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RARE DISEASES IN THE SLOVAK REPUBLIC
EUROPLAN NATIONAL CONFERENCE

Poster session – Abstract 1

PROPHYLAXIS IN HEMOPHILIA A CHILDREN IN SLOVAKIA

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!On Behalf of the Slovakian Hemophilia Working Group

Prophylaxis has been considered to be a standard treatment in severe hemophilia. Gradual introduction of prophylaxis in children in Slovakia was enabled by progressive increase of FVIII supply during the 1990s. At the current level of factor supply of 4.0 IU/inh/year, 75% of 72 severe non-inhibitor hemophilia A children below 19 years are on prophylaxis. The treatment was evaluated in a group of 25 children born between 1997–2007. The first joint bleed occured at median age of 20 months (range 11–48), however, 17/25 (68%) patients developed the first hemarthrosis before the age of 2 years. Currently. 17/25 children (68%) are on the secondary prophylaxis which has started at the median age of 3.8 years (1.5–6.0) with median number of previous joint bleeds of 2.5 (0–10) and target joint in 8/17 (41%) patients. In the youngest children, an escalating regimen starting with once a week factor administration was used. At present, 3. 8 and 6 children on prophylaxis are treated with one,. Two, and three factor injections per week and median dose of 30, 35, and 28 IU kg .respectively. Total factor consumption is 3640 IU/kg/year (range 1600–5800). Median number of joint bleeds on prophylaxis is 0/year (range 0–9/year). 82% patients have 0–1 joint bleeds/year and the number of patients with target joint decreased to 4/17 (23%).
Conclusion: The benefit of prophylaxis in hemophiliac children is indisputable. Currently the early start of prophylaxis and treatment regime in our children is influenced predominantly by the venous access and compliance of family.

Keywords: *prophylaxis – hemophilia – children – Factor VIII*

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Poster session – Abstract 2

EUROGENTEST - PROJECT AND INTERNET PORTAL ABOUT GENETIC TESTING IN EUROPE

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Introduction: EuroGentest is a project funded by the European Commission to harmonize the process of genetic testing, from sampling to counseling, across Europe. The ultimate goal is to ensure that all aspects of genetic testing are **of** high quality thereby providing accurate and reliable results for the benefit of the patients. As up to 80% of rare diseases are genetic, this activity is of great importance for the specialists providing health and laboratory care for the patients with rare diseases, as well as for the patients and their families themselves. Many references from Eurogentest web pages are naturally linked to Orphanet or other important sources on rare and genetic disorders.
Aim: The aim of this contribution is to bring EUROGENTEST to the awareness of Slovak professional and non-professional society as an important source of information on various questions concerning genetic testing, genetic evaluations and counseling, basic terminology in medical genetics, and many more.
Methods: All information presented here comes from an internet source http://www.eurogentest.org/. The leaflets for patients and families were translated from English to Slovak by the author of this contribution in 2008.
Results: This work brings simple reasons and instructions WHY and HOW to search for important information on EUROGENTEST pages. The information leaflets about genetic testing for patients and families in Slovak can be found on page: http://www.eurogentest.org/patient/leaflet/patients_slovakia.xhtml. The leaflets have been freely available since 2009, in both html and pdf forms (for reading and printing). The information for professionals is only available in English and can be divided into 2 main streams: for genetic laboratories (accreditation, certification, international and national standards, workshops…) and for health professionals (health services and genetic counseling). At this point it is important to mention a special block - the Clinical utility gene cards (CUGCs)**.** CUGCs are disease-specific guidelines regarding the clinical utility of genetic testing, reflecting a major challenge – to balance clinical validity, clinical profit and cost-benefit issues of genetic testing and they are authored and annually updated by an international expert team.
http://www.eurogentest.org/professionals/public_health/info/public/unit3/geneCards.xhtml
Conclusion: Eurogentest website provides important information for patients and professionals. Online information leaflets for patients and families are freely available also in Slovak!

Keywords: *Eurogentest – patients and family leaflets in Slovak – clinical utility gene cards*

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Poster session – Abstract 3

MULTIPLE MONGOLIAN SPOTS, PSYCHOMOTOR DELAY AND HEPATOSPLENOMEGALY IN AN INFANT – A DIAGNOSIS PUZZLED OUT „AT A GLANCE“? (GM1 GANGLIOSIDOSIS)

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Introduction: GM1 gangliosidosis is a rare inherited metabolic disorder caused by mutations of gene coding lysosomal enzyme acid β-D-galactosidasis whose deficient activity leads to storage of GM1 gangliosides and other metabolites in lyzozomes. The most affected systems are CNS, liver, spleen and some others. According to clinical symptoms and age of manifestation, 3 main types are distinguished: 1. early infantile, 2. late infantile/juvenile, and 3. adult form. Deficiency of acid β-D-galactosidase activity can, however, lead also to another clinically distinct disorder: Morquio syndrome (mucopolysacharidosis type IV B), with excess of keratan sulfate, and symptoms affecting mostly skelet, hearing and vision (cloudings).
Case report: The authors evaluated a 12-month old hypotonic boy with multiple birth defects: critical coarctation of aorta, micropenis with hypospadia, and massive bilateral scrotal hernia. The patient repeatedly overcame severe bronchopneumonias requiring artificial ventilation. Suspicion of GM1 gangliosidosis type 1, early infantile form, has arisen within genetic evaluation on the base of a distinct clinical picture: extensive mongolian spots increasing in size and number during the child´ s life, serious developmental delay, and significant progressive hepatosplenomegaly that was not explained by other reasons. Regarding the patient ´s clinical condition, the blood samples for enzyme activity analysis had been drawn immediately, before any results of extended metabolic screening were known. Markedly deficient activity of acid β-D-galactosidase (5% of lower norm) and specifically abnormal pattern of oligosaccharides in urine confirmed the diagnosis of GM1 gangliosidosis.
Conclusions: GM1 ganliosidosis can be, although rarely, associated with numerous mongolian spots, that could pose a diagnostic clue, as it was in our patient. Also, cases of mucopolysacharidoses (Hurler sy.) with excessive mongolian spots had been reported. Numerous mongolian spots in an infant with hepatosplenomegaly and significant develop-mental delay should thus always rise a question of a lysosomal disorder.

