Chronic interstitial nephritis: a long-term complication of methylmalonic acid(MMA)-emia.

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In a girl with a Cbl A mutant of MMA-emia treated since the neonatal period with a low protein diet, MMA conc. in urine (mol/mol creat.) varied from 0.9-3.5 (x=2.2) rising to max. 6.4 during infections. MMA plasma conc. (mmol/l) ranged from 0.1-0.4, occasionally up to 1-3. The patient was only partially B12-responsive. The only two episodes of metabolic acidosis could easily be controlled. Physical and psychomotor development (IQ 100) was normal until 12 yrs of age when growth retardation was noted. Laboratory studies revealed hyperuricemia (560-780 µmol/l), low urinary uric acid and impaired creatinine clearance: 45 ml/min/1.73 m². Hyperuricemia was normalized by allopurinol. By further restriction of protein intake (0.5 g/kg/d), oral OH-Cbl, l-carnitine and alkali MMA levels could be reduced to x=1.5 mol/mol creat., and there was catch-up growth. At age 17 yrs the girl was in good general health. Her renal function was: C_{inulin}: 54 ml/min/1.73m², C_{pAH}: 270 ml/min/1.73 m². Fractional excretion of sodium was increased to 5%. Blood pressure was elevated (145/100 mmHg). The renal biopsy showed a moderate focal interstitial nephritis with tubular atrophy, slight nephrosclerosis without glomerulonephritis, no urate deposits.

Conclusion: Chronic renal disease, not uncommon in patients with MMA-emia, may be caused by MMA itself or secondarily by hyperuricemia. In our case the renal function did not deteriorate over 5 years under a strict therapeutic regimen. MMA and urate levels must be carefully controlled in these patients. It remains to be shown whether the development of nephropathy can thus be prevented.

PERIVENTRICULAR LEUKOMALACIA: ULTRASOUND DIAGNOSIS AND FOLLOW-UP

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Periventricular Leukomalacia (PVL) is defined as ischemic infarction of the white matter located around the lateral ventricles of the premature infant's brain. PVL is caused by the hypoperfusion of and arteries that supply the

white matter in the watershed areas between the major cerebral arteries.

From January 1984 to October 1989, 506 newborns with a gestational age ≤ 34 weeks, admitted to NICU of Padua were routinely scanned. Thirty newborns (5.9%) were diagnosed to have cavitory PVL. Concomitant PVL-IVH occurred in 14 infants (46.7%). Twenty-seven babies survived and 3 died. Twenty-four (80%) of the 30 newborns showed areas of increased echogenicity in the periventricular regions prior to the development of cystic changes. The mean age for the appearance of hyperechogenicity was 3 days (range 1-26). The mean age for the appearance of cysts was 23 days (range 8-52). PVL was divided into localized and extensive lesions. Twenty newborns had localized PVL, 13 unilateral (2 frontal, 4 parietal 7 occipital) and 7 bilateral (2 frontal, 5 occipital). Ten newborns had extensive and bilateral PVL (8 frontal, 9 parietal, 10 occipital). Discharged babies were followed-up by repeated ultrasound scans. In 14 infants followed beyond 6 months postnatal age the cysts disappeared, in 6 they were still visible. Fifteen infants had associated mild-moderate ventricular dilation, 5 had cerebral atrophy. The 12 months (corrected age) neurodevelopmental outcome of 17 survivors is reported. Eleven babies showed cerebral palsy, 4 of them had a severe mental delay, 3 a moderate mental delay and 4 were normal. One baby showed a mild motor delay and a normal mental development. Five babies had a normal motor development, 1 of them had a moderate mental delay and 4 were normal. In conclusion, PVL is related with a poor neurodevelopmental outcome, particularly when lesions are extensive, localized and bilateral, above all when the occipital lobe is involved.

Brain damage and recovery in hyperphenylalaninemia

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Experimentally induced hyperphenylalaninemia (hyperphe) during the period of myelinogenesis leads to a decreased myelincontent in the rat brain. We asked the

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question whether this can be corrected if the animals are allowed to recover after the period of the brain growth spurt. Hyperphe was induced by injections of ³H-Methylphenylalanine and phenylalanine from day 3 to 17 postnatally. Myelin related enzymes CST, CNP and myelin enriched glycolipids, Sulfatide and Cerebrosides were estimated biochemically at day 17 and after a period of recovery at day 59. The results are shown in Tbl. 1. Values are given in mean and SD n=12.

