduce the PCR and NGS method.

Key words: Alport syndrome, thin membrane disease, North Macedonia

Nora Abazi Emini

Nora Abazi Emini was born in 1976 in North Macedonia. Graduated from Medical Faculty Skopje in 2002. Completing training in pediatrics in 2011. Since 2013 she is working in the nephrology department, at University Children's Hospital. Also, she is a Ph.D. candidate in pediatric nephrology. Her research field is hematuria in children especially familial hematuria and genetic aspects. During her career, she participated in several national and international projects also she is the author and co-author of several publications in professional journals.

TYPE - IV - COLLAGEN - RELATED NEPHROPATHIES IN NORTH MACEDONIA

Nora Abazi Emini, VeliborTasic
University Children's Hospital – Medical Faculty, University Ss Cyril and Methodius Skopje, North Macedonia

Two major forms of familial hematuria are Alport syndrome and thin basement membrane nephropathy, also named Type-IV-collagen-related nephropathies. They are associated with disease-causing variants in COL4A3-5 genes and manifest by a wide range of clinical signs, from isolated microscopic hematuria to end-stage kidney disease. In Republic of North Macedonia, there are no official data on the number of patients with Alport syndrome.The University Children's Hospital in Skopje is a tertiary institution where children with hematuria are treated.
In our series, we analyzed 320 children with macroscopic and microscopic hematuria in whom the etiology of hematuria was sought. In patients with persistent hematuria, family screening for hematuria is also performed, and in 70 families, the existence of hematuria was confirmed in another member of the family .Genetic testing was doneat Technical University Munich Germany, thanks to the cooperation within the project. 27/62 patients (43.5%) have disease-causing variant in COL4A3-5 genes.
Early genetic diagnosis is a very important step for early initiation of renoprotective therapy with ACE inhibitors. Patients with rare diseases are subject to stigmatization, there is distrust in clinical and genetic diagnosis and there is also a poor follow-up of patients.

Key words: familial hematuria, COL4A3-5 genes, ACE inhibitors, stigmatization

Velibor Tasic

Graduated:	Medical School, Skopje, 1980
Employment:	Clinic for Children's Diseases, Skopje 1980
Specialization in pediatrics:	1986
Stipends:	The British Council 1991- London; International Society for Peritoneal Dialysis 2001 Hannover
Training in pediatric nephrology:	Belgrade 1986, London 1991, Birmingham 1991, London 1998, Hannover 2001
PhD:	"Clinical, biological and prognostic aspects of acute poststreptococcal glomerulonephritis in children, University Sv. Kiril i Metodij-Skopje, 1997
Academic degree:	Full Professor of Pediatrics and Pediatric Nephrology, Medical School, Skopje
Actual position:	Consultant Pediatric Nephrologist, Chief of the Department of Pediatric Nephrology, University Children's Hospital Skopje
Membership:	International Pediatric Nephrology Association, European Society for Pediatric Nephrology, EDTA-ERA, European Academy of Pediatrics, Macedonian Pediatric Association
Working Groups:	South Eastern European Pediatric Nephrology Working Group, Inherited Renal Disorders (ESPN), CAKUT/UTI/ Bladder dysfunction (ESPN), WGIKD (ERA-EDTA), Macedonian Enuretic Study group (MESD), Tertiary Working Group for Rare Disease (European Academy of Pediatrcis).

Secretary General:	Macedonian Pediatric Association 2004-2006
Council Member:	European Society of Pediatric Nephrology 2009-2012
Director:	SEPNWG Teaching Course Ohrid 2012. Skopje 2016
Scientific Chair:	Alport Macedonia, Meeting, Ohrid 2018
Invited Lecturer:	ESPN/IPNA/EDTA teaching courses in Pediatric Nephrology
Moderator and Lecturer:	Nephrology Session at Serbian, Croatian, Kosovo and Macedonian Pediatric School
Scientific Chair:	Rare Disease Conferences Skopje 2012, 2013
Publications:	200 Pubmed Papers.
Conference papers/abstracts	≈400

PROJECTS AND STUDIES:

- Hereditary and tubular disorders-inherited disorders of magnesium metabolism with M Konrad and S. Weber (Germany)
- Cystic kidney diseases with Carsten Bergmann (Germany), Peter Harris (Mayo, USA)
- Alport syndrome with J Hoefele (Germany)
- Dent1/Dent2 disease with M Ludwig (Germany),
- Congenital anomalies of the kidney and urinary tract – S. Weber, F. (Germany), F. Hildebrandt (Harvard, US), S Sanna-Cherchi (Columbia, US) J Hoefele (Germany), R. Weber (Germany).
- Primary distal renal acidosis with F. Karet (UK), HI Cheong (Korea)
- Study on genetic basis of cystinuria in SouthEastern Europe, Macedonian Academy of Sciences and Arts
- Rare and inherited kidney diseases in Macedonian Children and adolescents (national project)

The result of abovementioned collaboration and projects are papers published in the following journals:

New England Journal of Medicine, American Journal of Human Genetics, Journal of the American Society of Nephrology, Kidney International, American Journal of Kidney Diseases, Pediatric Nephrology, Journal of Medical Genetics, Nephrology Dialysis Transplantation etc.

