Diffusion Tensor Imaging Detects Abnormalities in the Corticospinal Tract of the Brain 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. Its pathology is characterized by primary axonopathy and secondary demyelination that most dramatically affects the corticospinal tract (CST) as well as the dorsal column of the spinal cord [1]. In this study we evaluated the cerebral involvement in a tract-specific manner with Diffusion Tensor Imaging (DTI). We hypothesize that abnormal water diffusion properties can be detected in the cerebral portion of the CST with DTI. This may enable early detection of tissue abnormalities in AMN.

Methods: Population: 29 healthy volunteers and 39 male AMN patients, who were part of a larger Lorenzo's Oil study, were evaluated after signed, informed consent. All studies were approved by the IRB. All scans were performed on a Philips 1.5T MRI system (Philips Healthcare, Best, The Netherlands) with a body coil excitation and an 8-channel SENSE head coil for reception. The AMN patients were scored on the expanded disability status scale (EDSS) [2], and we compared these 39 men who were severely affected (having a pyramidal subscore in EDSS of 2.5-4) to controls. **DTI acquisition**: multi-slice spin echo with single-shot EPI. Diffusion weighting was encoded along 30 independent orientations (b = 700 s/mm^2) and 5 averages of the minimally diffusion-weighted scans (b = 33 s/mm^2). Other parameters were: TR ranged from 6489 ms to 8433 ms, TE = 80 ms, nom. resolution of 2.5mm x 2.5mm x 2.5mm, with 50-60 slices covering the entire hemisphere and brainstem without gaps. **Data Analysis:** Motion correction and the diffusion tensor calculation were performed with CATNAP [3] and fractional anisotropy (FA), the perpendicular diffusivity ($\lambda_\perp$), parallel diffusivity ($\lambda_\parallel$), and mean diffusivity (MD) are reported. From the DTI datasets the left and right CST were reconstructed by drawing ROIs around the anterior pons and the ipsilateral cerebral hemisphere at the level of the subcortical white matter, following methods similar to those in [4]. These ROIs seeded the fiber tracts (thresholds: FA = 0.4, turning angle = 40^o) created in DTIStudio [5]. From these reconstructed tracts, tract-specific metrics were obtained in a similar fashion as [6]. The CST was divided into three sections: Pons-Midbrain (P-MB), Midbrain-Thalamus (MB-TH), and Thalamus-Cortex (TH-C). Unpaired t-tests were used to compare whether or not the mean DTI metrics differed within these three sections between healthy volunteers and patients with AMN.

Results and Discussion: Fig. 1a shows a sagittal view of a 3D reconstruction of the CST fiber tracts (yellow) in an AMN patient, and in **Fig. 1b** we show a 2D axial view of the fibers at the level of the pons. **Fig. 2** shows the mean tract-profile for FA indicating the disparity between healthy (black) and AMN (red) CST values with SEM error bars. The mean AMN values differ significantly from controls in both the P-MB ($p<0.01$) and MB-TH ($p<0.001$) sections. **Table 1** shows the quantitative (mean $\pm$ SD) values of the CST metrics for healthy controls and AMN. These numbers were obtained by averaging the slice-wise values from each of the three sections in both patients and controls. The FA, MD, and $\lambda_\perp$ values differ significantly ($P<0.01$) from controls in both the P-MB and MB-TH sections (table values highlighted in red), yet $\lambda_\parallel$ remains unchanged. Diffusion anisotropy is due, in part, to the presence of axonal and myelin barriers to diffusion. Thus the decrease in FA may indicate a change in the underlying health of the tract. The elevation of $\lambda_\perp$ may indicate the loss of myelin, which is consistent with the pathologic findings.

Conclusion: Our data suggests that DTI-derived metrics can sensitively detect the pathway-specific abnormalities in the corticospinal tract of individuals with AMN, which is in corroboration with the knowledge that cerebral damage is present in AMN.

References: [1] Dubey P et al. Ann Neurol 58; 2005. [2] Kurtzke JF. Neurology 33;1983. [3] Landman et al. Neuroimage 36; 2007. [4] Wakana S et al. Neuroimage 36; 2007. [5] Jiang H et al. Comput Methods Programs Biomed 81; 2006. [6] Reich D et al. Neuroimage 38; 2007.

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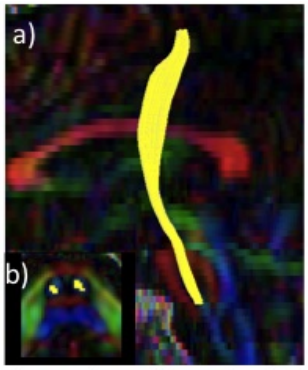
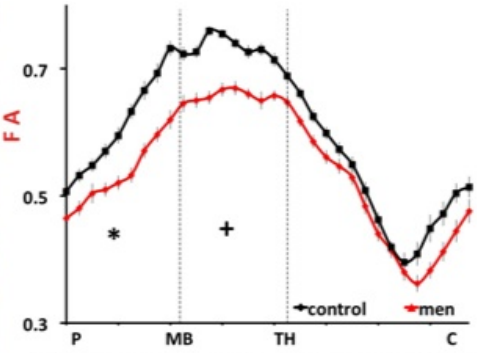


Figure 1: Reconstructed corticospinal tract in an AMN patient (a), and the pons ROI selection (b).



	FA		MD		$\lambda_\parallel$		$\lambda_\perp$	
	Ctrl	AMN	Ctrl	AMN	Ctrl	AMN	Ctrl	AMN
P–MB	0.62± 0.07	0.54±0.05	0.84±0.01	0.88±0.02	1.53±0.13	1.47±0.1	0.50±0.06	0.58±0.04
MB-TH	0.74±0.005	0.67±0.01	0.8±0.02	0.89±0.01	1.66±0.07	1.71±0.03	0.38±0.01	0.47±0.01
TH-C	0.54±0.1	0.51±0.09	0.76±0.01	0.82±0.02	1.29±0.16	1.37±0.15	0.50±0.07	0.56±0.05

Table 1: Mean DTI-derived metric values in the corticospinal tract of both controls and the most severely impaired (pyramidal EDSS score > 2.5) AMN men, n = 39.

Figure 2: CST profiles show the average FA values for each slice, averaged across healthy controls (black) and severely impaired male AMN patients (red). Profiles are plotted against a normalized distance along the CST, abbreviated by: pons (P), midbrain (MB), thalamus (TH), and cortex (C). Error bars show one standard error of the mean. Significant differences were determined by unpaired t-tests and symbols located under the curves indicate level of significance: *, $p<0.01$; +, $p<0.001$.