		CST (pmol/h/g)	CNP (nmol/h/g)	Cerebroside (mg/g)	Sulfatide (mg/g)
Controls	17d	348.6±100.6	8.20±1.20	0.62±0.14	0.11±0.02
Tests	17d	201.8± 69.3	4.70±0.90	0.23±0.06	0.06±0.02
	p	<0.001	<0.001	<0.001	<0.001
Controls	59d	152.8± 21.5	26.80±6.1	6.59±1.51	1.33±0.29
Tests	59d	160.2± 17.7	24.80±7.6	6.11±1.30	1.18±0.23
	p	ns	ns	ns	ns

There is a clear recovery of myelinogenesis at 59 days, which is corroborated by immunohistochemical staining. We conclude from our results, that catch up of myelinogenesis in experimental hyperphe is possible even after the period of the brain growth spurt.

Noninvasive assessment of maturation of corticospinal tract

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Magneto-electrical stimulation of the motor cortex provides a noninvasive technique to study the normal development of the corticospinal descending system. Fifty children aged between 3 month and 10 years were studied. Using a Cadwell-MES10 magneto-electric stimulator with a maximum magnetic flux of 2 Tesla latencies of moto-responses after cortical and cervical or lumbar root stimulation were obtained from thenar and abductor hallucis muscles. The latency differences between cortical and root stimulation provided an estimate of central conduction times for the fastest descending cortical spinal fibres. Central conduction times decreased down to the age of ten years before reaching adult values. Thresholds for cortical stimulation were significantly higher for lower extremity than for upper extremity muscles. The results demonstrate that the maturation of fastest cortical spinal fibres is not completed before the age of 9 to 10 years. This is in contrast to the faster maturation of conduction velocities in the peripheral nervous system as measured from cervical or lumbar root stimulation.

INFLUENCE OF CORTICOSTEROIDS ON THE DEVELOPING CHOROID PLEXUS

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The choroid plexus contains Na K-ATPase-dependent transport systems responsible for the production of the major part of the cerebral spinal fluid (CSF) and the removal of polar metabolites from the ventricular CSF. In adult rabbits, treatment with betamethasone for 5 days decreases choroid plexus Na K-ATPase activity and consequently CSF production and in vitro choroid plexus transport capacity for choline. Choroid plexus Na K-ATPase activity is low in rabbit fetuses. A rapid increase starts at birth and adult levels are reached in around 3 weeks. This increase is paralleled by an increase in the in vitro transport capacity for choline (base) but not for penicillin (acid). Kinetic studies showed no change in K_m but an increase in V_{max} with age, suggesting that the same carrier system is involved in young and adult animals. Administration of betamethasone to the doe during the last week of pregnancy for 5 days increases fetal choroid plexus Na K-ATPase activity and choline transport capacity by 58-81% and 35% respectively.

ANALYSIS OF CEREBROSPINAL FLUID (CSF) FROM NEONATES USING PROTON MAGNETIC RESONANCE SPECTROSCOPY (MRS).

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Samples of CSF from 13 full-term newborn infants were studied using high resolution proton MRS. CSF (0.5mls) was stored at -70°C, freeze-dried, reconstituted in deuterium oxide and a marker added for quantitation and chemical shift referencing. Spectra were obtained at 300 MHz, using presaturation to suppress the water signal. Ten samples were from neurologically normal infants. Spectra showed peaks attributed to lactate, acetate, citrate, glutamine, glucose, alanine, 3-hydroxybutyrate, creatine, formate and inositol. Spectra from the CSF of 3 infants with post-asphyxial encephalopathy and seizures showed a peak attributed to the drug carrier propylene glycol and another peak representing millimolar concentrations of unknown compound. Quantitative differences in the CSF spectra also occurred following asphyxia.

	Non-asphyxiated	Asphyxiated
CSF lactate (mmols/l)	1.16-3.33 (med. 1.73)	2.49, 2.52, 11.76
CSF glutamine (mmols/l)	0.47-1.09 (med. 0.62)	1.16, 1.33, 1.85

Non-selective assay of multiple metabolites using proton NRS may help to define CSF markers of cerebral ischaemia which would be suitable for conventional analysis.