Quantitative MT (qMT) characteristics of the human spinal cord *in vivo*

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Introduction: Magnetization Transfer (MT) MRI has been used to detect and quantify central nervous system tissue *in vivo*, and has found many applications in disease (e.g. multiple sclerosis, neuropsychological, adrenoleukodsytrophy). Conventional MT experiments are quantified by the MT ratio (MTR): the ratio of images acquired with and without an off-resonance MT prepulse (1). However, the MTR depends on the pulse sequence, field strength, and power of the MT pulse. Alternatively, quantitative MT imaging (qMT) uses the information contained in the MT z-spectrum, i.e. the dependence of water intensity on irradiation offset, to extract physiological constants of the tissue of interest (2). qMT applications have been limited to white matter diseases in brain. In this study we investigated the efficacy of qMT to characterize a non-inflammatory spinal cord disease, Adrenomyeloneuropathy (AMN). AMN is the adult variant of X-linked adrenoleukodystropy (X-ALD), a peroxisomal disease leading to the accumulation of very long chain fatty acids in the central nervous system. AMN is characterized by a distal, progressive, and retrograde axonopathy with secondary demyelination with little to no inflammation and presents as slowly debilitating spastic paraparesis of the extremities. Pathological findings indicate myelin pallor in the ascending dorsal columns in the cervical region and similar findings in the descending, lateral columns in the thoraco-lumbar region. Females (X-ALD females) heterozygous for the X-ALD gene show some of the aforementioned symptoms but to a lesser degree and in general, later in life (3).

Methods: In this study, we reanalyzed MT data from a previous study of six healthy adults, 4 males with AMN, and 5 females heterozygous for the X-ALD gene (4). MT-weighted images were acquired at 10 offset frequencies (**Fig. 1**) logarithmically sampled between 1 kHz and 63 kHz. Nominal resolution: 0.9x0.9x1.5 mm. Four slices taken at C2 were used for analysis. Quantitative MT data were fitted to a "two pool" model i.e. an unrestricted liquid pool and a semi-solid pool with restricted mobility each in exchange with each other (2). This model estimates: R the rate of MT exchange, Mob is the fraction of semi-solid magnetization and T2b the transverse relaxation time of semisolid component. MT analysis was performed on regions of interest in the dorsal and lateral column white matter and dorsal horn gray matter each of which contained approximately 60 voxels. An unpaired t-test was used to compare mean values of fitted parameters in the dorsal and lateral columns between healthy volunteers, severely affected AMN males, and mildly affected X-ALD females.

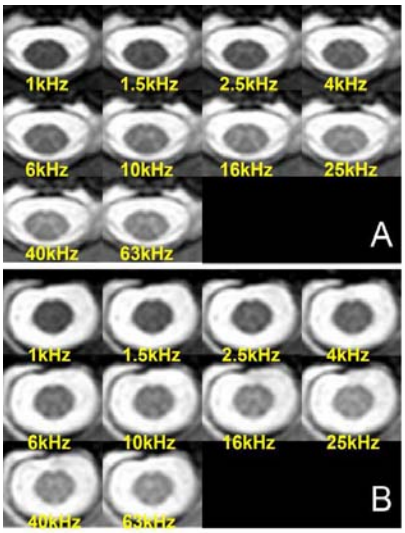

Figure 1: MTw images as function of offset frequency for healthy (A) and mildly affected AMN patient (B).

Results and Discussion: **Fig. 1A** shows typical MTw imaging data at each the offset frequency in a healthy control. Excellent discrimination between the white matter (dark) and butterfly shaped grey matter (lighter) can be appreciated at higher offset frequencies and uniform saturation can be seen at lower offset frequencies. **Fig. 1B** shows the same acquisition in a mildly affected AMN patient. Of note is the loss of grey-white distinction with concomitant hyperintensity in the dorsal column. **Fig 2A** shows two representative normalized MT z-spectra from healthy control (black) and patient with AMN (blue) taken from an ROI in the dorsal column. Regional qMT values are reported in **Fig. 2B-D** and **Table 1**. It can be seen that the control values for grey and white matter in the lateral and dorsal columns and grey matter are similar to values for brain tissue (2). **Fig. 2B-D** shows magnetization transfer rates (R), bound pool size (Mob) and relaxation time (T2b) for control (black), females (red), and males (blue) in dorsal and lateral column white matter and grey matter. No significant difference in magnetization transfer rate was seen (**Fig 2B**). At the site of pathology in AMN, dorsal column Mob values (**Fig 2C**) were significantly decreased: between healthy controls and AMN males ($p < 0.01$) and trending between control and mildly affected females ($p = 0.06$). No difference was appreciated in lateral columns and grey matter. Semisolid pool transverse relaxation rate comparisons are shown in **Fig 2D**. Group comparison showed no difference between controls and patients. It should be noted, however, that the fitting procedure was robust in both patients and controls. Variability in T2b was 3 times larger in patients vs. controls which in part contributes to the lack of statistical differences between the groups.