EXTRARENAL FEATURES OF COL4A NEPHROPATHIES

Velibor Tasic
University Children's Hospital, Skopje, North Macedonia

Sensorineural deafness is a cardinal extrarenal manifestation of Alport syndrome. Hearing loss is never present at birth. Interestingly some patients with Alport syndrome may have severe nephropathy but preserved hearing. Hearing loss is bilateral, affecting high-frequency and usually begins in early adolescence, before the onset of kidney failure. In the early stages of the disease, hearing loss is detectable only by means of audiometry.
With progression of hearing loss, there is affection of low frequencies, including those of human conversation, and therefore patients require hearing aids. Hearing impairment is always associated with renal involvement.
About 50% of male patients with X-linked Alport syndrome show sensorineural deafness by age 25 years, and about 90% are deaf by age 40 years. Hearing loss in females is present at low percentage.
Anterior lenticonus, which occurs in approximately 25% of patients with XLAS, is the pathognomonic feature of Alport syndrome. In this condition, the lens surface protrudes conically into the anterior chamber of the eye because of a thin and fragile basement membrane of the lens capsule. Anterior lenticonus is not present at birth but is manifested by a slowly progressive deterioration of vision, requiring patients to change the prescription of their glasses frequently. The condition is not accompanied by eye pain, redness, or night blindness, and no defect in color vision occurs.
Dot-and-fleck retinopathy is the most common ocular manifestation of patients with Alport syndrome, and occurs 85% of males with XLAS. It is very rare in children and usually manifests at the onset of kidney failure. The patients are asymptomatic; there is no associated visual impairment or night blindness.
Posterior polymorphous corneal dystrophy is rare condition in Al-

port syndrome. Majority of patients are asymptomatic, although some of them may develop slowly progressive visual impairment. In some patients temporal macular thinning may be observed on ophthalmologic examination.
Leiomyomatosis is a very rare extrarenal manifestation in Alport syndrome. Diffuse leiomyomatosis of the esophagus and tracheobronchial tree has been reported in some families with Alport syndrome. Characteristic symptoms are dysphagia, postprandial vomiting, substernal or epigastric pain, recurrent bronchitis, dyspnea, cough, and stridor. Diagnosis is established by computed tomography scanning or magnetic resonance imaging.

Key words: Alpot syndrome, hearing loss, lenticonus, leiomyomatosis

Nikola Gjordjievski

Ass. Dr. Nikola Gjordjievski was born in 1984 in Skopje. He completed primary and secondary education in Skopje, continuously with excellent success. In 2002, he was chosen as the best student of his generation at the medical school DSMU "Dr. Panche Karagjozov"-Skopje. At the Medical Faculty in Skopje at the University "Ss. Cyril and Methodius" enrolled in 2002, and graduated on July 16th, 2008, with an average grade of 9.21 as the first graduate student of his generation.

Since March 2014, he has been employed at the University Clinic for Nephrology, and in 2016 he was selected as a doctoral assistant at the Department of Internal Medicine at the Faculty of Medicine at the University of "Ss. Cyril and Methodius" Skopje. In October 2019, he successfully passed the specialist exam and acquired the title of specialist in Nephrology.

In 2021, he successfully completed his doctoral dissertation entitled "Application of Doppler ultrasound in monitoring the maturation of an arteriovenous fistula for hemodialysis."

Continuous medical education is achieved through participation in a large number of home and international scientific congresses.

He attended a one-month training in November 2015 at the University Clinical Center of Ljubljana, and in May 2017 he successfully completed a one-month course under the title "Doppler Ultrasound Diagnostics of Blood Vessel Diseases" at the Faculty of Medicine of the University of Zagreb, Republic of Croatia.

He is a participant in an international study entitled "AIM.SIM project" coordinated by the Department of Biomedical Bioengineering at the "Mario Negri" Institute for Research Pharmacology, Bergamo, Italy.

Since March 2020 he has been appointed as the national coordinator from Macedonia at the European registry of patients with renal replacement therapy of ERA-EDTA.

Ass. Dr. Nikola Gjordjievski is the author and co-author of over 50 published scientific articles and international awards.

ALPORT SYNDROME - WHEN SHOULD ONE CONSULT NEPHROLOGIST?

Nikola Gjorgjievski
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Alport syndrome is a genetic disorder characterized by kidney disease, hearing loss, and eye abnormalities. The changes in the collagen protein of the tissue is resulting from mutations in the collagen IV genes COL4A3, COL4A4, and COL4A5. According to the data from the European Renal Association and European Dialysis and Transplant Association(ERA-EDTA) registry, the Alport syndrome is classified in group VII as a primary etiology in patients with end-stage kidney disease (ESKD)which requires renal replacement therapy. The availability of effective intervention for Alport syndrome-related kidney disease makes early diagnosis crucial. Implementation of the last guidelines for treatment and monitoring of the overall health condition provides a better quality of life in these patients, as well. The nephrological approach should be fast, efficient, and available for any diagnosed or suspected patients with Alport Syndrome. In this way, the review should enhance early diagnosis and achieve optimal outcomes in the treatment.

