Correlating Spinal Cord Diffusion Tensor Imaging Metrics to Clinical Measures in 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 to a lesser degree the descending corticospinal column in the same region [1]. Understanding the evolution in AMN is 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. Thus, the assessment of spinal cord involvement in AMN has been mainly limited to clinical and pathological testing. We hypothesized that Diffusion Tensor Imaging (DTI) metrics may be sensitive enough to detect abnormalities in tissue microstructure and that DTI-derived metrics will correlate with the disease severity and neurological and physiological deficits. We therefore examined DTI-derived metrics in each of the large tracts (lateral and dorsal columns) that subtend the cervical spinal cord of clinically evaluated patients diagnosed with AMN and assessed the relationship between these somatotopically organized columns and clinical measures of function.

Methods: MRI Acquisition: Nine healthy volunteers and 40 AMN patients (20 male, 20 female) were studied after signed, informed consent; all studies were approved by the local IRB. All scans were performed on a Philips 3T MRI system (Philips Healthcare, 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 [2]. Other parameters were: TR/TE = 3000/58ms, nom. resolution = 1.5mm x 1.5mm x 3mm, 16 slices, 2 averages, and scan time = 1 min. per average. To evaluate overall disability, each patient had a neurological exam that included the expanded disability status scale (EDSS) [3], as well as the functional measures: timed get-up and go (Guag), walking speed, standing balance and vibration sensation.

Data Analysis: The diffusion tensor was estimated in the standard fashion [4] and from the tensor the fractional anisotropy (FA), transverse diffusivity ($\lambda_\perp$), longitudinal diffusivity ($\lambda_{||}$), and mean diffusivity (MD) were calculated. From the DTI datasets, the lateral and dorsal columns were reconstructed (**Fig 1 a,b)** by selecting ROIs in the dorsal (green) and lateral columns (red/yellow) 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 [5]. From these 3 reconstructed tracts, tract-specific metrics were obtained and tract profiles were calculated using the methods similar to those found in [6]. The spinal cord microstructure is assumed to change only gradually over the cervical region given that AMN diffusely affects the cervical cord. The mean values were therefore obtained by averaging the slice-wise values over the entire extent of the cervical C1-C3 segment in patients and controls; lateral values were averaged from right and left lateral columns. We then performed correlations between the mean DTI-derived metrics and the EDSS scores and functional measures.

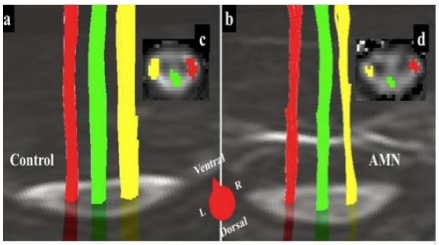

Figure 1: Reconstructed spinal column tracts in both a control (a) and AMN patient (b), showing ROI selection on the FA map (c,d).

Results and Discussion: To better understand how DTI-derived metrics relate to functional measures we used correlation analyses. Spearman's rank correlation test was performed to compare all mean DTI values in both lateral and dorsal columns for male and female AMN patients to their functional measures. Of these correlations, only those for the dorsal column in men were significant. **Table 1** shows the Spearman's rank correlations (R) and the corresponding p-value between male AMN DTI metrics and functional measures; significant correlations are highlighted in red. **Figs 2a,b** show two correlations in the male patients: between the get-up-and-go measure and dorsal $\lambda_{||}$ (a) and balance and dorsal $\lambda_\perp$ (b). The link between balance, a functional measure of sensation, and transverse diffusivity, supports the structure-function relationship between the somatotopically organized columns and neurophysiological dysfunction. Those individuals who are more progressed in their clinical evaluation (i.e., higher EDSS, slower get-up-and-go or poor balance) also present with worse DTI measures.

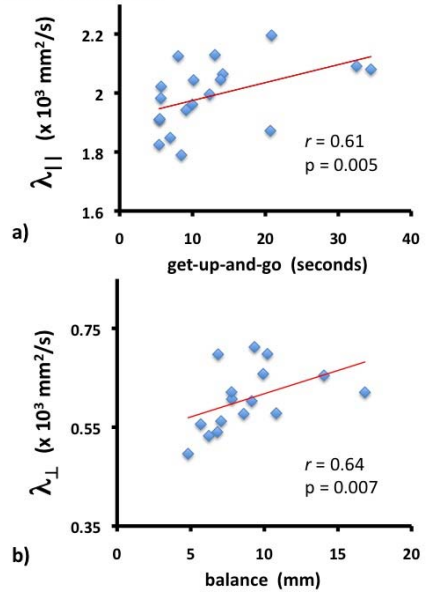

Figure 2. Correlation between the functional measures, get-up-and-go **(a)** and balance **(b)**, and the dorsal column $\lambda_{||}$ and $\lambda_\perp$ DTI metrics respectively, for the same 20 male AMN patients. The best-fitting linear regression line is shown in red, and Spearman's rank rho and associated P-value are also listed.

		EDSS	Guag	Walking	Balance	Vib (L)
Dorsal Column	FA	R = -0.49 P = 0.03	R = -0.06 P = 0.81	R = 0.03 P = 0.09	R = -0.39 P = 0.14	0.05 0.87
	MD	R = 0.25 P = 0.29	R = 0.61 P = 0.006	R = -0.49 P = 0.03	R = 0.65 P = 0.007	R = 0.42 P = 0.11
	$\lambda_{||}$	R = 0.02 P = 0.94	R = 0.61 P = 0.005	R = 0.50 P = 0.03	R = 0.57 P = 0.02	R = 0.66 P = 0.005
	$\lambda_\perp$	R = 0.34 P = 0.14	R = 0.36 P = 0.13	R = 0.25 P = 0.31	R = 0.64 P = 0.007	R = 0.20 P = 0.46

Table 1: Spearman's rank correlation and associated p-value of for the comparison between DTI-derived metrics in the dorsal column of AMN males to the functional measures. Significant correlations are highlighted in red.

Conclusion: Our data suggests that there is a strong relationship between tract-specific DTI-derived metrics of the cervical spinal cord and clinical dysfunction. The ability to probe the structure-function relationship in patients with AMN may improve our understanding of the pathologic abnormalities associated with AMN and has promise for use in evaluating future therapeutic interventions.

References: [1] Powers J et al. J Neuropathol Exp Neurol 59; 2000. **[2]** Landman B et al. Magn Reson Imaging 26; 2008. [3] Kurtzke JF. Neurology 33;1983. **[4]** Mori S et al. NMR Biomed 15; 2002. **[5]** Jiang H et al. Comput Methods Programs Biomed 81; 2006. **[6]** Reich D et al. Neuroimage 38; 2007.

Grant Acknowledgment: FDA R01FD003030-01A1 and P41RR015241