Myelin Metabolites and Brain Water are abnormal in Patients with Vanishing White Matter Disease (VWMD)

BD Ross*, KS Seymour*, M Philippart‡, J Tan# and S Bluml#

*MRS Unit, Huntington Medical Research Institutes;
#Rudi Schulte Rudi Institute; ‡Pediatric Neurology, UCLA

Aim

To elucidate pathogenesis of VWMD by, quantitation of myelin metabolites phosphocholine (PC), phosphethanolamine (PE), glycerophosphorylethanolamine (GPE) and glycerophosphoryl-choline (GPC).

Background

A new leukodystrophy, characterized by late onset, chronic progress, episodic course and distinctive MRI (abnormal WM takes on the appearance of csf in all sequences), and 1H MRS (lactate and glucose, the predominant metabolites of csf replace the usual brain metabolites, NAA, Cr, Cho and mI) hence 'vanishing white matter' [1-3]. Pathogenesis is axonopathy [1], or hypomyelination [2;3].

Patients and Methods

Five patients (males, aged 1.5 -13yrs) with VWMD referred from a single pediatric neurologist (MP) and 12 age-matched normal controls were examined, using a clinical GE 1.5 T MR scanner equipped with a second channel. Clinical and radiological diagnoses were confirmed independently. All VWMD had MRI segmentation, brain water/CSF T2 quantitation, quantitative 1H MRS of grey and white matter [4]; 3/5 had repeated quantitative proton decoupled 31P (q{^{1}H}-^{31}P) MRS (7 exams in all) [5].

Results

Fractional BW/CSF/dry matter (33/38/29%) differed between patients and from normal (62/3/35%). BW fell and CSF increased % CSF from MRS-T2 was significantly greater than that determined by segmentation (38 ± 12 % vs 24 ± 8 %), suggesting the extent of disease exceeded that observed with MRI.

1H MRS of occipital GM was relatively normal for age (not shown), but within WM varied from severe, glucose plus lactate (1/5), moderate, reduced brain [NAA], [Cr] with increased glucose and lactate (3/5) to mild (1/5) (Fig. 1).

Striking reduction of GPE was noted in 3/3 VWMD (Fig. 2). GPE was absent (Fig. 2 lower), or reduced (middle)with relative preservation of GPC. PE was increased in 2/3 patients.

Dietary therapy with docosohexaenoic acid (DHA) (100mg/day for 3 weeks) was without effect on GPE, PE or GPC in 2 VWMD (not shown).

Discussion

In VWMD, MRI appearances are explained by increasing proportions of the prolonged water T2 compartment. Metabolite concentrations, including NAA, within cell water of residual WM are well conserved, perhaps explaining the chronic course of the disease.

The present results suggest the earliest metabolite change may be in GPE (and PE), constituents of myelin cephalins and plasmalogens rather than lecithins (Scheme).

Acknowledgements: We are grateful to Drs. Mario van der Knaap, Rafael Schiffman and Hugo Moser for reviewing clinical information and to Dr. Jorge Carrera Mardones, Puerto Montt, Chile for therapeutic monitoring in his patients receiving DHA. SB acknowledges generous financial support of RSRI, Santa Barbara.

References: **1.** van der Knaap et al. *Neuropediatrics,* 1995;26:338. **2.** Schiffman et al. *Ann. Neurol.,* 1994;35:331-40. **3.** Hanefeld et at. *Neuropediatrics,* 1993;24:244-248. **4.** Kreis et al. *J. Magn. Reson.,* 1993;102(1):9-19. **5.** Bluml et al. *Magn. Reson. Med.,* 1999;42:643-654.

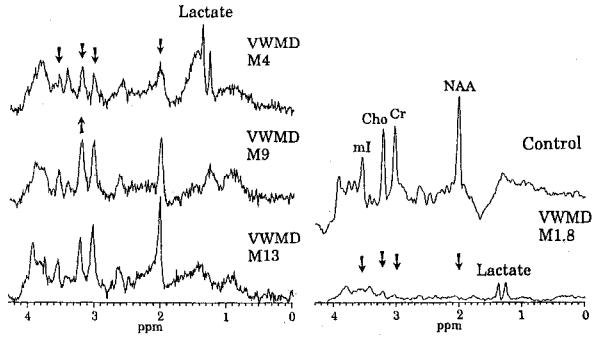

Fig. 1: Quantitative 1H MRS in white matter of four of five patients with VWMD. Note excess glucose at 3.4 ppm.

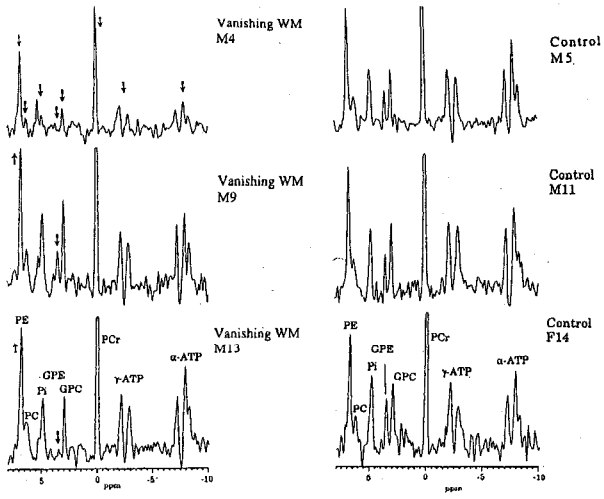

Fig. 2: 1H dc 31P MRS in 3 VWMD patients and controls.

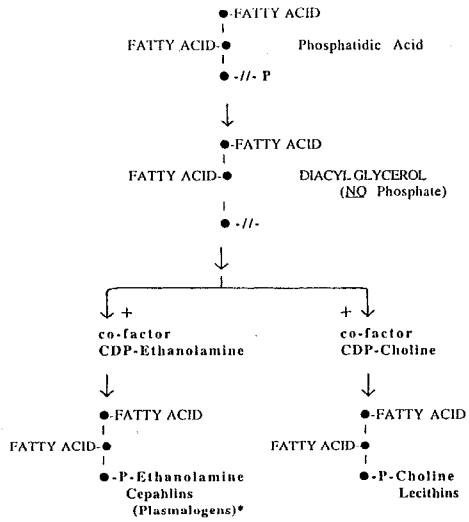

Fig. 3: VWMD: Disorder of myelin-cephalins and plasmalogens?