Key words: Alport syndrome, hearing loss, eye abnormalities, early diagnosis

Danko Milosevic

I was born on 05.01.1955 in Brcko, Republic of Bosnia and Herzegovina. I am a specialist in pediatric nephrology with a particular interest in kidney metabolic diseases, urolithiasis, and hemolytic-uremic syndrome. I am the president of the Croatian Society for Pediatric Nephrology. My research field is covered by internationally peer-reviewed articles cited in Current Content, SCI, and other publications written in Croatian. I collaborate with other medical institutions (Boston Children's Hospital, Harvard Medical School; Shaare Zedek Medical Center, Jerusalem; Kinderspittal Zurich: Columbia University New York) and pediatric nephrologists from Skopje, Macedonia. We are currently working on similar pediatric nephrology topics, intending to maintain and widen our present cooperation. In 2021, was the president of the IX SEP-NWG Congress in Brijuni, Croatia.

COL4A NEPHROPATHIES IN CROATIAN CHILDREN

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Republic of Croatia has approximately 4.6 million inhabitants. Nearly 4 decades ago we systematically did a follow up of our children in search of Alport syndrome/Thin basement membrane disease (AS/TBMD). The regular check was performed by systematic monitoring of microhematuria and/or perceptive hearing loss. All children/adults underwent kidney biopsy to conform/exclude AS/TBMD. A retrospective analysis of clinical and histopathological data of 565 children aged < or =17 years, who presenting to 9 hospitals in Croatia from 1991 to 2004, in whom kidney biopsy was performed were analysed. Among hereditary glomerulopathies, Alport syndrome was the most common (83.6%), On follow-up, 7 of 33 children with changes consistent with Alport syndrome/TBMD developed clinical signs of the syndrome during childhood age. After confirmation of diagnosis, all children were regulary followed-up for signs of disease progression until age of 18 yr. Although some of them decided to maintain in pediatric nephrologist care for additional few years, all patients above this age are regularly transferred to the adult nephrologist care. In case of renal failure and in a need of renal transplantation a child/adult was appointed for renal replacement. Kidney transplantation in Croatia is well organized and Croatia is a member of Eurotransplant association..A recently conducted national survey for AS/TBMD is a part of wide genetic search for COL4A3, COL4A4, and COL4A5 mutations (Genotype-Phenotype correlation in AS/TBMD. Using targeted next-generation sequencing(NGS), 34 AS/TBMN patients (58.8% male) from 12 unrelated families were found positive for heterozygous c.2881+1G>A variant of theCOL4A3 gene, which is considered disease-causing. We believe that early diagnosis, genetic counselling and regular biochemistry check is the base of timely and appropriate care for these patients.

Key words: COL4A nephropathies, Alport syndrome, children, Croatia

Todor Arsov

Born in Skopje, where he completed medical studies and received a MS degree in molecular medicine in the area of human genetics – inherited thrombophilia, Todor holds a PhD ini genetics from the Australian National University, where he held a position of a Senior Research Fellow at the Centre for Personalised Immunology. Following two postdoctoral positions at Stanford University and The University of Melbourne where he started a new molecular genetics laboratory, he furthered his qualifications by completing professional MS studies in genetic counselling (Sydney University) and diagnostic genomics (Queensland University of Technology). His research interests are in the area of human monogenic genetics, particularly in the areas of immunology, neurology, cardiology and metabolic conditions, as well as ethics of genomic testing. Currently, Todor is a professor of Genetics and a genetic counsellor at the Medical School in Skopje and holds a visiting scientific position at the Francis Crick Institute in London, UK.

CHALLENGES IN GENETIC COUNSELLING FOR ALPORT SYNDROME IN THE AGE OF GENOMIC MEDICINE

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The ongoing genomic revolution afforded increased access to genetic testing in clinical practice, bringing changes to the traditional understanding of many conditions, including Alport syndrome (AS). Traditionally, this is a childhood onset condition inherited in an X-linked fashion (XLAS), related to pathogenic variation in COL4A5, manifested by renal and extra-renal symptoms. The subsequent identification of girls with the same condition widened the AS spectrum to include the autosomal recessive forms (ARAS) linked to pathogenic variation in COL4A3andCOL4A4.
We now start to appreciate that the heterozygous carriers of pathogenic variants in COL4A3,COL4A4 и COL4A5are not necessarily and/or fully asymptomatic, as most COL4A5 carrier mothers will develop (micro)hematuria and up to one third may progress to end-stage kidney disease by 40-60 years of age. In addition, heterozygous carriers of some pathogenic COL4A3 or COL4A4 variants manifest similar features and are, by some, considered to have autosomal dominant AS (ADAS).
Mirroring the evolution of the clinical understanding of the condition, the genetic counselling strategies also evolve to include counselling about all forms of Mendelian inheritance, including the “de novo” genetic mechanisms and counselling about predictive and diagnostic testing of seemingly asymptomatic adults in the family.
This presentation will discuss clinical experiences with counselling about AS from a genetic counsellor’s perspective, in the context of the dynamic evolution of the clinical entity, including examples of incidental testing for an adult onset condition and the genomic uncertainty related to the phenomena of reduced penetrance and variable expressivity and to the interpretation of genomic variants.