Keywords: *GM1 gangliosidosis – mongolian spots – hepatosplenomegaly – coarctation of aorta – acid β-D-galactosidase*

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RARE DISEASES IN THE SLOVAK REPUBLIC
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Poster session – Abstract 4

RARE DISEASES AND SLEEP MEDICINE

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Sleep medicine in children is now a rapidly developing field of medicine that allows confirming not only relatively frequent diagnosis of obstructive sleep apnea associated with snoring in children but also brings the possibility of correct diagnosis and treatment of rare diseases associated with sleep. Their correct and early diagnosis improves the prognosis of patients and reduces the risk of secondary complications from respiratory disorders associated with sleep is especially chronic hypoxemia with its other pathophysiological implications.
The most serious rare diseases associated with sleep related breathing disorders include central sleep apnea syndrome, sleep-related hypoventilation/hypoxemic syndrome and sleep-related hypoventilation/hypoxemic syndrome linked to other rare diseases (e.g. intestitial lung disease, idiopathic lung hypertention, neuromuscular diseases). Furthermore, in addition to sleep apnea, rare diseases in sleep medicine include also: familial advanced sleep-phase syndrome, fatal familial insomnia, idiopathic hypersomnia, idiopathic hypersomnia with/without long sleep time, and other.
Diagnosis is based on the anamnesis, sleep questionnaires, sleep diary, and overnight polysomnographic examination in particular. Polysomnography is the gold standard for diagnosis of sleep disorders, especially sleep apnea in children. The treatment is applied depending on the diagnosis of non-pharmacological, pharmacological and ventilatory support (CPAP). The aim of this presentation is to present the experience of the pediatric sleep medicine center, which enables an early diagnosis and subsequent treatment of rare diseases associated with sleep.

Keywords: *sleep medicine – rare diseases – polysomnography*

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RARE DISEASES IN THE SLOVAK REPUBLIC
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Poster session – Abstract 5

MARFAN SYNDROME AND THE IMPORTANCE OF PATIENT ORGANISATIONS

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Marfan syndrome (MFS) is a genetic disorder caused by a mutant gene *FBN1* encoding the protein fibrillin and affects connective tissues throughout the body, mainly skeletal, cardiovascular and ocular systems. MFS is diagnosed according to the revised Ghent criteria where aortic root aneurysm/dissection and ectopia lentis are the cardinal features. In the absence of any family history, the presence of these two cardinal features is sufficient for the unequivocal diagnosis of MFS, irrespective of the presence or absence of systemic features in other organ systems, except where these are indicative of differential diagnosis. The confirmed *FBN1* mutation or combination of systemic manifestations is required when one of the cardinal features is absent.
There is no cure for MFS. However, lifestyle adaptation and proper follow-up care by qualified professionals from multiple medical disciplines are important. Regular echocardiograms (even in childhood) and eyes examinations are necessary. Aortic replacement or lens and retina surgery are sometimes required. Patients have to protect their bodies by limiting of physical activity. The disease is permanent with a worsening tendency. The lack of information on MFS causes, that disease is often underestimated by doctors and patients. In complex diseases affecting more organ systems, special centres play important role in treatment and follow-up care.
In Slovakia, there is the only institution which performs activities as a Center and works as a voluntary, non-profit patient organisation - The Slovak Marfan Association (http://marfan.szm.sk). It provides patients with counselling and contacting medical specialists, and keeps a database of patients as well as of doctors specialized in MFS and cooperating with the Association. It maintains contacts with every single patient, family, and follows the development of the disease.
Table below demonstrates major health problems in 71 members/patients of the Association, who provided their data. The information is subdivided according to their age when MFS was diagnosed, or surgery was carried. Data from other 23 patients is not shown.

Table 1 Major heath problems in the studied group

Diagnosis at age	**Health problems**						
	Heart	*Eyes*	*Lungs*	*Skeleton/joints*	*Nervous syst*	Fatique sy	*Patients*
0 - 10 years	27	23	5	35	9	14	39
11 - 20 years	10	3	3	12	4	6	15
21 - 30 years	1	1	0	3	1	2	3
above 30 years	11	3	2	13	4	6	14
Total	49	30	10	63	18	28	71
Surgery at age	*Aorta/valve*				*Eyes*		
0 - 10 years	1				2		
11 - 20 years	5				6		
21 - 30 years	10				7		
above 30 years	11				3		
Total	27 (38%)				18 (25%)		

Keywords: *Marfan syndrome – aortic dilatation – ectopia lentis – fibrillin – patient organisations*

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Poster session – Abstract 6

BECKWITH-WIEDEMAN SYNDROME - DIAGNOSTIC EXPERIENCES IN SLOVAKIA

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Beckwith-Wiedeman syndrome (BWS) is a rare genetic disease associated with owergrowth and predisposition to tumor development. The incidence of BWS in different ethnic group is estimated to be 1 out of 13 700 (Weksberg, 2010).
We present prevalence data in Slovakia, clinical data, diagnostic approaches and testing strategy for patient with BWS phenotype (figure 1).

