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EFFECT OF DIETARY COPPER DEFICIENCY ON BRAIN CATECHOLAMINES OF NEWBORN RATS.

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To investigate the effect of dietary copper deficiency on brain catecholamines of newborn rats an experimental model was developed. Three groups of 10 female Sprague - Dawley rats were used. Group I, copper deficient group, was fed with a copper-free diet 5 weeks pre-gestation and during gestation until delivery. Group II, the control, received a copper addecuate diet (6ppm). Group III, the pairfed, received a copper addecuate diet, but restringed according to the caloric input of the copper deficient group. Inmediatly after birth, the newborn rats from a total of 7; 4 and 7 litters of the groups I, II and III, respectively were decapited. Eleven assays of each group were performed. For each assay we used 1, 2, 3, or 4 whole brains minus cerebella. Whole brain dopamine and noradrenaline levels were quantified by high performance liquid chromatography with electrochemical detector. Copper deficient group showed a highly significant decrease in brain noradrenaline levels (50% lesser than others two groups: $p = 0.0341$), whereas dopamine concentrations remained largely unaltered. The levels of brain copper in the newborn rats in group I were significantively reduced ($p = 0,0001$) as well as brain weight ($p = 0,0012$). The CA1 sector neuronal counting was unaltered, however the girus dentatus counting showed a significant decrease in neuronal cellularity in Group I. We conclude that the materno-fetal copper deficiency altered the synthesis of noradrenaline. This could be a consequence of a functional impairment (possibly Dopamine - - hidroxilase enzyme disminished activity), however the possible role of the hypocellularity as the one observed in the girus dentatus sector can not be excluded.

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METHYLMALONATE AND PROPIONATE EFFECTS ON CO_2 PRODUCTION AND LIPID BIOSYNTHESIS IN BRAIN OF SUCKLING RATS

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Methylmalonic acidaemia and propionic acidaemia are inherited metabolic disorders characterized respectively by methylmalonate (MMA) and propionate (PA) accumulation in tissues of affected patients. Both diseases have severe clinical expression and many undiagnosed patients have a fatal outcome. Those who survive presente neurological dysfunction and a variable degree of neuromotor delay/mental retardation. We investigated the in vitro effects of MMA and PA on CO_2 production and lipid biosynthesis in rat brain. Brain prisms of suckling animals were incubated in Krebs Ringer bicarbonate buffer in the presence of [2-^{14}C]-glucose and 5.0 mM MMA or 5.0 mM PA. Controls did not contain the metabolites. After incubation, $^{14}CO_2$was trapped into Whatman No. 3 paper filter, lipids were extracted from brain prisms and the radioactivity determined in a scintillation counter. We found that MMA but not PA inhibits signicantly CO_2 production from glucose. Lipid biosynthesis was also diminished by MMA but not by PA. These results indicate that MMA may impair brain energy metabolism and normal brain development.

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CEREBELLAR INVOLVEMENT IN BILIRUBIN ENCEPHALOPATHY DUE TO CRIGLER-NAJJAR TYPE I DISEASE.

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Patients suffering from Crigler-Najjar (CN) type I disease, a rare inborn error of bilirubin metabolism due to a deficiency in hepatic bilirubin uridine diphosphate glucuronosyltransferase (B UDPG-T) activity, are at permanent risk of developing neurotoxic effects of bilirubin (kernicterus). While cerebellar hypoplasia occurs in new born Gunn rats, the animal model of CN type I, cerebellar symptoms are not prominent in kernicterus observed in children.

Cases reports: 3 infants (2 girls and 1 boy) became jaundiced at 2 days. Despite treatment all of them underwent exchange-transfusions at the age of 9 days. Then, phototherapy had to be continued and phenobarbital was not efficient. At the age of 4 months, hepatic B UDPG-T was found to be nil in the 3 patients. At the age of 3 years, 4 years and 6 years, respectively, these children presented with cerebellar symptoms a week after a reduction of phototherapy. Serum bilirubin concentrations at the time of admission were 581, 514 and 600µmol/L, respectively. Under correct treatment cerebellar symptoms slowly and partially decreased in the 3 children, while moderate mental retardation became obvious; none of them has any evidence of deafness and brain CT scan is normal in 2 of them.

Conclusions: 1) These 3 cases illustrate a new clinical aspect of kernicterus, 2) kernicterus may have different clinical manifestations in infants and in older children, 3) the cerebellum may be the preferential target of bilirubin in children while it is not so in infants.

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PROGRESSIVE ATAXIA AND MENTAL RETARDATION ASSOCIATED WITH LEUCODYSTROPHY IN 4 PATIENTS WITH L-2-HYDROXY-GLUTARIC ACIDURIA Hoffmann, G.F., Barth, P., Lehnert, W., Duran, M., Hunneman, D.H., Jaeken, J., Rating, D., Schutgens, R.B., Voss, W. and Hanefeld, F. Depts. Pediatrics Heidelberg, Freiburg, Göttingen, FRG, Amsterdam, Utrecht, The Netherlands, and Louvain, Belgium.

