31 HEREDITARY DEFECT IN MEMBRANE TRANSPORT OF CARNITINE

K-G Sabel, B.O Eriksson, S Höyer, S Lindstedt, I Nordin, A Oldfors, Depts of Pediatrics, Pathology and Clinical Chemistry, Gothenburg University, Gothenburg, Sweden

Of 3 siblings one boy died unexpectedly at 18 mo, one girl is healthy and one girl was admitted at 3 yrs 9 mo with heart failure and signs of dilated cardiomyopathy. Analyses of blood collected for PKU-screening showed low carnitine conc in the patient and her brother, but normal in her sister. Endocardial fibroelastosis and cardiomyopathy was found at autopsy of the dead boy, and similar changes in endomyocardial biopsies of the patient. Carnitine conc in her plasma was 1.2 µmol/l, in skeletal muscle 0.01 µmol/g non-collagen protein (NCP) and in heart muscle 0.05 µmol/g NCP. Skeletal muscle showed lipid accumulation in type 1 fibres and marked atrophy of type 2 fibres. The renal clearance of carnitine was very high (72 ml/min/1.73 sqm BSA). When labeled carnitine was given i.v., 5% was retained after 10 days (in parents 85-90%). Skin fibroblasts grown in a medium containing carnitine, had a carnitine conc <5% of controls. Treatment with oral L-carnitine resulted in rapid clinical improvment, normalization of echocardiographic variables and of the myocardial and skeletal muscle biopsies. Carnitine conc remained low in heart and muscle.

In conclusion this family expresses a hereditary defect in carnitine transport over different cell membranes.

32 INTESTINAL ABSORPTION OF PTERIDINES IN CHILDHOOD

D. TURCK, J.L. DHONDT, J.M. HAYTE, J.P. FARRIAUX. Service de Pédiatrie, CHU, et Laboratoire de Biochimie Faculté Libre de Médecine, Lille, FRANCE.

Oral tetrahydrobiopterin (THB) load has been recommended for the recognition of THB deficiency among hyperphenylalaninemic infants. In some patients with dihydropteridine reductase (DHPR) deficiency, the test has been reported to be ineffective. To explore such a resistance to THB, intestinal absorption of pteridines was investigated . In 10 control children the maximum biopterin (B) serum value was observed 4 hours after oral administration of 5 mg/kg THB. A wide range of B increase (14.6-190.5 nmol/l, mean : 73.2 nmol/l) was noted, suggesting a great variation in the intestinal absorption of THB. A constant rate intestinal perfusion study using a double lumen tube and polyethylene glycol 4000 as non absorbable marker was performed in 8 control infants and 1 adult.Pteridines were separated after acid and alcaline oxydation by ion-exchange HPLC chromatography. THB,B, and pterin mean absorption rates were as follows : THB = 14% (n=9), B=3% (n=3), pterin = 80 % (n=3). These results show a very low intestinal absorption of THB and B in man, and suggest the limiting role of the lateral chain 6-dihydroxypropyl, present in THB and B, and absent in pterin. They could explain the resistance to THB during the oral loading test in DHPR deficient patients.

33 PROTEINASE INHIBITOR CBZ-PHE-ALA-CHN$_2$ (CBZ): A DRUG FOR TREATMENT OF PATIENTS WITH METACHROMATIC LEUCODYSTROPHY (MLD)?

K. Ullrich, St. Schmiereck, K. von Figura+ Kinderklinik und Physiologisch-Chemisches Institut+, Universität Münster, FRG

In cultivated fibroblasts from late onset forms of MLD the degradation of the mutant enzyme is prevented in the presence of CBZ (Proc. Natl. Acad. Sci. USA 80, 6066, 83). - When CBZ (inhibitor of cathepsin B) was given i. v., i. p. or p. o. to female mice a time and dose dependent inhibition of the enzyme was demonstrated in the homogenates of different organs. Using 2 mg/kg i. v. (solvent: propanediol) the highest inhibition was found in the heart muscle (~80 %) and the lowest in the brain (~20 %). After 24 h the residual activity of the enzyme was 60 and 90 % of that of controls, suggesting de novo synthesis. Similar results were obtained by i. p. and p. o. administration of CBZ when 10 and 100 x higher doses were used (solvents: propanediol, DMSO). - Experiments with H^3-CBZ revealed no correlation between accumulation of radioactivity and inhibition of cathepsin B in different organs. - Though CBZ permeates the blood-brain barrier it seems to be of no therapeutic benefit as it's solubility in organic solvents is low.

