De- or Hypomyelination in Myelinopathia Centralis Diffusa/Leukoencephalopathy with Vanishing White Matter? Insights from Localized Proton MRS

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Introduction

White matter (WM) disorders in children can be caused by different pathogenic processes affecting myelin. For example, de- and hypomyelination produce distinct metabolite patterns readily detectable by proton MRS. While demyelination is characterized mainly by elevated choline-containing compounds (Cho), hypomyelination leads to a low Cho concentration [1,2]. Myelinopathia Centralis Diffusa (MCD) or Leukoencephalopathy with Vanishing White Matter (VWM) was first distinguished from the vast group of leukoencephalopathies with unknown origin by Hanefeld et al. in 1993 [3]. Already at the onset of symptoms widespread, diffuse, homogeneous, and symmetrical WM signal alterations are present. During the course of the disease MRI and proton MRS of affected WM appear progressively similar to CSF [4]. Mutations in each of the five subunits of the eucaryotic translation initiation factor 2B (eIF2B) have been found to cause the disease [5]. EIF2B plays an essential role in regulation of cell protein synthesis. However, contradictory histopathological reports of this diffuse leukodystrophy discussed hypomyelination, demyelination, and a primary axonopathy as the underlying process leading to the onset of symptoms [4,6]. Here, we hypothesized that quantitative proton MRS will allow us to distinguish between hypo- and demyelinating processes.

Patients and Methods

Ten patients (6 female, age at entering the study 20 mo to 26 yrs), 9 with a genetically proven diagnosis of MCD/VWM underwent multiple follow-up localized proton MRS studies over a maximal period of 8 yrs. One patient, fulfilling all clinical and neuroradiologic criteria for MCD/VWM [4], was examined 13 yrs ago and no material was available for genetic analysis. Before each examination informed written consent was obtained from the parents. If necessary, children where sedated and monitored by pulse oximetry.

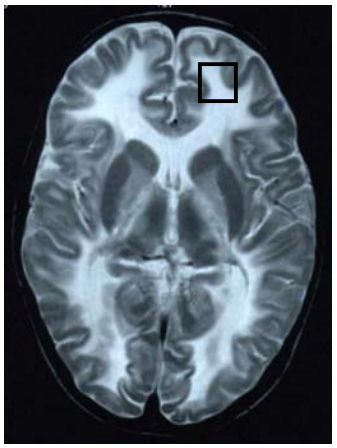
Localized proton MRS (VOI = 3.9 – 7.1 ml) focused on frontal and parieto-occipital WM (2.0 T, STEAM, TR/TE/TM = 6000/20/10 ms, 64 accumulations). Absolute concentrations of N-acetylaspartate and N-acetylaspartylglutamate (tNAA), creatine and phosphocreatine (tCr), choline-containing compounds (Cho), inositol (Ins), glucose (Glc), and lactate (Lac) were determined by LCModel [7].

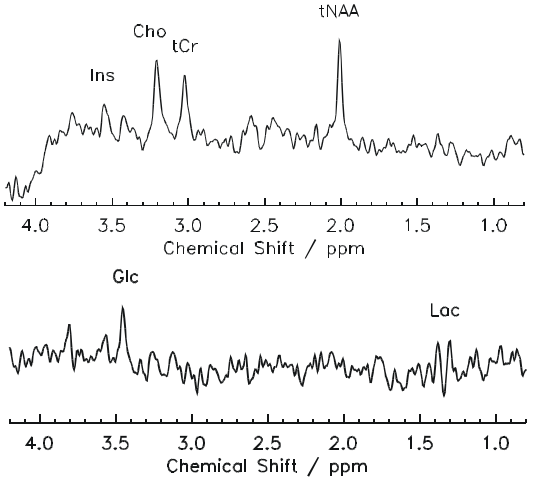
Results and Discussion

The figure demonstrates marked WM alterations detectable already during early disease stages. The table summarizes the mean metabolite concentrations in WM obtained by proton MRS within the first two years after onset of symptoms. The most striking finding was a significant reduction of tNAA, tCr, and Ins already during that initial stage of disease course (≥ 2 SD of controls). Cho, however, remained within normal ranges. The spectrum in the middle trace of the figure illustrates the relatively high Cho peak compared to other metabolites. Three of the five patients showed an elevated Lac concentration of 1.9 mmol/l (mean) and four patients presented with an increased Glc level of 3.5 mmol/l (mean). Over the long course of the disease a progressive reduction of all metabolites was observed in our patients until resonances were no longer discernable from noise. Simultaneously Lac and Glc increased, thus resembling a spectrum of CSF (Figure: bottom trace).

Our MRS findings over the whole course of the disease are consistent with an overall tissue loss in WM the histopathologic hallmark of MCD/VWM. However, during the early phase of the disease the Cho concentration was found to be normal and thus relatively higher than all other metabolites showing already significantly reduced concentrations. This relative increase in turn points towards a demyelinating process. From the MRS results of the early disease stages it can be concluded that the general pattern in MCD/VWM reflects at least two coexisting processes, that is demyelination and vanishing of the WM. In fact, neuropathologic studies describe a profound loss of myelin leaving vast cystic areas with severe rarefaction of axons. At the margins of these cysts and even more pronounced in the transition zones towards regions of better preserved myelin components of active demyelination has been observed contemporaneously [3].

In summary, the MRS-detectable neurometabolic pattern of WM during the early phases of the disease course resemble those of demyelination and do not support the concept of hypomyelination. In this case, MRS has added valuable information on the pathogenic processes causing white matter abnormalities in a devastating leukodystrophy in children.





MRI: Axial T2-weighted image of a 4-year-old patient acquired 1.8 yrs after onset of symptoms displaying VOI in WM.

MRS of WM: (middle) 11 months and (bottom) 3.8 yrs after onset of symptoms. The relatively high Cho compared to tNAA, tCr, and Ins transforms into a pattern comparable to that of CSF.

Table: Mean absolute concentrations of WM metabolites (mmol/l) of MCD/VWM patients within the first two years after onset of symptoms vs. age-matched controls [8].

	patients	controls (mean ± SD)
tNAA	3.35*	6.9±0.6
tCr	2.6*	4.9±0.4
Cho	1.1	1.6±0.3
Ins	1.9*	3.7±0.6

References: 1. Frahm J et al., *Magnetic Resonance Spectroscopy and Imaging in Neurochemistry* 8: 329, 1997; 2. Hanefeld F et al., *Neurology* 65: 701, 2005 ; 3. Hanefeld F et al., *Neuropediatrics* 24: 244, 1993 ; 4. van der Knaap M et al., *Neurology* 51: 540, 1998 ; 5. van der Knaap M et al., *Ann Neurol* 51: 264, 2002; 6. Schiffmann R et al., *Ann Neurol* 35: 331, 1994 ; 7. Provencher SW, *MRM* 30: 672, 1993 ; 8. Pouwels P et al., *Pediatr Res* 46: 474, 1999.