Key words: Alport syndrome, COL4A5, genetic counselling

Macedonian Society
for Rare Diseases

ЗДРУЖЕНИЕ НА ПЕДИЈАТРИТЕ НА РЕПУБЛИКА МАКЕДОНИЈА

Poster sessions

Acute tubular necrosis in a child with steroid sensitive nephrotic syndrome

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Acute tubular necrosis is a kidney disorder involving damage to the tubule cells of the kidneys,which can lead to acute kidney failure. The prevalence of AKI also correlates with ATN severity in patients with nephrotic syndrome. Emergence of AKI in children with NS requires the diff dig between ATN and glomerular proliferative lesions since the therapeutic approach differs, ATN requires support treatment without immunosuppresion.In patients with SSNS, ATN is a sporadic but significant complication. With this abstract we want to present a rare case of a patient with SSNS who manifested with ATN.Retrospective analysis of a patient with SSNS diagnosed 2019 who is still hospitalised in our nephrology department.Based on clinical exam, urine sample and expanded laboratory analysis-urea, creatinin, electrolyte in serum, acid-base balance and differential blood cell count. On clinical exam the patient presents with generalized oedemas, dyspnea, hypertension and anuria. The evaluation shows urine with proteinuria, urea 25.4 mmol/L, creatinin 736.2umol/L, electrolytes- Na 141mmol/L , Kalium 3.4mmol/l, Calcium 1.36 mmol/l, Phosphor 3.08mmol/l, Magnesium 0.78 mmol/l, acid-base balance with metabolic acidosis.Acute renal insufitiention is more common in children with SDNS (steroid-dependent) and SRNS (steroid-resistant) in relation to SSNS (steroid-sensitive NS). Hypertension, proteinuria and hypoalbuminemia are also risk factors for AKI in this patients. Early detection of this condition is important to remove the possible etiologycal causes and to treat them before chronic lesions appear in kidneys and to avoid CRI.

Key words: Steroid sensitive nephrptic syndrome, child, acute tubular necrosis, outcome

PRIMARY HYPEROXALURIA TYPE I - IN A COUNTRY WITH LOW RESOURCES

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Backgrounbd: Primary Hiperoxaluria is a serious inherited autosomal recessive metabolic disorder leading to excessive oxalate production, nephrolithiasis, nephrocalcinosis and end stage kidney disease. The aim of the study is to present difficulties in management of PH1 in low resource country.

Case presentation: A 3 year old girl was referred to University Children's Hospital Skopje due to abdominal pains, vomiting and passage of calculi. Initial abdominal X ray showed many calculi in both kidneys. Ultrasound investigations showed presence of calculi in all calyces of both kidneys. There was no hydronephrosis. Family history was negative for nephrolithiasis . Laboratory investigation revealed urine positive for blood 3+ and numerous eumorphic red blood cells. Almost normal renal function: urea 3.3 mmol/l, uric acid 178 umol/l, creatinine 44 umol/l (eGFR 70 ml/min/1,73m2 New Schwartz formula). Acid base staus: pH 7.39, HCO3 24 mmol/l, BE 1.3 mmol/l, Serum electrolytes with normal values (Mg 0.8 mmo/l, P 1.45 mmol/l). Random Urinary ratios Calcium, Mg, Uric acid to creatinine within referent values. Nitroprusside reaction for cystinuria negative. Oxaluria 24 urine sample (0.87 mmol/1.73m2/d). Genetic investigation (Bodo Beck, Cologne, Germany) - Sequence analysis identified the pathogenic variant c.508G>A in exon 4 of the AGXT gene in homozygous state. This mutation leads to an amino acid exchange from glycine to arginine at the amino acid position 170 (p.Gly170Arg). Pyridoxine test (100 mg≈8 mg/kg) showed oxaluria before and after vitamin B6 1.04 and 0.56 mmol/1.73m2/d respectively. Urinary glycolate was not elevated. In the meantime she had one symptomatic urinary tract infection, treated with antibiotics. She underwent minimally invasive surgery, during which most of the stones were removed. Her current treatment is potassium citrate 1 mmol/kg/d and Pyridoxine 100 mg/d. In the absence of RNA interference therapy (Lumasiran) , even after minimally invasive treatment and Pyridoxine, the girl continues to form new

kidney stones. Her younger brother was prenatally diagnosed with PH1 , has been followed up regularly and treated with Pyridoxine, but small deposits of crystalline oxalate were detected in the renal medulla.

Conclusion: This report illustrates difficulties in management PH1 in a country with limited resources. RNA interference therapy with Lumasiran showed very promising results. Our patients deserve this modern treatment due to their early and severe course of the disease.

