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

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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.

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HEMIMEGALENCEPHALY AND OHTAHARA SYNDROME CAUSING NEONATAL SEIZURE – A CASE REPORT

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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.