Quantitative Proton MRS of Pelizaeus-Merzbacher Disease: Evidence for Dys- and Hypomyelination

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Introduction

Pelizaeus-Merzbacher disease (PMD) is a rare neurological disorder characterized by dys- and hypomyelination during early development. The disease is caused by mutations in the proteolipid protein (PLP) gene resulting in an absence of or a defect in PLP, one of the main proteins in myelin membranes. Accordingly, T1-weighted MRI reveals almost no distinction between gray matter and non-/abnormal-myelinated white matter, T2-weighted images show white matter hyperintensities.

Although there have been reports of proton MR spectroscopy (MRS) in PMD, the published results are rather heterogeneous including increases, decreases, or no changes of concentrations of the various cerebral metabolites [1-9]. As these discrepancies are tentatively explained by technical differences and/or limitations of respective studies, the purpose of this work was to re-examine PMD patients with fully-relaxed, short-echo time quantitative proton MRS, to assess cerebral metabolic and structural alterations with use of absolute metabolite concentrations, and to determine whether pertinent abnormalities can be distinguished from the metabolite patterns of controls and patients with other leukodystrophies.

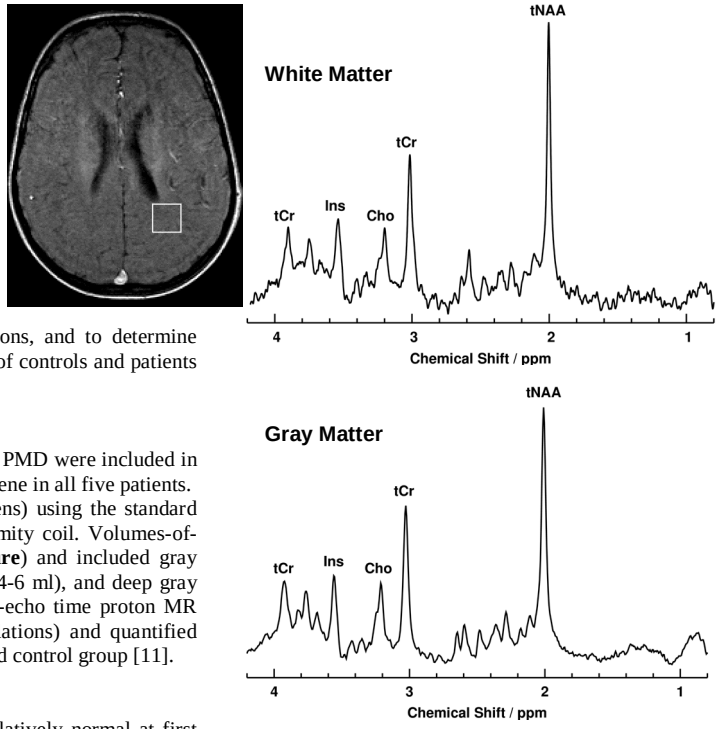

Figure: T1-weighted MRI (left) of a 6.8-year-old PMD patient. The distinction between cortical gray matter and `white' matter is hardly possible. The white matter location for localized proton MRS is indicated. The spectral pattern of `white matter' is very similar to the metabolic composition of cortical gray matter, suggesting dys-/hypomyelination.

Methods

Five boys (age range: 0.6-6.8 years) with clinical and MRI features consistent with PMD were included in this study. The diagnosis of PMD was confirmed by mutation analysis of the PLP gene in all five patients. MR examinations were performed at 2 T (Magnetom SP4000 and Vision, Siemens) using the standard imaging headcoil or, for children with a body weight less than 20 kg, the extremity coil. Volumes-of-interest (VOI) for MRS were selected from T1- and T2-weighted images (**Figure**) and included gray matter of parietal cortex (GM, 8-12.5 ml), parieto-occipital `white matter' (WM, 4-6 ml), and deep gray matter structures containing the basal ganglia (BG, 4-6 ml). Fully relaxed, short-echo time proton MR spectra were acquired (STEAM, TR/TE/TM=6000/20/30 or 10 ms, 64 accumulations) and quantified using LCModel [10]. Patient data were compared with a corresponding age-matched control group [11].

