Diffusion Tensor Imaging Study of Pelizaeus-Merzbacher Disease.

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Introduction: Mutations of the Proteolipid protein 1 (*PLP1*) gene which encodes the major protein in central nervous system myelin, cause a spectrum of neurological disease, from Pelizaeus-Merzbacher disease (PMD) to spastic paraplegia 2 (SPG2). The most common mutation causing PMD is complete duplication of the *PLP1* gene, which most likely causes overexpression of PLP1 and secondary oligodendrocyte (the myelinating cells in the CNS) dysfunction through unknown mechanisms. Pathologically CNS axons are hypomyelinated and myelin degeneration and gliosis are found. Severe missense mutations strongly activate the so-called unfolded protein response (UPR) which causes oligodendrocyte apoptosis, with consequent severe hypomyelination and gliotic change. In contrast, null mutations cause little if any hypomyelination, do not cause oligodendrocyte apoptosis, and result in relatively late-onset length-dependent axonal degeneration (1). We speculated that the severity of the early PMD phenotype predominantly is dictated by the degree of oligodendrocyte dysfunction and/or apoptosis, while the rate of clinical deterioration after childhood was dependent on the degrees of demyelination or axonal degeneration. The purpose of this study was to investigate whether DT-MRI technique is helpful for assessing the degree of axonal disruption and whether changes in white matter diffusion parameters correlated with the expected clinical pathology in PMD patients with confirmed *PLP1* mutations.

Material and Methods: We analyzed the brains of 7 PMD patients (mean age = 7.8 ± 5.9 ys) and 7 age matched normal control subjects (mean age = 8.6 ± 5.1 ys). All subjects underwent diffusion tensor MRI (DT-MRI) on a 1.5T scanner with single-shot spin echo EPI and diffusion sensitization gradients applied on 6 directions plus one T2W series (Figure 1) covering the whole brain and averaged 6 times. This sequence is added to a clinical exam including 3D-T1W SPGR, T2-FLAIR, double-echo FSE, and MRS. Mean diffusivity (ADC) and fractional anisotropy (FA) of internal capsule (IC) (Figure 1) were quantified for both groups in left (Lt) and right (Rt) hemispheres by manual ROI selection over colored encoded FA maps and automatically copy/pasted over ADC and FA maps. The ADC and FA were averaged over at least three adjacent slices.

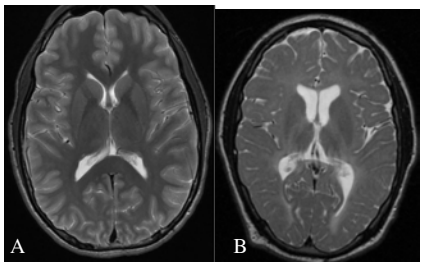

Figure 1: A) T2W image of control subject with good gray white matter contrast , and B) compared to that of PMD patient #5 .

Results: There was no significant difference of ADC and FA values between left and right IC within PMD patients as well as normal subjects. Paired t-tests on PMD patients versus age-matched normal controls demonstrated significantly lower ADC in the IC (Figure: 2): Lt $p < 0.001$, and Rt $p < 0.001$. We also noticed significantly lower FA in each IC of PMD patients when compared to the control group (Lt $p = 0.001$, Rt $p < 0.001$). The decrease in FA and ADC are most noteworthy in (Patients #1 and #5) with null or probably functionally null mutations of the *PLP1* gene. These observations are consistent with MR spectroscopy studies demonstrating an overall decrease in white matter NAA concentrations, however they do indicate more severe changes in patients with null mutations or mutations that prevent expression of full-length PLP1. Patient mutations consist of: #1del 403-419 (causes frame shift at residue 135); #2: IVS6-1G>T (causes exon 7 skipping); #3: Y206H; #4: L80R (8 yr); #5: *PLP1* deletion; #6: L84R: #7: L80R (5 yr).

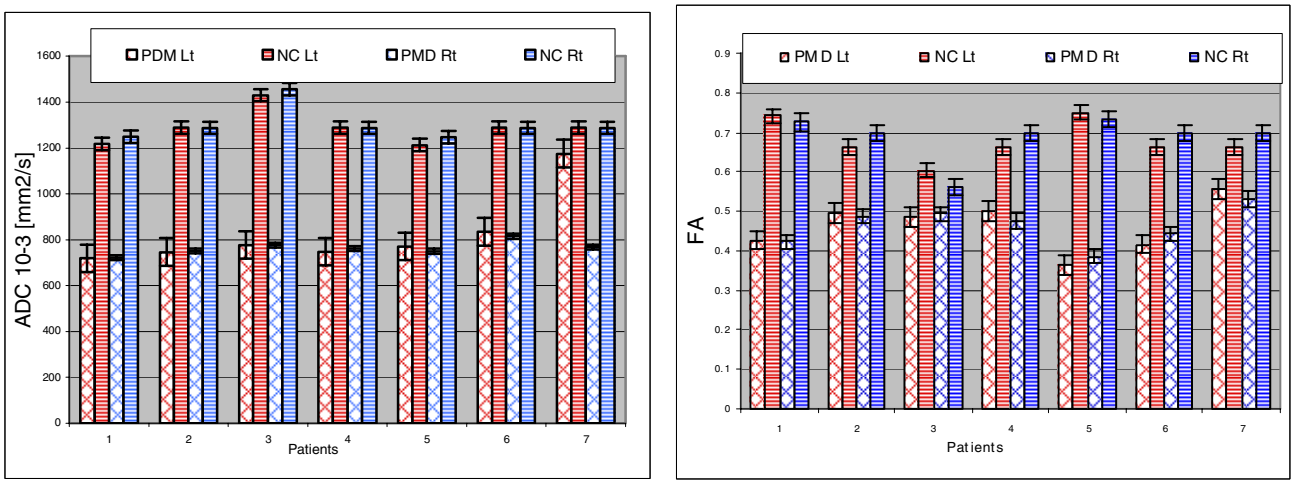

Figure 2 : Graphs comparing ADC and FA of PMD and age-matched normal control children.

Conclusion: To the best of our knowledge, this is the first investigation of PMD using DT-MRI. Neuropathological observation in PMD has reported an increase in astrocytic swelling with gliosis and myelin breakdown in more severe cases, while we have shown axonal degeneration in null and relatively mild missense mutations, and which are corroborated by MRS studies (1;,2). Using DWI with 2 directions, Ono et al, (3) reported an increased diffusivity parallel to the optic nerve fibers while it decreases perpendicular to it in PMD. Our results may suggest, in addition to axonal degeneration, the diffusion properties of the CNS tissue is impaired by an increase in astrocyte proliferation or swelling, which we and others have observed and production of extracellular matrix components (4) making the diffusion properties more restricted, as suggested by the decrease in ADC. Transition of water from the solid to the gel state found in metachromatic leukodsytrophy (5) may also explain our findings. Furthermore, reduction in FA demonstrates a loss of fiber directionality suggesting axonal degeneration with secondary demyelination. Further investigations need to be performed involving more diffusion directionalities, other white matter structures, MRS, and a larger sample of patients with PMD and additional mutation types.

References: (1) Garbern et al, Brain, 125:551, 2002. 2) Edgar et al. Acta Neuropath 107 :331-335, 2004 (2) Ono et al, Pedr Neurol, 1997. (3) Roitbak et al, Glia, 28:40-48, 1999. (5) Branco et al., AJNR, 2002 ;