Abstracts

HYPONKETOTIC HYPOGLYCEMIA AND HYPERAMMONEMIA AS PRESENTING FEATURES OF EARLY ONSET MULTIPLE ACYL-COA DEHYDROGENASE DEFICIENCY

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Introduction Multiple acyl-coenzyme A dehydrogenase deficiency (MADD) or glutaric aciduria type II is a rare, autosomal recessive disorder of fatty acid and amino acid oxidation. Disease is caused by pathogenic mutations in ETFA or ETFB genes, which encode two subunits of electron transfer flavoprotein (ETF), or ETFDH gene, encoding for ETF-dehydrogenase. Phenotype is heterogenous, from severe neonatal acute metabolic decompensation, with or without congenital anomalies, to milder, late onset forms. Diagnosis is made by acylcarnitine and urinary organic acid analysis, and gene testing. Treatment is based on restricted fat and protein intake, high carbohydrate diet, with carnitine, riboflavin and CoQ10 supplementation.

Case Report Patient is a second child of unrelated parents. Family history unremarkable. Pregnancy was complicated by oligohydramnios. Delivery was on term, uneventful, BW 3740 g, BL 53 cm, AS 10,10. Tremor occurred as manifestation of hypoglycemia (BG 1.8 mmol/l), corrected with 10% oral glucose, on the first day of life. The newborn was euglycemic until 20 hours of life when irritability and somnolence were noticed in hypoglycemia (capillary glucose 2.3 mmol/l, venous glucose was immeasurably low). Glucose infusion was started but patient deteriorated to bradypnea and bradycardia.

Cardiopulmonary reanimation lasted 40 minutes. Upon admission in NICU, patient was cardio-respiratory stable, but unconscious, hypertonic and soon developed seizures. Laboratorv findings revealed metabolic acidosis (pH 7.3, BE -15.6), hyperlactatemia (14 mmol/l), hyperammonemia (230 μmol/l), increased aminotransferases and CK, normal blood glucose and positive urinary ketones. Brain MRI revealed cortical cytotoxic edema, restricted diffusion in corticospinal tracts and pons, and temporal atrophy. Ammonia normalized following high caloric intake, nitrogen scavengers, L-arginine, L-carnitine and vitamin B12. Urgent metabolic work-up revealed typical plasma acylcarnitine and urine organic acid profile for MADD. We started low protein and fat, high carbohydrate diet, continued with L-carnitine and added CoQ and riboflavin in therapy. Ultrasound showed mild hypertrophic cardiomyopathy and no malformations of other organs. Gene analysis revealed homozygous mutation c.1250C>A (p. Thr266Met) of the ETFA gene. In further course patient was stable, but with severe developmental delay, epilepsy and impaired vision.

Conclusion Beta oxidation defects, even with positive ketones, should be in differential diagnosis of neonatal hyperammonemia, as treatment is different than for other diseases. Lipid infusions, used to provide adequate caloric supply in other disorders, are contraindicated. Urgent metabolic work-up is mandatory for early diagnosis and optimal patient management. Clinical course with early acute cardio-respiratory failure, hypoglycemia and moderate hyperammonemia may be indicative for beta-oxidation defects.

ALG6-CDG- CONGENITAL DISORDER OF GLYOSYLATION WITH RECOGNIZABLE PHENOTYPE


Congenital disorders of glycosylation (CDG) is a large group of genetic metabolic diseases that usually affects many different organ systems. Glycosylation is a complex process
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-sialotransferrin, 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.

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 phenotypetically 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) in 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.