Quantitative Evaluation of Diffusion Tensor Imaging at 3T in the Cervical Spinal Cord of Patients with Adrenomyeloneuropathy

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Introduction: Adrenomyeloneuropathy (AMN) is the noninflammatory adult variant of X-linked adrenoleukodystrophy (X-ALD), a genetic disorder characterized by accumulations of very long chain fatty acids (VLCFA) in the CNS, adrenal cortex, and testes. Pathologic changes in AMN are associated with the spinal cord and are characterized by a primary, distal axonopathy with secondary demyelination which most severely affects the ascending dorsal columns in the cervical region and the descending corticospinal tracts in the lower thoracic and lumbosacral regions [1]. Evaluation of natural history and therapeutic intervention in AMN are hampered by the slow and unpredictable rate of progression and ultimately by the lack of quantitative markers that are sensitive and specific to the disease pathology. The assessment of spinal cord involvement in AMN has been mainly limited to clinical and neurophysiologic testing. One potential reason for this is that pathologic reports show little to no inflammatory component in AMN, and since there is no overt increase in water content T1- and T2-weighted MRI show only cord atrophy (in the late stages) and are not sensitive to subtle white matter abnormalities present in AMN. However, magnetization transfer weighted imaging has shown signal hyperintensity in the dorsal cervical column [2]. We hypothesize that Diffusion Tensor Imaging (DTI) may be sensitive to change in tissue microstructure to such a degree that it may be possible to follow tissue evolution in AMN. However, DTI of the spinal cord is difficult due to the high resolution necessary to detect specific columns (lateral and dorsal), yet with the advent of higher field MRIs, tract-specific DTI can be evaluated in the spinal cord [3]. We therefore examined DTI in the cervical spinal cord of patients diagnosed with AMN and healthy controls to quantitatively assess the pathway-specific changes known, pathologically, to exist in AMN.

Methods: MRI Acquisition: Nine healthy volunteers and twenty AMN patients were studied after signed, informed consent. All studies were approved by the local institutional review board. All scans were performed on a Philips 3T MRI system (Philips Medical Systems, Best, The Netherlands) with a body coil excitation and a 16-channel neurovascular coil for reception. The imaging volume was centered at the chin and covered the superior aspect of C1 to the inferior aspect of C3. DTI of the cervical cord was performed using a multi-slice spin echo with single-shot EPI. Five averaged minimally weighted (b_0) and 16 diffusion-weighted volumes (b-value = 500 s/mm^2, non-collinear directions optimized, *a priori*, to sample a prolate tensor such as is found in the spinal cord) were acquired [4]. Other parameters were: TR/TE = 3000/58ms, nom. resolution = 1.5x1.5x3 mm, 16 slices, 2 averages, and scan time = 1 min. per average. **Data Analysis:** The diffusion tensor was estimated in the standard fashion [5] and from the tensor the fractional anisotropy (FA), perpendicular/transverse diffusivity ($\lambda_\perp$), parallel/longitudinal diffusivity ($\lambda_\parallel$), and mean diffusivity (MD) were calculated. From the DTI datasets, the lateral and dorsal columns were reconstructed (**Fig 1 a,b)** by selecting ROIs on the FA images where the differentiation between gray and white matter can be appreciated (**Fig. 1c,d)**. These ROIs were used to seed the fiber tracts (thresholds: FA = 0.2, turning angle = 60) created in DTIStudio [6]. From these 3 reconstructed tracts, tract-specific metrics were obtained in a similar fashion as the tract-profile method used in the brain to assay the corticospinal tracts [7]. As the spinal cord is expected to change very little over the extent of the cervical cord in healthy volunteers and given that AMN diffusely affects the cervical cord, we compared the mean DTI-derived metrics over the entire extent of the cervical C1-C3 segment. Unpaired T-tests were used to compare whether or not the mean metrics differed between healthy volunteers and patients with AMN in each column.