Results and Discussion

Despite marked dys-/hypomyelination, the observed metabolic patterns appear relatively normal at first glance. Remarkably, however, spectra of `white' matter have significantly smaller linewidths than those of age-matched children with normal myelination. The underlying improved microscopic magnetic field homogeneity may be caused by the absence of anisotropically oriented myelin sheaths which would lead to a structurally more homogeneous tissue at the cellular level. It may also reflect a reduced content of paramagnetic iron, as especially the myelin-forming oligodendrocytes contain iron.

As shown in the **Table**, MRS of GM reveals slightly enhanced concentrations of N-acetylaspartate and N-acetylaspartylglutamate (tNAA), myo-inositol (Ins) and glutamate (Glu). In agreement with the morphological abnormalities, spectral findings from WM resemble the metabolite pattern of gray matter (**Figure**) comprising an increase of tNAA concentrations and a slight reduction of the level of choline-containing compounds (Cho) relative to controls. In addition, high concentrations of Ins, creatine and phosphocreatine (tCr), and Glu are observed. Spectra of basal ganglia are normal with respect to metabolite concentrations.

The resonance of Cho mainly consists of phosphorylcholine and glycerophosphorylcholine, which are involved in the turnover of myelin lipids. The lack of normal myelin in PMD patients clearly leads to lower Cho levels. The high concentration of tNAA should be connected with a high neuroaxonal density in white and cortical gray matter. This is also in line with the simultaneous observation of high Glu, which is present predominantly in neurons. The elevation of Ins is due to an increase of glial cells (astrocytes). Both effects, a high neuroaxonal density and an increase of astrocytes, result in a higher concentration of tCr, which is indeed observed.

This metabolic pattern is consistent with dys-/hypomyelination, i.e. lack of normal myelin, but is completely different from demyelinating diseases. For comparison, the metabolic changes in affected white matter in adrenoleukodystrophy are characterized by high levels of Cho and Ins, due to myelin breakdown and gliosis, and a decrease of tNAA and Glu as a result of neuronaxonal loss. Thus, together with the other MRS findings, the observation of a reduced rather than increased Cho concentration seems to represent a pathological hallmark of dys-/hypomyelination.

Conclusion

MRS in PMD reveals a characteristic pattern consistent with histopathologic alterations known to occur in dys-/hypomyelination. The spectral profile is clearly different from the MRS features of demyelination.

Table: Absolute concentrations (mmol/l) of brain metabolites in patients with PMD (n=5) and age-matched controls (mean±SEM).

	Gray Matter		White Matter		Basal Ganglia	
	PMD	Control	PMD	Control	PMD	Control
tNAA	8.7 ± 0.3*	7.7 ± 0.2	8.4 ± 0.2*	6.7 ± 0.1	8.5 ± 0.6	7.6 ± 0.2
tCr	6.5 ± 0.3	6.3 ± 0.1	6.4 ± 0.2*	5.0 ± 0.1	8.5 ± 0.4	7.7 ± 0.1
Cho	1.2 ± 0.05	1.2 ± 0.03	1.5 ± 0.06*	1.8 ± 0.04	1.8 ± 0.1	1.8 ± 0.1
Ins	5.5 ± 0.2*	4.6 ± 0.1	6.7 ± 0.5*	3.6 ± 0.1	5.3 ± 0.6	3.8 ± 0.1
Glu	10.3 ± 0.5*	9.0 ± 0.2	8.3 ± 0.3*	6.6 ± 0.2	8.3 ± 0.9	8.2 ± 0.2

*Significant differences compared to controls (two-sided Students t-test, $p<0.05$).

References

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