We present the clinical, neuroradiological and biochemical data of 4 patients with L-2-hydroxy-glutaric aciduria, which appears to be a new neurometabolic disorder. Two male siblings of Marocco ancestry presented with psychomotor retardation and dystrophy in early childhood. Consequently they developed a progressive ataxia, slight extrapyramidal signs and mental retardation (IQ< 48 at the age of 18 y and IQ= 48 at the age of 12y). One of them suffered from convulsions. Two additional female patients (To., A., age 15y, and Fi., A., age 19y) of Turkish and Greek ancestry followed a similar course with short stature, progressive ataxia and mental retardation. In addition, To, A., developed an oligoepilepsy with generalized seizures in early infancy and showed pyramidal signs with the age of 10 y. Neuroradiological investigations revealed distinct extensive subcortical hypodensities, resembling spongy degeneration and a (sub)cortical and cerebellar atrophy in all four patients. Urinary excretion of L-2-hydroxyglutaric acid was in the order of 1-3 mol/mol of crea. in all patients as determined by GCMS and 1H-NMR spectroscopy (controls < 0.002 mol/mol of crea.). Plasma levels of L-2-hydroxyglutaric acid were 20-30 µmol/l and in the CSF 40-50 µmol/l (controls n. d.). The very similar clinical findings as well as the distinct neuroradiological picture in 4 patients from 3 families pinpoint a hitherto unrecognized neurometabolic disorder. The relation of L-2-hydroxyglutaric acid to human metabolic pathways is unknown. In patient Fi., A., we observed a small decrease in the urinary excretion of L-2-hydroxyglutaric acid under a carbohydrate rich diet and an increase after an oral load with plant oil. In To., A., a 24h fast produced a 4-fold increase in L-2-hydroxyglutaric aciduria. A therapeutic trial of a carbohydrate rich, low fat diet did not result in any clinical improvement. A number of other in vivo loading experiments and in vitro investigations in fibroblasts using radiolabelled precursors were unrewarding.

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LONGTERM FOLLOW UP OF 16 CHILDREN AFFECTED WITH THE "LATE ONSET" VARIANT OF ARGININOSUCCINATE LYASE DEFICIENCY: NO IMPAIRMENT OF THE NEUROLOGICAL AND PSYCHOMOTORIC DEVELOPMENT.

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At present, two variants of ASL-deficiency, the second most common enzyme defect of the urea cycle, have been described according to the mode of onset and the clinical course. Nearly all previous studies reported on an impaired neurological and intellectual development in affected children. Our study demonstrates for the first time, that these children can develop physically and mentally appropriate for age if treated with low protein diet and/or arginine supplementation.

Since 1975 16 Austrian children have been detected to be suspicious for this enzyme defect. After having confirmed the diagnosis, a daily arginine supplementation (3-4 mmoles/kg body weight/day) was initiated in all but three children in addition to normal diet respectively to recommended protein restriction of 1,2 - 1,5 g/kg body weight/day. Except for slight elevations, blood ammonia levels remained within the normal range over the time. EEG patterns showed paroxysmal abnormalities in 5 out of 16 children, whereas physical and mental development were within the normal range.

It can be concluded, that early diagnosis of ASL-deficiency within a routine screening program followed by dietetic treatment (low protein and/or arginine substitution) seems to be able to prevent intercurrent hyperammonemic episodes, that cause severe neurological and psychomotoric abnormalities. Furthermore, an accumulation of argininosuccinic acid and its anhydrids does not seem to have a neurotoxic effect.

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SEIZURES ASSOCIATED WITH TOXIC LEVELS OF CYCLOSPORINE A IN LIVER TRANSPLANTED CHILDREN.

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In our series of 210 children having undergone 256 liver transplantations from 4/1984 to 12/1990, four patients presented with convulsions unrelated to a common etiology. Clinically they displayed tonico-clonic seizures either generalised or lateralised with secondary generalisation. EEG showed either generalised or lateralised encephalopathy pattern with irritativity. None showed hypertensive encephalopathy on ophtalmic examination. None showed electrolyte, glucose or hepatic function abnormality. Magnesium was normal. In two children cholesterol was normal (no data for others). LCR analysis showed no infection. In all four children Cyclosporine (CSA) through serum level reached supra-therapeutic levels, the "toxic" period lasting from 1 to 2 days and occuring from 2 to 10 days before seizures. CSA levels on specific RIA were normal or moderately perturbated. CT-scan in one patient showed subcortical and cortical diffuse hypodense lesions 3 days after seizures, resolving afterwards. Seizures responded well to antiepileptic drugs. No child showed permanent impairment. We conclude that seizures under cyclosporine therapy may be related with toxic levels of CSA and that discordance between specific and non specific assay suggests the role of metabolites.