Conclusion: qMT has been used primarily in the brain to characterize physiological metrics reporting on the nature of the tissue. This report shows for the first time qMT imaging and analysis in the human cervical spinal cord. qMT parameters derived from these experiments show good comparison with reports of brain tissue, while, in a non-inflammatory disease (AMN) the bound pool fraction was observed to be aberrant. It is hypothesized that much of the clinical deficits arising from diseases such as AMN or MS are due to spinal cord involvement, and future studies examining qMT changes metrics may shed light on the nature of pathology in the human spinal cord. Ultimately, it may lead to a metric for comparison with clinical presentation and effects of therapeutic intervention.

References: 1) Wolff SD, Balaban RS. MRM 10(1):1989, **2)** Morrison C, Stanisz G, Henkelman RM JMRB 108(2):1995, **3)** Powers J, et al. J Neuropathol Exp Neurol. 59(2) 2000. 4) Fatemi A, Smith SA, et al. Neurology 64(10) 2005.

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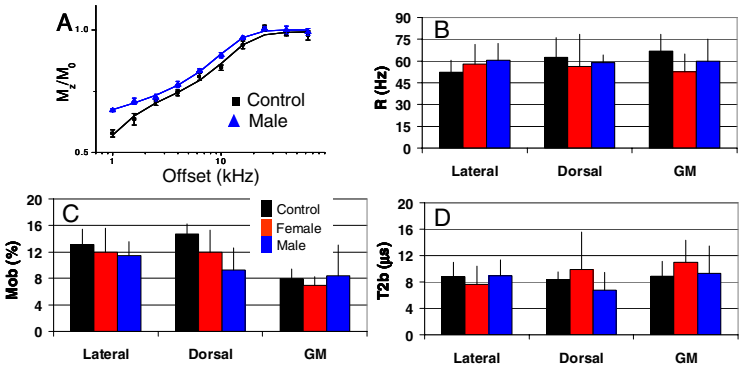

Figure 2: A) MT z-spectrum and fit for one control (black) and AMN male taken from the dorsal column. Standard deviation is over 60 voxels. B-D) Mean qMT fit results in healthy controls (black), X-ALD Females (red), and AMN males (blue). B) Magnetization transfer rate shows slight increase in lateral column (NS) for each of the patients. C) Mob is significantly decreased in dorsal column white matter (site of myelin loss, (2) compared to controls ($p < 0.01$) and a trending between healthy control and mildly affected females ($p = 0.06$). D) T2b shows no difference between controls and AMN patients

Table 1: Comparison between control, AMN male, and X-ALD female fitted qMT values for lateral and dorsal column white matter and grey matter.

	R (Hz)			Mob (%)			T2b (us)		
	Lateral WM	*Dorsal WM*	*GM*	*Lateral*	*Dorsal*	*GM*	*Lateral*	*Dorsal*	*GM*
Control	52.3 ± 8.4	62.5 ± 13.7	66.7 ± 11.9	13.1 ± 2.4	14.7 ± 1.6	7.9 ± 1.5	8.8 ± 2.2	8.3 ± 1.2	8.9 ± 2.3
X-ALD Female	58.1 ± 13.3	56.2 ± 22.4	52.8 ± 12.2	11.9 ± 3.6	12.0 ± 3.2	7.0 ± 1.3	7.6 ± 2.7	9.9 ± 5.6	11.0 ± 3.4
AMN Males	60.5 ± 11.7	58.7 ± 5.6	60.0 ± 15.1	11.4 ± 2.1	9.3 ± 3.4	8.4 ± 4.6	9.0 ± 2.4	6.7 ± 2.7	9.3 ± 4.1