Key words: Primary Hyperoxaluria, nephrolithiasis ,
genetic investigation, mutation, RNA interference therapy

Duplication 10q26.3 and Deletion 15q26.3 in a child with growth hormone deficiency, pituitary adenoma, SGA and mental retardation

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A 13-year-old boy was referred for shorts stature, mental delay and dysmorphic phenotype. Born SGA with length of 42 cm and weight 3050 g. First words were uttered at age of 3 years, while he still has poor language skills although he seems to understand normal speech. His IQ is 68. At the age 13 years his height is 128 cm (-3.6SD), weight 15.7 kg, head circumference within normal limits. There were epicanthal folds, low-set ears and hyperextensible joints. Two tests of pituitary reserve reached a maximum growth hormone concentration of 6.5 ng/ml. The IGF-1 was low and did not increase during GH Treatment. IGFBP-3 was not available. The GH treatment resulted in poor response of the growth velocity (almost parallel

to the third percentile). The MRI of the pituitary and hypothalamus revealed normal size and position of the pituitary with a central pituitary micro-adenoma of 5 mm. Multiplex Ligation Probe amplification (MLPA) with the panel P242-A2 Microdeletion Syndromes-1 revealed a duplication 10q26.3 and deletion 15q26.3. aCGH is pending and might provide additional data on possible distinction with Drayer syndrome [involvement of insulin-like growth factor I receptor gene (IGF1R)].

Key words: duplication 10q26.3, deletion 15q26.3, hypopituitarismus, mental retardation.

A girl with pre-B acute lymphoblastic leukemia on maintenance therapy with hereditary complement-mediated thrombotic microangiopathy (aHUS)

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A 3-year old girl with acute lymphoblastic leukemia (pre-B immunophenotype, medium risk, treatment protocol ALL IC-BFM 2009) during maintenance therapy (MTX 10mg/weekly/and 6-mercaptopurine 50mgm2 daily) had sudden onset of pallor, oliguria, and microhematuria (128 RBC/mm3). Initial complete blood count revealed normocytic anemia (Hb 59 g/L, Htc 16.3%, MCV 85.3 fL, platelets 26 x109/L) alongside elevated bilirubin (67

umol/L), urea (17.6 umol/L), creatinine (82 umol/L) and LDH (2296 U/L) and a reduced haptoglobin level (0.03 g/L). Plasma-free hemoglobin was elevated (154 mg/L), as well as d-dimers (2.87 mg/L), antithrombin III (126.8%), and fibrinogen(6 g/L). Immunohematological analysis (direct and indirect Coombs test, antiplatelet antibodies) was negative.Hematological data: Hb level (45g/L), minimum platelets count (3x109/L), maximum LDH level units (704.8 U/L), schistocytes seen (no). Renal impairment: oliguria with macrohematuria, maximum serum creatinine (86 μmol/L), creatinine clearance (Schwartz formula) 23 ml/min/1.73m2. Evidence of infective causes: no (stools O157:H7, Shigella sp, VTEC, Streptococcus pneumoniae). Endomysial antibodies (EMA), ANCA, methylmalonic aciduria, hyperhomocysteinemia negative. Renal histology: not done Laboratory investigation: reduced ADAMS-13 activity (40%, reference range 67-150 %) with normal C3 (0.75 g/L), C4 (0.27 g/L). Factor H level was high (1248 mg/L, reference range 250-880 mg/L) with terminal pathway activation marker level markedly increased (1315 ng/mL, ref. range 110-252 ng/mL), supporting pathological overactivation of the complement system. Treatment: The girl was initially treated with fresh frozen plasma, periodic RBC transfusions, and single plasmapheresis. On the 2nd day of admission, she received a first eculizumab infusion (300 mg). After application, we noticed an immediate increase in platelets and reticulocytes with a decrease in free plasma hemoglobin and global renal function recovery.The former maintenance therapy was immediately switched to cyclophosphamide. During follow up, she continued Eculizumab treatment on a recommended schedule for 8 months. Genetic analysis: The patient was found to be homozygous for the CFH H3 haplotype (involving the rare alleles of c.-331C>T, Q672Q, and E936D polymorphisms) reported as a risk factor of aHUS. The patient was homozygous for the MCPggaac haplotype of the CD46 gene reported as a risk factor of developing aHUS. Conclusion: A triggering factor for thrombotic microangiopathy was drug-mediated(6-Mercaptopurine), causing complement activation on a predisposing genetic background. To our best knowledge, this is the third similar case found in literature, the first to receive eculizumab in such cases as well as following early onset of complement activation disease.

Key words: acute lymphoblastic leukemia, thrombotic microangiopathy, eculizumab

Hemolytic uremic syndrome in a child with Lenox Gestaut syndrome

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Introduction: Hemolytic uremic syndrome (HUS) is a non-immune microangiopathic hemolytic anemia followed by acute kidney injury and thrombocytopenia.

Objectives
1. Early diagnosis
2. Emergency hemodialysis or peritoneal dialysis
3. Restoring kidney function

Methods: The diagnosis is proven according to the clinical presentation, biochemical analysis, feces for verotoxin, genetics.