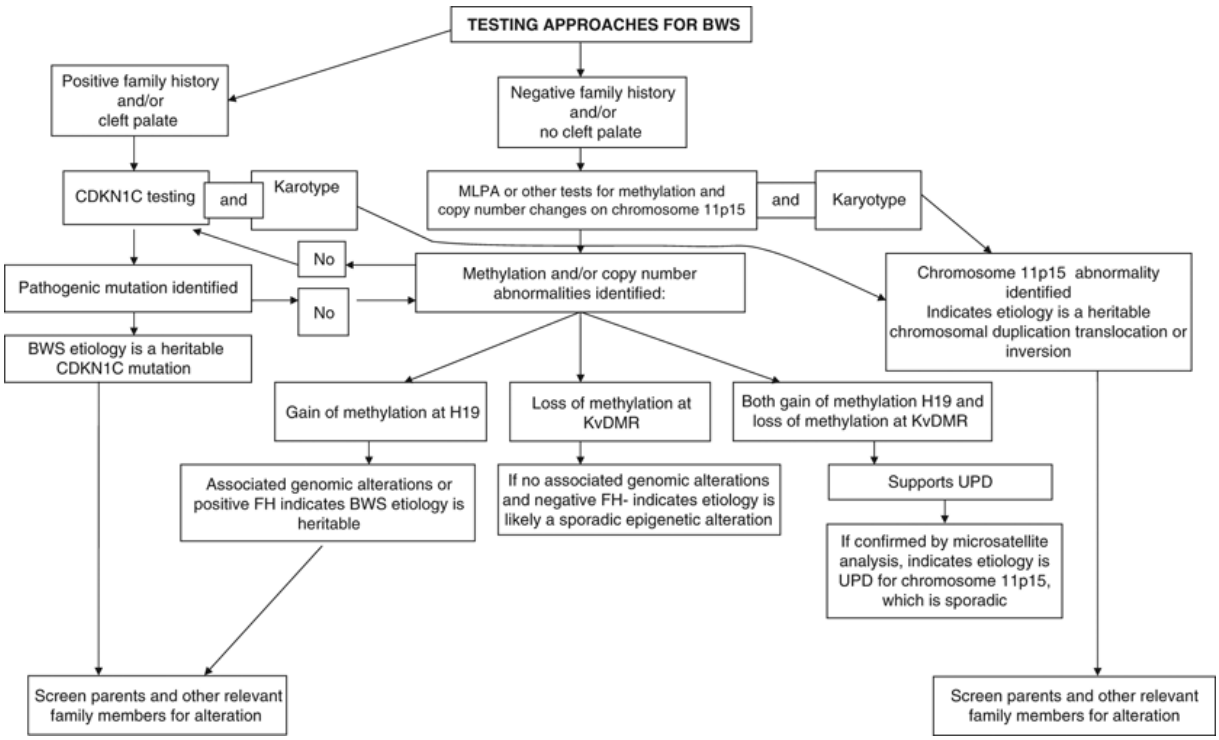

Figure 1: Testing approaches for BWS
(R .Weksberg et al., European Journal of Human Genetics (2010))

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BWS in our 3 presented children was caused by various genetic mechanisms that dysregulate the imprinted genes on chromosome 11p15.5. Generally, in patient with BWS phenotype, in addition to chromosomal analysis, determination of altered methylation, microdeletion at imprinting center 1(IC1)and/ or (IC2) or mutation in CDKN1 by DNA tests helped confirm BWS diagnosis definitelly. Positive results of genetic diagnostic tests may have a crucial role in the next health care managment as well as reproduction decision making in the family with BWS child.

Keywords: *Beckwith-Wiedeman syndrome phenotype – prevalence in Slovakia – diagnostic tests*

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RARE DISEASES IN THE SLOVAK REPUBLIC
EUROPLAN NATIONAL CONFERENCE

Poster session – Abstract 7

NON TREATED PHENYLKETONURIA – SCALE OF METABOLOMIC CHANGES

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Introduction: Phenylalanine hydroxylase deficiency (E.C.1.14.16.1) causes in patients biochemical and clinical phenotype termed as phenylketonuria (PKU). Based on data presented by Slovak neonatal screening centre, the incidence of all forms of hyperphenylalaninemia is 1:6500. High efficiency of neonatal screening programme enables early therapy and discrimination of the production of toxic metabolites which are in a causal relation to brain impairment and mental retardation. Thanks to screening programme it is practically impossible to come across a patient with expressed pathological metabolomic profile typical for phenylketonuria. However we had an opportunity to experience this rare situation and to see clear metabolic changes in two brothers with non-treated disease.
Material and Methods: Determination of amino acids in serum and urine was performed by thin layer chromatography (TLC) and quantitatively by high performance liquid chromatography (HPLC). The profile of organic acids in urine and determination of pathological metabolites was achieved by gas chromatography coupled with mass spectrometry (GC/MS). Molecular genetic methods included isolation of DNA from blood, PCR amplification, and sequence analysis of *PAH* gene.
Results: Positive Fölling test was demonstrated in patients' urine samples. In TLC test of serum and urine samples intensive zones of phenylalanine were present. Quantitative determination of serum amino acids revealed high values of phenylalanine in both patients – 2503 μmol/l and 1594 μmol/l respectively. GC/MS analysis of urine organic acid shows typical picture of phenylketonuria – extremely high values of phenyllactate, phenylpyruvate and presence of other typical metabolites. We have found secondary metabolomic changes as a result of impaired phenylalanine hydroxylation. In *PAH* gene, two mutations were detected R408W and IVS12nt1.
Conclusion: In two patients – brothers with non-treated phenylketonuria – we describe metabolomic changes. We present the findings as an educative model of hereditary metabolic disorder, which has not so important consequences for health today, thanks to neonatal screening and effective therapy.

