ROS levels and MnSOD expression while the other showed borderline ROS increase and MnSOD down-regulation. Our data highlights the main molecular pathways modulated in LCHADD as well as the role of ROS and ROS buffering in phenotype severity.

15. Disorders of pyruvate metabolism and the Krebs cycle

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Fumaric aciduria case

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Background: Fumaric aciduria refers to a mitochondrial disorder, due to lack of fumarase activity, and manifesting as progressive encephalopathy, hypotension, dyspnea, seizures and lactic acidosis.

Case report: – 10 days old, was examined in the ICU. History of the disease: 2 hours after birth dyspnea and diffuse hypotonia appeared. Hypotension increased, depression of reflexes, respiratory failure, cardiomyopathy, arrhythmia, hepatopathy, anemia (hemoglobin 88 g/L, platelets 86*109/L), hypoglycemia.

Examination: malnutrition, pallor, marbled skin, triangular face, flattened chest, valgus feet. Blood tests: lactate ↑2.63 mmol/l, ↑ammonia 122 μmol/l, ↑glutamate, ↑glycine, ↓tyrosine, ↓isoleucine, ↓tryptophan. Gas chromatography test: urine ↑↑fumarate 641.29 mmol/mol creat, ↑↑ lactate 2606.75 mmol/mol creat, ↑↑ oxoglutarate 3491.7 mmol/mol creat; ↑succinate. Periventricular leukomalacia.

The diagnosis: fumaric aciduria (fumarase deficit), secondary hyperammonemia. With a diet and metabolic therapy the child's condition has stabilized; hypotonia persisted, hypodynamy, cardiomyopathy.

Conclusion: Acute deterioration of the child after birth with the development of hypotension, cerebral depression, it is necessary to carry out tests to exclude congenital defect of metabolism, including mitochondrial dysfunction.

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Ketone bodies: a therapeutic option to replace ketogenic diet in PDH deficiency?

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Background: Ketogenic diet is the first line therapy for dystonia and other features of PDH deficiency and intractable seizures in a number of disorders, including GLUT1 deficiency. The effects of ketogenic diet are supposed to partly be mediated by its ultimate metabolites, i.e., ketone bodies. Because of limitations of this high fat diet, we investigated if oral administration of ketone bodies (racemic 3-hydroxybutyrate) could effectively replace the ketogenic diet.

Results: In three patients with GLUT1 deficiency, progressive partial substitution of ketogenic diet with 3-hydroxybutyrate led to clinical deterioration in terms of seizures and myoclonus frequency. By contrast, two patients with PDH deficiency showed dramatic improvement in terms of reduced frequency of dystonic crises and fatigability. In both children, 3-hydroxybutyrate fully replaced the ketogenic diet. Ketone body levels correlated negatively with plasma lactate levels (r-squared=0.59). In fibroblasts from PDH deficient patients, administration of 14C-labeled 3-hydroxybutyrate increased CO2 production consistent with improved Krebs cycle activity.

Conclusion: These results strongly argue for a direct beneficial effect in energy metabolism for ketone bodies in PDH deficiency. In GLUT1 deficiency, the results are consistent with proposals that additional metabolic requirements (possibly Krebs cycle anaplerosis) and mechanisms unrelated to energy metabolism may be involved.

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Ketogenic diet application in PDH deficiency during the course of 6 years

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Objective: To evaluate effects of a strict ketogenic diet (4:1) in a patient with X-linked PDH deficiency during the course of 6 years.

Case report: The disease revealed itself during the first months of age with psychomotor delay, infantile spasms, myopathy, swallowing difficulties and respiratory failure. Hyperintense lesions on T2-weighted head MRI were found. Activity of pyruvate dehydrogenase complex activity was found to be decreased in myocytes and skin fibroblasts. Diagnosis of pyruvate dehydrogenase deficiency was further confirmed by revealing missense mutation in PDHA1 gene. Ketogenic formula, sodium bicarbonate and a trial with thiamine was applied from the age of 9 months resulting in markedly improved general state, dysphagia, seizures, hypotonia and psychomotor development during the first 6 months. In biochemical parameters, the most pronounced improvement was observed on hyperlactacidemia, diminishing from maximal values of 15 mmol/l to normal ranges. Further improvements were considerably less after this initial period. Episodes of intercurrent ilnesses were complicated by marked deteriorations, however, regaining of lost skills was generally reported by parents with convalescence.

Conclusion: Ketogenic diet was successful during the course of 6 years in a patient with PDH deficiency.

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Pyruvate dehydrogenase complex deficiency: characterization of variant proteins in a search for alternative therapies

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Pyruvate dehydrogenase complex (PDC) catalyzes the conversion of pyruvate to acetyl-CoA, a key reaction in aerobic metabolism. Three catalytic, one structural and two regulatory subunits are assembled in this mitochondrial complex. The α-subunit of the E1 component ($\alpha 2\beta 2$) is pivotal for active and cofactor binding sites formation, being a target of tight catalytic regulation. Missense mutations in PDHA1, the gene encoding E1α, are the most frequent cause of PDC deficiency (PDCD), which displays a broad clinical spectrum.

Following recovery of a PDCD patient carrying the E1α p. R224G variant upon arginine aspartate intake, we undertook a biochemical and biophysical characterization of E1 variants. The recombinant proteins p. F205L, p. R224G, p. R349C and p. R349H (α and α+β) were expressed