Case presentation: We present a male infant aged 1 year and 11 months with gastroenterocolitis. The infant had a primary diagnosis of Lenox Gastaut Synrdome, regularly monitored in the Neurological department of the University Clinic for Children Diseases. The underlying disease was diagnosed in infancy due to the occurrence of afebrile convulsions, and confirmed by electroencephalography (EEG) and magnetic resonance imaging (MRI). The child is under antiepileptic therapy all the time due to the manifestation of epilepsy in conjunction with the underlying disease.
He comes to our clinic because of gastroenterocolitis, followed by fever and dehydration. The performed laboratory investigations with the finding of metabolic acidosis. Placed on parenteral rehydration. The fourth day of the stay with an increase in the number of liquid stools and a decrease in diuresis. Laboratory analyzes showed an increase in degradation products

(urea and creatinine) and lactate dehydrogenase (LDH). The peripheral blood smear confirmed schizocytes, and a positive verotoxin was obtained in the feces. The tests performed confirmed the diagnosis of HUS.
Treatment of acute kidney injury started with peritoneal dialysis. Dialysis was performed every day for 12 hours after 10 cycles with good ultrafiltration 250-300 ml. On the ninth day of hospitalization, diuresis appeared, which increased during the following days. After which the child showed a visible clinical improvement with a decrease in the values of degradation products and an increase in diuresis. After complete recovery disconnected from peritoneal dialysis.

Conclusion - Early diagnosis and adequate treatment is of particular importance in the outcome of HUS.

Key words: HUS, gastroenterocolitis, peritoneal dialysis, verotoxin, Lenox Gestaut

Case report of a child with Limb Girdle Muscular Dystrophy

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Introduction: Limb-girdle muscular dystrophies include at least 33 different inherited diseases, which first affect the muscles around the shoulder girdle and hips. In most cases, the inheritance is autosomal-recessive. The diagnosis of LGMD can be challenging due to genetic heterogeneity and to high similarity with other neuromuscular disorders1. The prevalence estimates range from 1:14 500-1:123 000.
Aim: To describe a case of genetically confirmed LGMD and discuss the challenges regarding the diagnosis.
Materials: Patient's and parents' blood was taken for genetic analysis for point mutations in DMD gene. Clinical features within the physical examination, as well as laboratory analysis were also used.

Methods: The genetic analysis was made using the Next Generation Sequencing (NGS) method.
Results: We present a boy on the age of 8 years, with clinical features and genetically confirmed Limb Girdle Muscle Dystrophy type 2C. Genetic analysis did not show the presence of a pathogenic variant in the DMD gene, but showed the presence of a pathogenic change in exon 8 of the SGCG gene in a homozygous state, inherited from both of the parents, who are carriers of this variant. The determined genotype confirmed the diagnosis of an autosomal recessive form of muscular dystrophy with early manifestation, type 2C (LGMD2C).
Conclusion: This case report highlights the clinical utility of NGS panels to provide accurate diagnosis. It is highly important that the application of NGS in the clinical practice should always be combined with pre- and post-genetic counseling in order to provide a clear explanation of the results, the possible implications on patients' phenotype, the recurrence risk within the family as well as to explain possible unexpected findings.

Keywords: muscular dystrophy, DMD gene, NGS.

RANBP2-ASSOCIATED FAMILIAL ACUTE NECROTIZING ENCEPHALOPATHY

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Acute necrotizing encephalopathy (ANE) is a rare, autosomal dominant disease with a wide spectrum of symptoms and an unpredictable outcome. The clinical spectrum includes frequent infections that may progress to acute necrotizing encephalitis complicated by permanent neurocognitive impairment and/or fatal outcome. The disease is caused by pathogenic variants in the RANBP2 gene, which encodes the same name protein, part of the pore protein complex in the nuclear envelope. RANBP2 dysfunction

leads to an inappropriate immune response (excessive, prolonged inflammation, cytokine storm, tissue damage) to viral infections, such as influenza, parainfluenza, herpes simplex, human herpesvirus-6 (HHV-6) and COVID-19. Diagnosis is based on the identification of a pathogenic variant in RANBP2, and timely administration of immunoglobulins and methylprednisolone during infection is associated with a more favorableoutcome.
We present a multi-member family with permanent neuro/cognitive disability and/or fatal outcomes following viral infections. The proband in the family is an 11-month-old infant with a clinical picture of acute encephalopathy in the context of HHV-6 viral encephalitis. A rich family history guided the clinical diagnosis of ANE, which was also confirmed by genetic testing, which identified a previously known pathogenic variant in RANBP2 - c.1754C>T (p.Thr585Met).
Timely clinical suspicion, timely genetic confirmation of the diagnosis are key to optimizing treatment during infection in people at risk for this extremely severe disease, and genetic testing opens up opportunities for genetic counseling associated with testing family members at risk for ANE and risk management for disease recurrence in the family.

Key words: acute necrtizing encephalopathy, RANBP2 gene, outcome

Homozygote cystinuria in two generations: A case report

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Introduction: Cystinuria is being defined as an autosomal recessive inherited disease, designated by diminished reabsorption of cystine, ornitine, lysine and arginin in the proximal renal tubule and also the gastrointestinal epithelial cells which ultimately leads to elevated concentration of the concerned amino acids in the urine. Transport mechanism of these amino

acids is mediated by the rBAT/b0,+AT transporter the subunits of which are encoded by the following genes: SLC3A1, located on chromosome 2p16.3-21, and SLC7A9, located on chromosome 19q12-13.1.