Keywords: *phenylketonuria – hyperphenylalaninemia – PAH gene,*

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EUROPLAN NATIONAL CONFERENCE

Poster session – Abstract 8

PRIMARY IMMUNODEFICIENCIES IN CHILDHOOD – A ONE-CENTRE EXPERIENCE

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Primary immunodeficiencies (PID) represent a heterogeneous group of inherited disorders with variable frequency in the population. In general, the more frequent immunodeficiency is, the better prognosis it possesses. The most serious forms of primary immunodeficiencies are usually rare and they belong to the group of so-called orphan diseases. The sooner a particular disease is revealed, the sooner it can be adequately treated. An early diagnosis improves the prognosis of the patients with PID significantly. In humoral defects, we apply immunoglobulins regularly. In serious and combined diseases, the treatment of choice is the transplantation of hemopoietic stem cells, if possible, before the onset of infectious complications.
The aim of this presentation is to show the overview of actual situation in the management of primary immunodeficiencies in Slovakia and present of one-centre experience with the diagnosis and treatment of primary immunodeficiency.

Keywords: *primary immunodeficiencies – rare diseases – management*

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RARE DISEASES IN THE SLOVAK REPUBLIC
EUROPLAN NATIONAL CONFERENCE

Poster session – Abstract 9

HYPOPHOSPHATASIA

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Introduction: Hypophosphatasia is a rare hereditary metabolic disease caused by the deficit of tissue nonspecific serum alkaline phosphatase (TNSALP). The incidence of all forms of hypophosphatasia is estimated at around 1:100 000 liveborns. Recent studies estimate the prevalence of mild autosomaldominant form at 1: 6370. During prenatal developement, this disease may cause severe damage of a fetus and even intrauterine death. During childhood, this disease manisfests with defects of mineralization with rickets signs. The following hypercalcaemia and hypercalciuria may even lead to death. In adults, the main manifestations are osteomalatia, skeletal deformities, fractures and early arthritis.
Material and methods: We present the clinical course of hypophosphatasia in two sisters and the clinical features in an unrelated adult woman. Extremely low values of TNSALP were observed (0.06 μkat/l; 0.08 μkat/l; 0.03 μkat/l). To find causal mutations, sequencing of ALPL gene was performed.
Results: Diagnosis of hypophosphatasia was confirmed in all three patients. We found a 436G>A and a 1183insT mutation in the adult woman. Very mild phenotype was observed and both mutations were previously not described. In silico 3D modeling of TNSALP was used to demonstrate the mutation causality. Segregation analysis was useful for genetic counselling in affected family. We found a 299C>T and a 571G>A mutation in two sisters, who were the first documented cases with childhood form of the disease in Slovakia.
Conclusion: Defects of mineralization of bones and teeth (in the presence of low or moderately decrased values of ALP) is a reason for considering hypophosphatasia. The molecular genetic diagnostics opens the possibility of determinig the molecular cause of hypophosphatasia in Slovak patients. The proper diagnosis is essential for an adequate therapy management, like avoiding the treatment with biphosphonates and excess of vitamin D, where higher risk of pseudofractures in adult patients with osteomalatia was described. After determining the causal mutation, genetic counselling and eventual prenatal genetic testing are recommended.

Keywords: *hypophosphatasia – alkaline phosphatase – rickets – ALPL gene*

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RARE DISEASES IN THE SLOVAK REPUBLIC
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Poster session – Abstract 10

ENZYME REPLACEMENT THERAPY OF FABRY DISEASE IN SLOVAKIA

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Introduction: Fabry's disease (FD) is an X linked lysosomal storage disorder characterised by deficient activity of the enzyme alfa - galactosidase A. The disease is rare, but its prevalence may be underestimated due to its variable clinical picture. FD takes a progressive course and the prognosis, if untreated, is bleak. Clinical symptoms, starting with acute and chronic pain, neurological symptoms of the extremities, usually arise in childhood (4 - 10 yrs). Diarrhea, nausea, vomiting, hypohidrosis, skin lesions and corneal changes are common. With increasing age, cardiac and cerebrovascular abnormalities, together with a gradual deterioration of renal function, are very frequent. Two commercial products of α-galactosidase A are available for enzyme replacement therapy (ERT). Both are produced artificially from genetically engineered cells: cultured human fibroblasts in case of agasidase-alfa (REPLAGAL ™); and Chinese hamster ovary cells in the case of agalsidase-beta (FABRAZYME®) but their long term safety and efficacy are still being investigated.
Material and methods: The survey of all diagnosed patients with FD in Slovakia is given. Hospital Pharmacy, 1st Department of Pediatrics and Centre for Inherited Metabolic Diseases, 2nd Department of Pediatrics at the Children's University Hospital in Bratislava are included. Monitoring of long term efficacy and safety of ERT (enzyme replacement therapy) is presented.
Results and Conclusion: Currently, 8 patients (5 males and 3 females) with Fabry disease are diagnosed in Slovakia. First two male patients started with recombinant human alfa galactosidase therapy in year 2003. They were involved in multicenter, open-label study of low dose maintenance treatment of Fabrazyme. The first, at that time 53-year-old patient, refused further therapy after the end of the study (2005), the other, then 26 years old, continues in the ERT. There are at present another two patients with FD, a 30-year-old man is treated with agalsidase-beta, and a 62-year-old woman with agalsidase-alfa. Clinical stabilisation was achieved in all treated patients. Safety of the ERT is continuously monitored, no serious adverse events have occurred yet. FD was also confirmed in two women and two male children without any serious clinical manifestations and therefore no ERT has been used, yet.