Results and Discussion: **Figs. 1a,b** show 3D reconstruction of the fiber tracks (red, yellow – lateral columns; green – dorsal columns) in the cervical spinal cord in a control (a) and AMN patient (b) and the 2D representation of the fiber pathways are depicted in **Fig. 1c,d**. Compared to a representative control, **Fig. 1e** shows that AMN FA images present with hypointensities in the dorsal column. Quantitative analysis of the spinal cord tract-specific metrics yields the mean $\pm$ SD of each metric and is shown in **Table 1**. These values were obtained by averaging the slice-wise values from C2 to C3 in both patients and controls; lateral values are averages of both right and left lateral columns. The mean FA, MD, and $\lambda_\perp$ in AMN are consistent with the controls in lateral columns, while $\lambda_\parallel$ is slightly decreased. In contrast, FA, and $\lambda_\parallel$ are slightly decreased relative to the control values in the dorsal column, yet MD is unchanged. Dorsal column $\lambda_\perp$ is significantly ($P<0.03$) increased in AMN. **Fig. 2** shows the mean dorsal column data in healthy controls (blue) and AMN patients (red). These observations are in agreement with expectations from pathology. Unchanged MD in the lateral and dorsal columns supports the lack of inflammation in AMN. The decrease in FA, a measure of diffusion anisotropy, which is in part due to the presence of axonal and myelin barriers to diffusion, indicates a change in the underlying health of the dorsal column. Interestingly, the combined increase in $\lambda_\perp$ and decrease in $\lambda_\parallel$ support the fact that AMN is characterized by a distal axonopathy with secondary demyelination [1]. The elevation in $\lambda_\perp$ may indicate the loss of myelin while the decrease in $\lambda_\parallel$ may indicate accumulation of debris limiting the diffusion of water along the dorsal column pathways.

Conclusion: Our data suggests that DTI-derived metrics can sensitively assess the pathway-specific changes in the spinal column of AMN. Therefore, by adding the quantitative capability of DTI to the existing clinical methods it is possible to develop a better understanding of the progression of the disease, and thus evaluate more effectively the effect of therapeutic intervention.

References: [1] Powers J et al. J Neuropathol Exp Neurol 59; 2000. **[2]** Fatemi A et al. Neurology 64; 2005. **[3]** Brenner C et al. J Magn Reson Imaging 28; 2008. **[4]** Landman B et al. Magn Reson Imaging 26; 2008. **[5]** Mori S et al. NMR Biomed 15; 2002. **[6]** Jiang H et al. Comput Methods Programs Biomed 81; 2006. **[7]** Reich D et al. Neuroimage 38; 2007.

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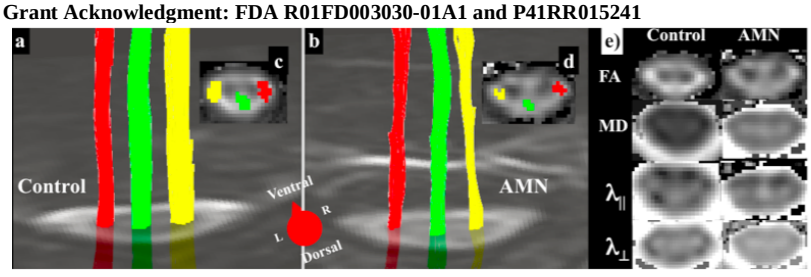

Figure 1: Reconstructed spinal column tracts in both a control (a) and AMN patient (b), including ROI selection (c,d) and DTI-derived metric maps (e).

	Ctrl Lat	AMN Lat	Ctrl Dor	AMN Dor
FA	0.72 $\pm$ 0.06	0.72 $\pm$ 0.05	0.71 $\pm$ 0.07	0.68 $\pm$ 0.04
MD	1.03 $\pm$ 0.12	0.99 $\pm$ 0.16	1.06 $\pm$ 0.09	1.05 $\pm$ 0.14
$\lambda_\parallel$	2.04 $\pm$ 0.17	1.94 $\pm$ 0.23	2.15 $\pm$ 0.13	2.03 $\pm$ 0.17
$\lambda_\perp$	0.53 $\pm$ 0.12	0.52 $\pm$ 0.14	0.52 $\pm$ 0.09	0.57 $\pm$ 0.13

Table 1: Average DTI-derived metric values in the lateral and dorsal columns of both controls and AMN patients.

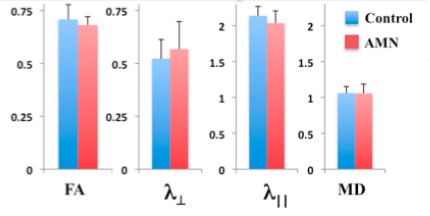

Figure 2: Comparing dorsal column DTI metric values in controls and AMN patients