MITOCHONDRIAL MYOPATHY: DEFICIENCY OF HEAT SHOCK PROTEIN 60 (HSP60)

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Mitochondrial (mt) myopathies are neuromuscular disorders caused by defects in mt metabolism. Hsp70 and 60 stabilize structures of mt polypeptides to assure membrane transport resp. assembly into functional enzymes. In one of 30 patient fibroblast cultures hsp60 was hardly detectable. The patient, from consanguineous parents, suffered from lactic acidosis and died 2 days after birth. Heat shock of the fibroblasts caused a minor increase of hsp60 and normal hsp70 induction. Increase of hsp60 mRNA was normal, suggesting defective translation or unstable hsp60 protein. Hsp60 deficiency is likely to cause defects in mt enzymes: activities of cyt. c oxidase, succinate cyt. c reductase and propionyl CoA carboxylase and leucine decarboxylation were deficient. Experiments to show the relation between hsp60 deficiency and the enzyme deficiencies will be discussed.

ACYL CoA CONTENT IN A PATIENT WITH A PEROXISOMAL DISORDER AND MITOCHONDRIAL DYSFUNCTION

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Very long chain fatty acids are increased in peroxisomal disorders. We have measured the Acyl CoA content, total and peroxisomal B-oxidation (TB-OX & PB-OX), and pyruvate dehydrogenase activity (PDH) in fibroblasts from a patient (P) with neonatal adrenoleukodystrophy and controls (C). CoA content was determined after perchloric acid extraction by a fluorometric enzymatic cycling method. Total CoA content for P, C in nmol/mg protein: Acyl CoA 0.129 ± 0.069, 0.045 ± 0.007, p 0.02; acetyl CoA 0.258 ± 0.077, 0.115 ± 0.04, p < 0.01; CoASH 0.003; 0.048. PB-OX was measured in the presence of rotenone and antimycin a. TB-OX in nmol/mg/min (PB-OX, % of TB-OX); P, C 0.198 ± 0.042 (39%), 0.184 ± 0.043 (47%) and PDH in nmol/mg/min; P, C 0.11 ± 0.02, 0.24 ± 0.01, P < 0.004. The increase in acyl CoA and acecyl CoA/CoASH ratio in P may result in decreased mitochondrial PDH activity. P also exhibits clinical evidence of mitochonurial dysfunction characterized by carnitine deficiency. Therefore, the defects in lipid metabolism caused by the peroxisomal disorder of P may contribute to secondary mitochondrial disorders documented clinically and biochemically.

A CASE OF 3-METHYLGLUTACONIC ACIDURIA WITH CONGENITAL NEUTROPENIA

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A 13-month-old girl with dysphagia, severe psychomotor retardation, spasticity, hypertonicity and Kostmann type neutropenia was diagnosed to have 3-metylglutaconic aciduria (3MGCU). Basal urinary excretion of 3-methylglutaconate (MGC) and 3-methylglutarate (MGR) were elevated (45.6 and 12.5mmol/mol·creat.) but that of 3-hydroxyisovalerate (HIV) was normal. Oral leucine loading (100mg/kg) rose the level of HIV in the urine 7 times higher than the basal level without obvious increase of MGC and MGR. Absolute neutophil counts (ANC) were always less than 1,000 /μl. Bone marrow aspiration revealed significantly hypoplastic myelopoiesis with the maturation arrest at the stage of promyelocyte. Serum G-CSF levels were elevated when ANC were lower than 500 /μl. G-CSF stimulated CFU-G proliferation normally in vitro but clinical response to rhG-CSF was poor. These findings suggest that this 3MGCU type 2 case may have circulating inhibitors to myelopoiesis.

NASOGASTRIC CONTINUOUS FEEDING AS THE ONLY TREATMENT IN NEONATAL MAPLE SYRUP URINE DISEASE.

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Peritoneal dialysis (PD) or hemodialysis (HD) are still recommended for the treatment of neonatal maple syrup urine disease (MSUD), but present many risks and disadvantages.
We treated 4 MSUD decompensated neonates with nasogastric continuous feeding programmed on the basis of daily plasma aminoacids. Before starting treatment their neurologic status was greatly deteriorated and leucine values were between 3.0 and 3.3 mmol/l. A normo - hypercaloric (100-130/kg/day) diet, with fluid intake ranging between 100 and 150 ml/kg/day and BCAA-free mixture (2g/kg/day) as the only source of aminoacids was then immediately administered by continuous nasogastric feeding. Valine and isoleucine were reintroduced 2-3 days later to avoid deficiencies.
This kind of feeding was well tolerated and dialysis was never necessary. Leucine values normalized (<0.5 mmol/l) in 7-12 days. All the patients, now between 17 months and 4 years of age have normal height and weight velocities and psychomotor development. This data show that also neonatal MSUD may be treated by diet alone provided it is carefully prepared on the basis of daily aminoacids plasma values.

HEMIARGINATE THERAPY FOR PORPHYRIA CRISES OF TYROSINEMIA

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Porphyria-like symptoms are common in hereditary tyrosinemia (HT). This is due to inhibition of δ-aminolevulinate (ALA) dehydratase (D) by succinylacetone (SA).

We present our experience with hemiarginate (HA) for porphyria crises in two pts with HT. Both showed low activity of erythrocyte ALA-D and sustained high urinary excretion of ALA and SA. The symptoms started at 18 mo (Pt 1) and 3 yrs (Pt 2) with irritability, drowsiness, vomiting, hypertension, and peripheral neuropathy. ALA excretion increased up to 15 times the upper normal limit. When intravenous HA was given (for 4 d), the pts became alert within the first day, painless and normotensive within 3 d, and the neuropathy vanished within 2 wks. Urinary ALA excretion decreased within 24 h. In all, 10 relapses occurred and were treated with HA. In Pt 1 prophylactic HA twice a wk for up to 9 mo prevented recurrences. No side effects of HA were noted.

Conclusion: HA is a safe and effective therapy for porphyria crises of HT.

^{31}PHOSPHOROUS MAGNETIC RESONANCE SPECTROSCOPY OF LIVER AND HEPATIC TUMOR IN GLYCOGEN STORAGE DISEASE TYPE I

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Three Patients with glycogen storage disease type I were studied by ^{31}phosphorous magnetic resonance spectroscopy. During fasting state, phosphomonoester (PME) peak was higher and inorganic phosphate (Pi) peak was lower in GSD livers than those of control. After intravenous glucose loading (0.5g/kg), PME peak decreased and Pi peak increased in the patient' livers. From chemical shift measurement, the main component of PME peak in GSD liver was thought to be sugar phosphate, probably glucose-6-phosphate. One of the patients had a hepatic tumor, which had been observed for 6 years without progression. The spectrum of the hepatic tumor had relatively weak signal. The PME peak of the tumor was high compared with ATP peaks. The PME peak was depressed by glucose loading. From above data, we speculate that the hepatic tumor of GSD patient has an accumulation of sugar phosphate, glucose-6-phosphate, by the same enzyme deficiency.