Keywords: *Fabry disease – orphan diseases – defect of lysosomal enzyme – alfa-galactosidase A*

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RARE DISEASES IN THE SLOVAK REPUBLIC
EUROPLAN NATIONAL CONFERENCE

Poster session – Abstract 11

PEROXISOMAL INHERITED DISORDERS IN SLOVAKIA

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Single-membrane surrounded organelles, the peroxisomes, are present in all eukaryotic cells. Main function of peroxisomes is the breakdown of very long chains of fatty acids through β-oxidation; synthesis of plasmalogens, which is the most abundant phospholipid in myelin; metabolisms of bile acids; and also detoxification of hydrogen peroxide.
Peroxisomes arise by division of pre-existing peroxisomes and also by de novo biogenesis from endoplasmatic reticulum. A set of approximately thirty proteins, known as peroxins or PEX proteins, have been identified as factors critical for correct peroxisomal biogenesis and maintenance of functional peroxisome. Because peroxisomes do not contain endogenous DNA, all peroxins involved in peroxisomal biogenesis must be encoded by nuclear PEX genes. Subsequently, all these proteins required for assembly and function of peroxisomes are synthesized on free polyribosomes in the cytosol before post-translational import into the peroxisome. Transportation of peroxisomal proteins requires the presence of specific import sequences known as peroxisomal targeting sequences (PTS1 and PTS2). These PTSs sequences are recognized by different receptors, which direct peroxisomal proteins to the membrane.
At present, about twenty genetically determined peroxisome diseases were described. Depending on the extent of damaged metabolic functions, they are divided into diseases of generalized loss of peroxisomal functions (for example Zellweger syndrome) and deficiencies of individual peroxisome enzymes (most commonly X-Adrenoleukodystrophy). Most of disorders are autosomal recessive; however, the commonest peroxisomal disorder X-adrenoleukodystrophy has an X-linked mode of inheritance. In the first step, human patients are correctly classified in the group of disease by detection of their metabolites and subsequently by detection of biochemical abnormalities using molecular genetic techniques to identify the exact cause of the disease.

Keywords: *Peroxisome – peroxisomal disorders – adrenoleukodystrophy – Zellweger syndrome – PEX*

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RARE DISEASES IN THE SLOVAK REPUBLIC
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Poster session – Abstract 12

NEUROMYELITIS OPTICA - A CASE REPORT OF 32-YEAR OLD SLOVAK PATIENT WITH THE VERIFIED PRESENCE OF ANTIBODIES AGAINST AQUAPORIN-4 IN SERUM AND CSF

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Introduction: Neuromyelitis optica (NMO) is a rare disease belonging to a group of CNS demyelinating diseases that has usually clinically serious course. Recent studies indicate that the autoantibodies against aquaporin-4 play important an role in the pathogenesis of NMO. The correct diagnosis and adequate treatment of the disease can cause significant problems.
Case report: Here we present the case report of 32-year-old woman treated for hypothyroidism in autoimmune thyroiditis, who underwent left unilateral retrobulbar neuritis in 02/2009. In 06/2009 this patient was sent to our Department of Neurology because of reccurent bilateral visual impairment. The severe bilateral visual disturbances were present, otherwise the objective neurological findings were normal. MRI examination of the brain did not demonstrate the presence of intracranial demyelinating lesions. In the cervical spinal cord at the level of C5 it showed T2WI-hyperintensive, paracentrally right located intramedullar lesion. CSF examination revealed mild hyperproteinorhachia (720 mg/L), mononuclear pleiocytosis (163/3); intrathecal synthesis of oligoclonal immunoglobulins was absent. CSF serological tests did not confirm the presence of neuroinfection. In both serum and CSF of the patient, the presence of antibodies against aquaporin-4 was detected, which show high specificity for the diagnosis of neuromyelitis optica. The patient received combined immunosuppressive therapy (prednisone, azathioprine) and a 5-days course of intravenous immunoglobulins. In order to prevent relapses the patient was set on a long-term combined immunosuppressive therapy (azathioprine 100 mg, 10 mg prednisone). There was a subsequent improvement of the vision in both eyes; currently, only a residual scotoma in the left eye remains. The efficacy of immunosuppressive therapy was confirmed by control MRI examination of cervical spinal cord, which revealed the disappearance of intramedullar cervical spinal cord lesions.
Conclusions: NMO diagnosis is based on clinical, CSF, MRI criteria and on the presence of autoantibodies against aquaporin-4. The basis of treatment is long-term immunosuppressive therapy with azathioprine in the dose of 100 mg/day, whose primary objective is to prevent relapses of the disease.