Case report: A female patient aged 11, was admitted to the University Clinic of Children's Disease in Skopje, concerned of repeated kidney stone formation, dysuria and urinary tract infections. Familiar anamnesis of kidney stones was positive from her maternal side. Considering clinical symptoms, physical exam, echo and blood and urine investigations, an indication for genetic testing was made. The modified genes of the disorder were also affirmative for both mother and daughter, ultimately leading the mother as a homozygote. The logic reason lies in their Roma nationality. They are coming from social and ethnic environment that's being segregated and very closed. The diagnose of aminoaciduria was confirmed, so therapy has been started and until today the patient is still ongoing for regular 6 months check- ups.

Conclusion: Cystinuria is the most common monogenic nephrolithiasis disease. Because of its poor solubility at a typical urine pH of less than 7, cystin excretion results in recurrent urinary cystin-stone formation. Reaching the proper and utmost management includes primary by prevention of stone formation, proper hydration, dietary restriction of salt and animal proteins and achieving urinary alkalization. Therapeutic strategy with D-penicliamin and troponin, should be considered and closely observed as second line treatment, mainly because of its frequent adverse side-effects.

Keywords: homozygote, cystinuria, female, two generations, rare disease

A case report of anophthalmia illustrates the variable expression of genetic mutations

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BACKGROUND
Mutations in OTX2 gene can result in different clinical syndromes, from isolated micro/anophthalmia to agnathia-otocephaly complex with brain malformations, pituitary gland abnormalities and short stature. We describe two sibs (brother and sister) with different degree of anophthalmia and a mutation in the OTX2 gene.

CASE PRESENTATION
A five year old boy and his newborn sister with variable degree of micro/anophthalmia were referred to the University Pediatric Clinic – Skopje. The newborn had bilateral anophthalmia and was small for the gestational age, while the 5 year old boy had unilateral microphthalmia. In addition he had short stature, due to growth hormone deficiency, without neurological or mental disabilities. His brain MRI was evaluated as normal except for eyeball changes. After initial diagnosis of Septooptic dysplasia, WES was performed to detect the possible underlying genetic defect. A pathogenic mutation in OTX2 gene was found (c.402dupC; p.Ser135Leufs2 heterozygote), leading to frameshift mutation and nonfunctional protein.
Genetic evaluation in the parents was unavailable. However ophthalmological examination in the mother showed small iris and parapapillary atrophic changes, without vision affection.

CONCLUSION
This case represents the variable penetrance and expression of OTX2 gene among family members. The gene encodes a protein that acts as a transcription factor with a role in brain and sensory organ development. Genetic testing of the parents has been offered in purpose of future genetic counselling.

Keywords: Anophthalmia, microphthalmia, OTX2 gene, parapapillary retinal atrophy.

Decompression craniotomy and tarsoraphy in a child with Crouzon syndrome

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Crouzon syndrome is estimated to make 4.8% of cases of craniosynostosis at birth, while the neonatal prevalence is 16.5 per million births. A newborn girl had hypertelorism, exophthalmos (luxation of the right eye bulb with severe proptosis), external strabismus, parrot-beaked nose, hypoplastic maxilla, and mandibular prognathism. This autosomal dominant syndrome is a de novo mutation of the FGR2 gene (C.1024 T>A, P. Cys342Ser) as has been detected in the proband and not in the unaffected parents and the proband's sister. It is of note, that this variant is found in several cranyosynostosis syndrome, Crouzon, Apert, Antley-Bixler, Beare-Stevenson etc. The proband's twin sister is not affected, and whole pregnancy and delivery were uneventful. At the age of 1,5 months the ophthalmologic evaluation and a CT of the head and the optical pyramids were performed at the University hospital in Rotterdam, Netherlands. The surgical decompression was indicated. Occipital expansion and tarsoraphy of both eyes were performed. The need for surgical decompression of the optic nerve and/or brain is rare in Crouzon syndrome. Usually, pediatric follow-up is done as those patients have a normal life span. The extreme proptosis was the main presenting sign requiring surgical intervention. We stress the need for the regular follow-up to find in a timely manner the possible indications for surgical intervention.

Key words: Crouzon syndrome, FGR2 gene, surgical decompression.