34 LEUKODYSTROPHY ASSOCIATED WITH HYPERLYSINORHACHIA AND 2-HYDROXYGLUTARIC ACIDURIA.

Jaak Jaeken, Herman Willekens, Lucien Corbeel University of Leuven, Gasthuisbergkliniek,Department of Pediatrics, Leuven, Belgium

Two daughters of related Turkish parents were investigated at the ages of 11 8/12 and 16 8/12 years for severe neurologic disease. This was characterised by pronounced psychomotor retardation, ataxia, dysmetria, dystonia and choreiform movements. Both girls were moderately obese and showed macrocephaly without dysmorphy. Laboratory investigation revealed increased protidorhachia (120 and 47 mg/dl), and increased cerebrospinal fluid lysine (80 and 50 µM; nl 10-25) and urinary 2-hydroxyglutaric acid (400-500 µM/g creatinine; nl < 1). Plasma and urinary lysine as well as cerebrospinal fluid 2-hydroxyglutaric acid were normal except for a slightly increased plasma lysine in one patient (270 µU; nl 60-230). Electromyography and nerve conduction velocity were normal. Computerised tomography of the brain was suggestive of leukodystrophy. Conclusion: this seems to be a previously unreported hereditary metabolic disorder. Its basic defect remains to be determined.

35 DIFFERENT TYPES OF MUTATIONS IN CHRONIC AND ACUTE FORMS OF TYPE 1 TYROSINEMIA.

Ruud Berger[1], Henk van Faassen[1], Inge van der Berg[1], Etienne Agsteribbe[2] and Erik Wiemer[3], University of Groningen, [1]Department of Pediatrics and [2]Laboratory for Physiolocal Chemistry, and University of Amsterdam, [3]Laboratory of Biochemistry, The Netherlands.

This study was undertaken to investigate the molecular basis of the two different clinical phenotypes (acute and chronic forms) of type 1 tyrosinemia (fumarylacetoacetase deficiency). Fumarylacetoacetase (FAA) was isolated from beef liver and antibodies raised in rabbits. Analysis of fibroblasts extracts by immunoblotting showed the absence of cross-reacting material in cells from acute patients and reduced amounts in cells from chronic patients. Fibroblasts from controls and from both acute and chronic patients were pulse-labeled with ^{35}S-methionine followed by a chase of 1-4 days. Radioactively labeled FAA was immunoprecipitated with proteinA-coupled antibody, dissociated and subjected to SDS-PAGE followed by fluorography. In control fibroblasts after pulse-labeling two bands could be visualized, the upper band having a molecular size of 41.200 daltons, the lower band 0.5-1.0 kilodaltons smaller.These bands disappeared after 4 days. In fibroblasts from acute patients the M=41.200 band after synthesis disappeared within 1 day while in cells from chronic patients the rate of disappearance was in between . These results indicate that the acute and chronic forms of type 1tyrosinemia are caused by different types of mutations.

36 HEREDITARY TYROSINEMIA WITH UNUSUAL PHENOTYPIC EXPRESSION.

O.Søvik, Haukeland Hospital, Bergen, E.A.Kvittingen, Rikshospitalet, Oslo, J.Steen-Johnsen, Telemark Hospital, Porsgrunn, S.Halvorsen, Ullevål Hospital,Oslo.

In the chronic form of tyrosinemia renal tubular dysfunction with secondary hypophosphatemic rickets usually is a major finding. Three patients, two brothers and one girl, had at the age of 5,12 and 15 years no generalized hyperaminoaciduria, nor clinical signs of rickets. Untreated the elder brother had only slightly elevated serum tyrosine, 141µmol (normal <80), and low excretion of p-OH-phenyllactate. He had pronounced trombocytopenia ($8x10^9$/l). The brother presented 21 months old with large liver. Serum tyrosine was 318µmol/l, the trombocyte count $48x10^9$/l. Succinylacetone was elevated in urine in both. The third patient was investigated for hepatomegaly in infancy, but developed normally without treatment until she contracted hepatoma at the age of 15 years. Her plasma tyrosine level was 600 - 700 µmol/l, she excreted large amounts of p-OH-phenyllactate and succinylacetone in urine was low but elevated, 8 mol creatinine. The fumarylacetoacetase activity in fibroblasts from both brothers and in lymphocytes from the girl was less than 5 % of normal level. Lack of renal tubular dysfunction in patients with the chronic form of tyrosinemia, is unusual. However, absence of this finding should not preclude the search for this diagnosis in patients otherwise suspected for hereditary tyrosinemia.