Keywords: *neuromyelitis optica – aquaporin-4 – azathioprine*

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Poster session – Abstract 13

JC VIRUS INFECTION AND PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY IN A PATIENT WITH THE B-CELL CHRONIC LYMPHOCYTIC LEUKAEMIA

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Introduction: B-cell chronic lymphocytic leukaemia (B-CLL) is characterized by an accumulation of long-lived, functionally inactive, mature-appearing neoplastic B-lymphocytes. It is associated with severe immunodeficiency. Chemotherapy or immunotherapy generally makes the immunodeficiency worse. JC virus (John Cunningham virus; JCV) is a type of human polyomavirus that causes the progressive multifocal leucoencephalopathy (PML). JCV is found in 70 to 90 percent of population. The virus remains in gastrointestinal tract or tubular cell of kidneys and may infect oligodendrocytes and astrocytes. Immunodeficiency or immunosupression associated with several drugs (e.g. monoclonal antibodies) or HIV infection allow the reactivation of JCV.
Case-report: The authors present here a case of a 62-years old patient with B-CLL that was diagnosed 6 years ago. The patient underwent 4 courses of the first-line COP chemotherapy consisting of vincristine, cyclophosphamide and prednisone. A partial remission of the disease was achieved and the patient was on the maintenance therapy with chlorambucil for 5 years. The second-line COP chemotherapy and immunotherapy with rituximab was used because of B-CLL progression. Treatment was complicated with ischemic stroke and quadriparesis with left predominance. Magnetic resonance imaging (MRI) showed several cortical and subcortical lesions in frontal and parietal lobes bilaterally. Anticoagulation, vasodilatation and rehabilitation transitorily improved patient's clinical status. After the fifth course of immunotherapy, the patient suffered from dysarthria, disorientation and deterioration of personality. B-CLL infiltration of brain was suspected. The cerebrospinal fluid examination excluded central nervous system infiltration with B-CLL. MRI discovered progression of brain lesions and the diagnosis of PML was supposed. PCR detected the presence of JCV in cerebrospinal fluid and confirmed that diagnosis. Patient died in several weeks after diagnosis.
Conclusion: Severe immunodeficiency during B-CLL treatment may lead to the reactivation of JCV in these patients and cause fatal PML. This work was supported by APVV 222-11; CEVYPET, and grant Vega 1/0016/12 projects.

Keywords: *B-CLL immunodeficiency – JC virus, progressive multifocal leukoencephalopathy – rituximab*

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Poster session – Abstract 14

DIAGNOSTIC METHODS OF ACHONDROPLASIA

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Introduction: Achondroplasia is a type of skeletal dysplasia inherited in an autosomal dominant pattern with complete penetrance and prevalence rate between 1:30000 and 1:10000. 80-90% of cases are sporadic, resulting from *de novo* mutation. This disorder is usually caused by gain of function mutations in exon 10 of *FGFR3* (4p16; 19 exons), gene encoding fibroblast growth factor receptor 3, which plays an important role in the metabolism of connective tissues. These mutations cause receptor activation and inhibition of chondrocyte proliferation, which leads to abnormalities of epiphyseal plate and bone tissues. The clinical manifestations with characteristic radiographic findings include disproportionally small stature (rhizomelic shortening of limbs), disproportionally small and long chest, large head with prominent forehead, midfacial hypoplasia and trident hand, and exaggerated lumbar lordosis later in infancy. Neurological complications and upper airway obstruction may also occur.
More than 99% of achondroplasia is caused by a glycine-to-arginine substitution at codon 380. About 98% of these substitution cases is based on a G-to-A transistion and about 1% of cases on a G-to-C transversion at nucleotide 1138. The homozygous state is often manifested with a more severe phenotype.
Material and Methods: The molecular analysis of exon 10 of *FGFR3* in our laboratory includes two molecular-genetics methods – PCR-RFLP and sequencing. In indicated cases (abnormal ultrasound findings during the third trimester of pregnancy), it is possible to perform molecular-genetics diagnostics also in amniotic fluid samples.
Results: Using this methods, we screened genomic DNA isolated from the leucocytes from patients with clinical features similar to achondroplasia. To date, we have confirmed the suspected diagnosis and found the 1138 G-to-A mutation in 4 patients.
Conclusion: We have developed a reliable diagnostics for the detection of most frequent mutations in suspected diagnoses of achondroplasia.

Keywords: *achondroplasia – FGFR3 gene – 1138 G-to-A transistion*

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Poster session – Abstract 15

SCREENING OF POMPE DISEASE BY MEASURING ALPHA-GLUCOSIDASE ACTIVITY IN DRIED BLOOD SPOTS

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Introduction: Pompe disease is autosomal recessive disorder caused by deficiency of the lysosomal enzyme acid α-glucosidase. Accumulation of glycogen in various tissues of the body and impairment of organ function is a consequence of this metabolic disorder. Pompe disease is classified into infantile, juvenile and adult types based on the onset and clinical manifestation of the disorder. Classic infantile form is the most severe form manifested with prominent cardiomyopathy, hypotonia and death before 12 month of life due to cardiorespiratory failure. The late-onset forms, referred to as juvenile and adult onset, have symptoms that are generally limited to skeletal muscles, with a slowly progressive proximal myopathy and a marked clinical involvement of respiratory muscles. The gene encoding acid α-glucosidase (*GAA*) is located on chromosome 17q25.2-q25.3 and contains 20 exons.
Material and methods: α-glucosidase activity in dried blood spots was measured using fluorogenic substrate 4-methylumbelliferyl-α-D-glucopyranoside and acarbose, inhibitor that eliminate isoenzyme interference of maltase-glucoamylase.
Results: By determination of α-glucosidase activity in dried blood spots, we have detected two patients with Pompe disease. Diagnosis was confirmed by determination of α-glucosidase in leukocytes. Molecular analysis revealed the presence of common mutation IVS1 (-13T→G).
Conclusion: The use of dried blood spots (DBS) for enzyme assays offers particular advantage over using conventional samples. In addition, it allows for large scale neonatal screening and high-risk population screening. Enzyme replacement therapy has been used as a treatment option, improving the quality of life and prognosis of patients. Early diagnosis and treatment of Pompe disease are considered to be critical for maximum efficacy of the enzyme replacement therapy.

