regulated by a numerous enzymes that modify and transfer sugar residues to amino acid side chains.

Over 150 different types of CDGs have been described. The most common are phosphomannomutase 2 (PMM2-CDG) and -1,3-glucosyltransferase deficiency (ALG6-CDG). Symptoms common to all CDGs are seizures, psychomotor delay, hypotonia, feeding disorders, liver disease and coagulopathy. Diagnosis is based on clinical presentation and sialotransferrin profiling and confirmed by gene analysis. Early diagnosis is critical in disorders for which specific therapy exists.

Female infant was born from a third, uneventful pregnancy. Parents are not related and older siblings are healthy. Since birth, the infant was severely hypotonic and exhibited developmental delay, feeding disorder and failure to thrive. At the age of three months she was transferred to our Department for further work-up. At that time, she had low body weight (4314 g, 1.c) and was hypotonic with reduced spontaneous movements. We had noticed dysmorphic features- hypertelorism, micrognathia, abnormal ears, flattened nose, rhizomelic limbs, inverted mamillae and abnormal fat distribution. She was fed with elemental infant formula through the nasogastric tube. The patient had small intestine malrotation that manifested with recurrent vomiting which was resolved after surgical intervention. She developed thrombosis of the brain venous sinuses due to coagulopathy (low concentration of antithrombin III, protein C and coagulation factors IX and XI). She was also diagnosed with hypothyreosis and suffered from generalised oedema with hypoalbuminemia as a consequence of protein losing enteropathy, treated with albumin infusions. Protein losing enteropathy improved on elemental formula.

Severe epilepsy was drug-resistant. Sialotransferrin profiling pointed towards a glycosylation defect (elevated di-sialotransferrins, lowered penta- and tetra-sialotransferrins). Gene analysis revealed biallelic mutations in the ALG6 gene, which codes for glycosylation enzyme -1,3-glucosyltransferase.

ALG6-CDG has a recognizable phenotype characterised by hypotonia and proximal muscle weakness, extrapyramidal signs, pharmacoresistant epilepsy, coagulopathy, protein losing enteropathy and dysmorphic features. Described patients had poor prognosis. There is no specific therapy available. Early diagnosis is important to predict and treat symptoms and to stop diagnostic odyssey. It enables prenatal diagnostics in future pregnancies.

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DIVERSITY OF CLINICAL PHENOTYPE OF PATIENTS WITH PYRUVATE DEHYDROGENASE DEFICIENCY DUE TO PDHA1 GENE MUTATIONS

Katarina Šikić*, Danijela Petković Ramadža, Tamara Žigman, Nina Barišić, Ivan Lehman, Johannes A Mayr, Holger Prokisch, Saskia B Wortmann, Wolfgang Sperl, Nikola Mesarić, Valentina Rahelić, Ksenija Fumić, David Ozretić, Maja Tomasović, Ivo Barić. *Department of Pediatrics, University Hospital Centre Zagreb, Zagreb, Croatia*

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Pyruvate dehydrogenase (PDH) is a mitochondrial multiunit complex which catalyzes pyruvate oxidation (derived mainly from glucose) to acetyl-CoA which then enters tricarboxylic acid cycle. Its deficiency results in accumulation of lactate and alanine. Lactate/pyruvate ratio is normal. Brain is almost always affected because it obtains energy primarily from oxidation of glucose. PDH deficiency is most commonly due to

mutation in an X-linked pyruvate dehydrogenase E1 alpha subunit gene (PDHA1). Diagnosis is a challenge especially in females not only because of variable clinical phenotype but also because of skewed X-chromosome inactivation – its pattern varies among individuals, but also among different tissues of the same individual. Therefore, measuring PDH activity is not a reliable guide to the diagnosis in females. Gene analysis may be used to confirm the diagnosis.

Causal treatment options include thiamine (cofactor of PDH), ketogenic diet and dichloroacetate. The goal of the study is to alert medical professionals to clinical variability of PDHC deficiency and thus make easier early diagnosis.

We present a spectrum of clinical phenotypes of six patients with PDH deficiency diagnosed and treated in our Center.