AN INFANT WITH TUBEROUS SCLEROSIS AND COEXISTING EPILEPSY

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Introduction: Tuberous Sclerosis Complex (TSC) is a rare disease with autosomal dominant inheritance pattern. Mutations on either of the two genes Tuberous Sclerosis Complex 1 (TSC1) or Tuberous Sclerosis Complex 2 (TSC2) play a role in the pathogenesis and result in tubers affecting organs like the brain, heart, kidneys, skin, lungs, and liver. [1]
Purpose: This review aims to provide essential points for early diagnosing and adequate multidisciplinary therapeutic approach in order to improve life's quality of the children with TSC.
Materials: Blood samples were taken from the patient and the parents for genetic analysis for mutations in TSC1 and TSC2 gene, neurological examination, as well as laboratory analysis, were also taken in consideration.
Methods: Genetic analysis, prenatal and postnatal ultrasound and brain MRi, neurologic examination.
Results: We present a case of a 11 months old female infant diagnosed with epilepsy and treated with AED. Delivered from well monitored pregnancy, by caesarean section at 39 weeks gestation, APGAR score 6/8, with olygohydramnion and prenatally noted tuberous formations in the right ventricle, suspect for tuberous sclerosis. Postnatal genetic analyses confirmed the diagnosis Tuberous Sclerosis, inherited from the father. The MRi scan of the brain and kidneys didn't show any abnormal findings.
Conclusion: Early diagnosis allows careful genetic counselling in the context of variable clinical expressivity and helps the family to arrive to their decisions for early and further treatment. Multidisciplinary team approach to management is essential to maximize the prognosis of this condition.

Keywords: tuberous sclerosis, epilepsy, TSC1, TSC2

Relapsing polychondritis- case report

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Relapsing polychondritis (RP) is a rare immuno-mediated systemic disease affecting one or more cartilages in the body and it is characterizedby recurrent episodes of inflammation of the affected areas with their progressive deterioration. It is a rare autoimmune disease with incidence of 1-3,5/ 1000000 population/year.
Most commonly affected are the cartilages of the ears, nose and laryngotracheobronchal tree. Other affected structures could be the eyes, cardiovascular system, peripheral joints, middle or inner ear, skin or central nervous system. Potentially all cartilages of the body could be affected.
Prognosis and survival rate of the RP is improved in the recent years, with the study of Trentham and Le finding the 8 year survival of 94%. Most common cause of death due to RP is airway compromise, infection due to corticosteroid treatment or systemic vasculitis.
We are presenting a case of a 13 year old girl with RP affecting the laryngeal cartilage. On first admission in our hospital she presented with the symptoms of severe breathing difficulties. Initial treatment was with Corticosteroids and Methotrexate, gradually replaced with Interleukin 6 inhibitor Tocilizumab as monotherapy. After 16 months of this treatment the condition of our patient is vastly improved, with complete regression of the respiratory symptoms and without new episodes of inflammatory relapses.
RP is serious and progressive inflammatory disease. With timely and novel medical treatments, prognosis and survival rates of the patients are vastly improved, with reducing or stopping of the episodes of recurrent inflammation of the affected cartilages.

Key words: relapsing polychondritis, reccurent inflammation, cartilages, rare disease

Alport syndrome in a patient with renal agenesis

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Introduction: Alport syndrom is a rare genetic disease, which affects the kidneys, causing recurrent hematuria, progressive kidney failure and sensorineural hearing loss. The symptoms are present because of mutations in the genes coding the collagen chains type IV, causing a Defective formation and therefore glomerular basal membranes become thinner with rough tears. Some patients also exhibit deformities on the front end of the eye lens, slight mental retardation and leiomyomatosis. 85% of patients have a mutation in the 5(IV) collagen chain located on the Xq22-24 chromosome. The rest 15% of patients have an autosomal recessive disease, with mutations on the (IV) or (IV) collagen chain located on the 2q35-37. There have also been reported cases of autosomal dominant genetic inheritance on the (IV) and (IV) chains.

Case report: A 13 year old patient presented with persistent hematuria is admitted to the University Clinic of Children’s Diseases. He was first diagnosed with Alport syndrome and renal agenesis at the age of 2, following frequent urinary tract infections with the presence of hematuria. Family history showed that the father also had renal agenesis, and the grandfather had persistent hematuria. An echo tomography and DMSA radioisotope scan were conducted which confirmed the renal agenesis, and genetic tests showed a mutation characteristic for Alport syndrome. The patient was released at that time with a prescription for an ACE2 inhibitor Enalapril, and iron supplements. Current tests show highly elevated creatinine, urea and uric acid blood levels, as well as persistent hematuria and proteinuria, which infer imminent kidney failure. The patient is currently hospitalized and treated for the kidney failure and the slight anemia caused by the hematuria.The fault for the recent condition lies in the neglect of therapy, and the non regular visits to the physician, in the last 3 years.
Conclusion: When a patient is diagnosed with this disease, it is of utmost

importance that the progressive destruction of the glomerular function is controlled and brought to a minimum. This is so that the patient can avoid being subjected to dialysis or kidney transplantation,early in his life. Considering that people can function with only using one kidney, most patients can regulate their condition using medication and prolong their treatment with these invasive methods.Kidney transplantation is the best course of action in patients where the kidney damage is extensive and kidney failure has occurred, be it acute or chronic. Most patients receive the graft without complications, even though there is a risk of an immune response towards the kidney in the form of Goodpasture syndrome.

Keywords: Alport syndrome, renal agenesis, congenital disease, hematuria, rare disease

8th Meeting for Rare Diseases in South Eastern Europe

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Ohrid, Republic of North Macedonia
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