Keywords: *Pompe disease – acid α-glucosidase – dried blood spots*

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Poster session – Abstract 16

OMPHALOCELE WITH COMPLETE LIVER EVISCERATION – CASE REPORT

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Introduction: Omphalocele is a congenital developmental disorder that occurs in 1:3.000 – 1:10.000 liveborns with male predominance of 3:1. Omphalocele occurs if the intestinal loops fail to return to abdominal cavity at 11 week gestation, and it is associated with the abdominal wall defect. Because of abnormal embryologic development, it has high risk (50%) of associated chromosomal anomalies. It can be diagnosed accurately by ultrasound in the second trimester and it should be completed with alpha fetoprotein levels, amniocentesis, and examination of other systems because of the high rate of associated anomalies. Vaginal delivery is possible only with small lesions, otherwise cesarean section is recommended. This condition needs operation in short period after birth, so delivery should be in a neonatology center. Primary closure is possible in case of small defects. In case of large lesions, surgical closure can be complicated due to the small volume of abdominal cavity causing an increase in abdominal cavity pressure, which results in hemodynamic, cardio-respiratory, and renal compromise. Therefore it is sometimes necessary to close the lesion in two (or more) steps using a mesh.
Case report: Authors present a case of a giant omphalocele with abdominal viscera eventration. Omphalocele was diagnosed by ultrasound in the 11^{th} week of gestation and amniocentesis confirmed normal karyotype 46,XX. The child was delivered by cesarean section in the 36^{th} week of gestation. After the birth, the child underwent operation with only a partial reposition of abdominal viscera, and a prosthetic mesh placement over the liver was needed. Second step surgery was necessary to close the lesion and cover the displaced liver. Postoperative follow up was without complications. The child was discharged at its fortieth day of life.

Keywords: *omphalocele – congenital developmental disorders – abdominal viscera eventration – liver evisceration*

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Poster session – Abstract 17

BARRIERS TO ACCESSIBILITY OF MEDICAL DEVICES FOR PATIENTS WITH EPIDERMOLYSIS BULLOSA HEREDITARIA IN THE SLOVAK REPUBLIC

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Introduction: Epidermolysis bullosa hereditaria (HEB) is a hereditary (autosomal dominant/recessive) rare disease with extremely low prevalence, 0.01 – 0.09 in 10 000 people in the European Union. The main symptom of EB is blistering in different areas of the body due to highly sensitive skin. The only and efficient therapy of choice still remains regular use of medical devices (MD).
Aim: We examined Recessive dystrophic EB, RDEB and Junctional EB, EBJ in relation to accessibility and cost of MD needed for their one-month treatment in the Slovak republic.
Materials and Methods: Monthly demands of RDEB or EBJ were provided by the Slovak patients'organization Debra SR. For information about the MD such as the price, reimbursement by health insurance, patients' contribution to the payment, prescription, indication and amount limits, the official documents provided by Ministry of Health in the SR were used.
Conclusions: Although dressing material is only a small part of the complex care of EB, it might be financially devastating for the patient and his/her family, as well as inefficient as the only health care. However, the rarity of the disease combined with the solidarity of the Slovak health care system forms opportunities to built clear rules acceptable for both sides: the health care payers as well as the patients.

Keywords: *Epidermolysis bullosa hereditaria – dressing material – costs of treatment*

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Poster session – Abstract 18

CLINICAL AND RADIOGRAPHIC PICTURES OF OCHRONOTIC ARTHROPATHY

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Alkaptonuria is an inherited disorder of metabolism of aromatic aminoacids phenylalanine and tyrosine. The defect activity of the enzyme homogentisic acid oxidase leads to the accumulation of homogentisic acid in organism and its excretion in urine. Its polymer – the ochronotic pigment – impregnates the bradytrophic tissues. In clinical and laboratory pictures, pigmentation of scleras and ears can be seen, which are functionally insignificant; restricting changes of the locomotory system, as well as the presence of homogentisic acid in urine can be found. The patients are generally of lower height and they indicate further decrease of their height. The average height of our patients with ochronotic arthropathy is 158.5cm in men and 151cm in women. Compared to the overall population, men are lower by 12.9cm and women by 6.1cm. Their height even decreases with the progress of the disease.
First subjective as well as objective symptoms are localized in the area of vertebral column. The patients indicate an undefined feeling of stiffness in the lumbosacral area, which might be accompanied by a minor pain. Some patients feel a certain block while back straightening, which can be overcome only with pain. This stiffness is later accompanied by a significant pain, which is however less severe than in inflammatory diseases of the spine. The pain remains localized and limited to the lumbal area without any radiation into surrounding areas and without any periodical fluctuation in its strength. It seems that the disproportion between the less significant pain and the progressive movement restriction is typical of ochronotic arthropathy.
Among radiographic changes in manifest ochronosis, we repeatedly found a formation of marginal osteophytes of the vertebral bodies, which were often very massive. Almost always, smaller porotic pseudocystic deposits were found in the imminence of those osteophytes. Regressive changes of the discs accrue and calcifications become more intense with further development of the disesase process.