In patients 1 and 2 disease started antenatally – ultrasonography revealed brain ventriculomegaly. After birth MR demonstrated agenesis of corpus callosum, ventriculomegaly, cerebellar hypoplasia. Afterwards those patients had seizures and severe psychomotor retardation. Patient 3 had conatal hypotonia, respiratory difficulties and severe lactic acidosis. MRI revealed mild diffuse brain atrophy. At 8 years he has generalized hypotonia, walks with support. At age 6 months patient 4 presented with somnolence, metopic synostosis and mild white matter atrophy and ventriculomegaly. At 6 years she has hypotonia, moderate psychomotor retardation and ataxia. Patient 5 presented at 3 months with acute encephalopathy of unclear etiology. At 7 years she has isolated epilepsy and normal psychomotor development. Her older brother died at the age of 17 days due to cardiorespiratory failure of unknown cause. Patient 6 have had intermittent ataxia since 1 year and 8 months of age. Now at 10 years he has normal cognition. All patients had elevated plasma alanine and lactate (2,66-19,9 mmol/L; ref. range 0,63-2,40), and CSF lactate (3,64-8,52 mmol/L; ref. range 1,2-2,1), with normal lactate/pyruvate ratio. All patients were on ketogenic diet and thiamine treatment. No patient had regression or deterioration while on therapy.

PDH deficiency should be in differential diagnosis of most neurological signs and symptoms. Early diagnosis may enable optimal treatment and proper genetic counseling.

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EARLY ONSET LIVER FAILURE DUE TO MITOCHONDRIAL DNA DEPLETION: CLINICAL COURSE OF FOUR PATIENTS

Danijela Petković Ramadža*, Tamara Žigman, Ruža Grizelj, Dorotea Ninković, Lana Omerza, Mirna Natalija Aničić, Marijana Čorić, Johannes A Mayr, René Feichtinger, Saskia Wortmann, Holger Prokisch, Ksenija Fumić, Jurica Vuković, Ivo Barić. *University Hospital Centre Zagreb and*

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Mitochondrial DNA depletion syndromes (MDS) are a group of autosomal recessive disorders caused by disruption of mtDNA maintenance that results in reduced mtDNA content and disturbed energy production. MDS are genetically and phenotypically heterogeneous. One common phenotype is the hepatocerebral form that manifests in first months of life and causes early death due to liver failure. Liver transplantation (LTx) is not recommended in patients with neurological involvement. Our objective is to raise awareness about the clinical spectrum of early onset liver failure due to MDS.

We report clinical course and genotype of four patients with hepatocerebral form of MDS.

Patients 1 and 2, daughters of consanguineous Roma parents, presented with liver failure at six and two days of life, respectively. The older sibling had lactic acidosis and progressive liver failure, without clear neurological involvement. Liver histology revealed gigantocellular hepatitis, fibrosis, cholestasis, hemosiderosis and steatosis. Working diagnosis was neonatal hemosiderosis. Despite the treatment, disease progressed to death at 40 days. Younger sibling had similar clinical course and MDS was suspected. Immunohistochemical staining of the deceased sibling's liver showed combined respiratory chain deficiency. Homozygous variant in the DGUOK gene in both patients confirmed the diagnosis. Despite cofactor/antioxidant treatment, patient 2 died at the age of two months.

Patient 3 presented with recurrent nonketotic hypoglycemia, cholestasis and hypotonia at the age of two months. Liver disease was slowly progressive, with permanently elevated lactate and alanine. Histology showed gigantocellular hepatitis, fibrosis, cholestasis, hemosiderosis, polymorphous mitochondria and microvesicular steatosis. MDS was suspected, but immunohistochemical staining was uninformative. Due to end-stage liver disease, LTx was performed at the age of six months. Patient died in early postoperative period. Whole exome sequencing (WES) revealed biallelic mutations in the MPV17 gene.

Patient 4 had intrauterine growth retardation, severe hypotonia and developmental delay since birth. Acute liver failure, presenting with ketotic hypoglycemia, lactic acidosis, hepatomegaly and coagulopathy, occurred at the age of four months. The individual additionally developed nystagmus. Brain MRI was normal. Liver biopsy showed steatosis and abnormal mitochondria. Immunohistochemistry and clearly decreased mtDNA copy number per nuclear genome in liver pointed to MDS. The disease progressed rapidly and patient died three weeks after admission. WES revealed two biallelic mutations in the POLG gene.

Revealing genetic basis of liver failure due to MDS, with WGS as an important option, is pre-requisite to decision on LTx. It is also essential for genetic counseling and prenatal diagnosis in future pregnancies.

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METHYLATION BIOMARKERS S-ADENOSYLMETHIONINE AND S-ADENOSYLMOCYSTEINE AND METHYLATION POTENTIAL IN NEWBORNS WITH CONGENITAL HEART DISEASE AND THEIR MOTHERS

Dorotea Ninković*, Ksenija Fumić, Iva Bilandžija Kuš, Tarik Kapić, Ivana Križić, Danijela Petković Ramadža, Boris Filipović-Grčić, Vesna Benjak, Andrea Dasović Buljević, Ruža Grizelj, Ivo Barić. *Department of Pediatrics, University Hospital Centre Zagreb, Zagreb, Croatia; School of Medicine, University of Zagreb, Zagreb, Croatia*

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The low availability of folic acid or vitamin B12 in the early pregnancy and consequent mother's hyperhomocysteinemia are associated with the risk of having a child with congenital heart disease. The goal of this study was to determine whether homocysteine itself is a risk factor for congenital heart disease or changes in methylation biomarkers S-adenosylmethionine (AdoMet) and S-adenosylhomocysteine (AdoHcy) and methylation potential are responsible for a higher incidence of congenital heart disease.

In order to reach goals of this study, we included 127 newborns with congenital heart disease and 103 mothers of affected newborns with congenital heart disease. We measured AdoMet and AdoHcy in their plasma by high performance liquid chromatography tandem mass spectrometry and then calculate their methylation potential and compare them with the reference values.

In the group of newborns with congenital heart disease we have found statistically significant increased AdoMet compared to the referral group (289 vs. 184 nmol/L). There was no statistically significant difference in the concentration of AdoHcy (67 vs. 81,5 nmol/L). Methylation potential in this group was consequently statistically significantly higher (4,34 vs. 2,35). In the group of mothers of newborn with congenital heart disease we have found statistically significant increase of AdoHcy compared to the referral group (20 vs. 15,2 nmol/L), but no statistically significant difference in the concentration of AdoMet (81 vs. 81,9 nmol/L). Methylation potential was statistically significantly lower (4,55 vs. 5,54).

Increased concentrations of AdoMet or AdoHcy measured in our groups of examinees and statistically significant differences in the methylation potential values in our groups of examinees compared to the reference values point to changed methylation processes which could contribute to the pathogenesis of congenital heart disease. Further studies are needed to elucidate the exact mechanism by which disturbed methylation leads to higher risk for congenital heart disease and changes in methylation processes in the fetus.

Neonatology

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HEMIMEGALENCEPHALY AND OHTAHARA SYNDROME CAUSING NEONATAL SEIZURE – A CASE REPORT

Katarina Pavičić Klancir*, Vlasta Đuranović, Sanja Pejić Roško, Milan Stanojević, Anita Pavičić Bošnjak, Ana Šimečki Butajla, Ivan Zovko. *University hospital "Sveti Duh"*

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Hemimegalencephaly (HME) is rare congenital, hamartomatous malformation of the brain cortical development characterised by enlargement of all or a part of one cerebral hemisphere. It is estimated that prevalence range is from 1 to 3 cases per 1000 children with epilepsy, and 1-14% among children with disturbed cortical development. Ohtahara syndrome is a rare infant epilepsy syndrome, characterised by "burst suppression" pattern in EEG (high amplitude spikes followed by little brain activity or flattening of the brain waves). It is accompanied by severe neurodevelopmental delay, presumably caused by HME as a structural malformation.

We present a case of female premature newborn from bichorionic, diamniotic twin pregnancy, who was delivered vaginally after 35 weeks and 6 days, as the first twin. Apgar scores after 1 and 5 minutes were 10, physical examination was uneventful. The first in vitro fertilization resulted in twin pregnancy of 27-year healthy mother. Apart from oligohydramnios before delivery, pregnancy was uneventful. Family history of both parents was unremarkable. At the age of 24-hours baby girl developed first tonic spasms lasting one minute and spontaneously ceasing, without losing consciousness.