Keywords: *Alkaptonuria – lumbar pain without radiation – lumbosacral stiffness*

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Poster session – Abstract 19

HAIRY CELL LEUKEMIA (ORPHA58017, ICD10: C91.4) – SINGLE CENTER EXPERIENCE

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Introduction: Hairy cell leukemia (HCL) is a rare indolent B-cell chronic lymphoproliferative disorder characterized by splenomegaly, pancytopenia, presence of hairy cells in peripheral blood/bone marrow and reactive marrow fibrosis. The annual incidence of HCL is estimated to be 0.3 cases per 100,000. The disease accounts for approximately 2-3% of all adult leukemias. The median age at diagnosis is 52 years.
Materials and Methods: The aim of the present study was to compare the outcome of patients affected by typical HCL treated with cladribine. We retrospectively examined medical records of patients with HCL treated at the Department of Hematology and Transfusiology in Martin University Hospital between JAN 1998 to DEC 2012. We used Microsoft Office Excel for Mac 2011 (version 14.3.0) to do some basic data analysis.
Results: The analysis included 11 patients (7 non-pretreated patients, 3 patients with relapse after previous treatment of cladribine, and 1 patient with progressive disease during a treatment with interferon). There were 4 women and 7 men. Mean age was 50.9 ± 13.3 years. All patients were treated with cladribine 0.14 mg/kg/day by subcutaneous bolus injections for five consecutive days. Cladribine caused predominantly hematological toxicity, in particular an initial neutropenia and long-lasting lymphocytopenia. Febrile neutropenia occurred in 3 patients during post-chemotherapy bone marrow suppression. The patient's condition has improved after administration of empiric antibiotic and antifungal therapy. Eleven (100%) patients achieved partial remission or minimal residual disease within three months of therapy.
Conclusions: One course of cladribine given by subcutaneous bolus injections is very effective in HCL. Treatment appears to be safe, especially if associated with growth factors. However, longer follow-up is required to establish the real impact of this drug.

Keywords: *hairy cell leukemia – cladribine – febrile neutropenia*

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Poster session – Abstract 20

IDENTIFICATION DE NOVO OF COMPLEX CHROMOSOME REARRANGEMENTS INVOLVING CHROMOSOMES 2,5,6,9 AND 18 IN NEW-BORN CHILDREN WITH ABNORMAL PHENOTYPE

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Complex chromosome rearrangements are rare structural abnormalities of chromosomes caused by at least three breakpoints with follow-up exchange of genetic material between two or more chromosomes. Within total population they are observed rarely although their frequency can be higher in balanced states without phenotype presentation. We are presenting the case of de novo complex chromosome rearrangements involving 5 chromosomes found in a new-born child with hypotrophy and facial dysmorfism. By means of standard cytogenetic examination, we found chromosome rearragements involving chromosomes number 2,5,6,9 and 18, and the constitutional karyotype was assigned 46,XY,t(2,5,6,9,18)(p15-16;q23-24;q22.3-23.1;q21.3-22.1;q21-22), by M-FISH method, translocations t(2;18), t(5;6), t(6;9) were confirmed.
Array CGH analysis revealed an interstitial deletion on chromosome 6(q23.3;q24.3).
Phenotype of our patient correlates with the phenotype in two published cases of patients with similar deletion 6(q23.3;q24.2). The case report points out the individual contribution of the method arrayCGH used in cytogenetic diagnosis of cases with complex chromosomal aberrations and evidently balances rebuildings associated with abnormal phenotype.

Keywords: *interstitial deletion on chromosome 6(q23.3;q24.3) – hypotrophy and facial dysmorfism*

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Poster session – Abstract 21

VITAMIN D DEPENDENT RICKETS – SHORT REVIEW AND CASE REPORT

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Introduction: Rickets is a failure of enchondral mineralisation of new formed bone in a growing persons. There are three groups of causes of rickets – the failure of bone mineralisation, disorders of phosphate homeostasis, and disorders related to vitamin D. The Vitamin D aquires its biological activity after the activation in two steps. The microsomal 25-hydroxylase provides course of first step in liver. The deficiency of this enzyme causes vitamin D dependent rickets type 1B with low serum level of 25-hydroxyvitamin D and with normal serum level of $1,25(OH)_2D$. The rate-limiting step of biological activation of vitamin D is the reaction catalysed by the mitochondrial 1α-hydroxylase in kidney. Mutations of *CYP27B1* (gene for 1α-hydroxylase) causing deficiency of 1α-hydroxylase enzymatic activity lead to decreased serum level of biological active form of vitamin D (with normal serum level of recirculated form of the vitamin D - 25OHvitD) and cause the vitamin D dependent rickets type 1A. The defect of nuclear receptor for vitamin D (VDR) or the defect of another member of nuclear hormonal receptors family (retinoid X receptor) forming heterodimer with VDR cause the vitamin D dependent rickets type 2. This type is associated with increased level of serum $1,25(OH)_2D$.
Case report: We present the case of a 2 yrs old girl with the diagnosis of vitamin D dependent rickets type 1A. She had typical clinical features (dental problems, caput quadratum, rachitic rosary, widening of wrist, bowed legs, bone pain, muscle weakness, retardation of growth), and the following laboratory findings: hypocalcemia, hypophosphatemia, elevation of serum alkaline phosphatese and parathyroid hormone. Radiografic findings showed skeletal deformities, cupping and fraying of metaphyseal region.
Material and metods: The DNA was isolated from periferal blood leukocytes and all exons of *CYP27B1* gene were analysed by DNA sequencing.
Results: The mutation c.1166G>A (p.Arg389His) was detected in homozygous state in our patient.
Conclusion: The molecular analysis of rickets helps to determine the precise type of the vitamin D dependent rickets and to start the treatment in childhood early.

***Keywords**: rickets – vitamin D – 1α-hydroxylase deficiency – vitamin D receptor*

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