DIFFUSION ABNORMALITIES IN THE SPINAL CORD GREY MATTER RELATES TO DISABILITY IN RELAPSE-ONSET MULTIPLE SCLEROSIS

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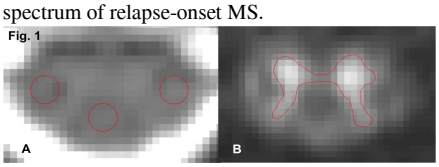
TARGET AUDIENCE: Clinicians with an interest in multiple sclerosis (MS) and physicists working with diffusion weighted imaging in the spinal cord.
PURPOSE: To investigate spinal cord grey and white matter tract microstructural abnormalities in MS using diffusion tensor imaging (DTI).
INTRODUCTION: The spinal cord is frequently involved in MS[1], however the pathology is complex, with features including inflammation, demyelination and axonal loss[2, 3]. Due to these heterogeneous abnormalities, T2-weighted lesions seen in the spinal cord on magnetic resonance imaging (MRI) may not accurately reflect clinical status in MS[4]. Axonal loss may occur in normal appearing white matter in the spinal cord, furthermore it has been suggested that a decrease in axonal density may occur independent of focal demyelinating lesions[5]. A combination of these factors may contribute to the discrepancy seen between the number of spinal cord lesions detected on MRI and clinical status. To overcome this problem, quantitative MRI methods have been developed to better approximate pathology *in vivo*. Diffusion tensor imaging (DTI) is based on the principle of anisotropic movement of molecules within biological membranes, such as axons[6]. DTI provides the following indices: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD). However there are no previous DTI studies in the spinal cord that examine the full spectrum of relapse-onset MS.



METHOD: A) Study participants: We recruited 30 controls, 22 people with CIS, 33 relapsing remitting (RR) and 29 secondary progressive (SP) MS. We evaluated physical disability in each participant using the expanded disability status scale (EDSS)[7] and both the 25-foot timed walk test (TWT) and 9-hole peg test (9-HPT) and z-scores were calculated using published values[8]. Informed written consent was obtained from all subjects prior to participation. B) MR Imaging: Using a 3T Philips Achieva MRI system (Philips Medical Systems, Best, Netherlands) and a 16-channel neurovascular coil we acquired an axially orientated diffusion weighted scan in the upper cervical spinal cord covering from C2 to C4. We applied a reduced field-of-view (FOV) ZOOM-DTI sequence[9] with the following parameters: TE = 52 ms, TR = 12 RRs (cardiac gated), reduced FOV of 64 x 48 mm^2, SENSE factor = 1.5, acquisition matrix = 64 x 48 for a voxel resolution of 1 x 1 x 5 mm^3. The DW imaging protocol consisted of 30 b = 1000 s mm– 2 DWI volumes with gradient directions evenly distributed over the sphere and 3 non–DWI (b = 0) volumes. C) Image analysis: We processed the DTI data using Camino[10] software. We marked white matter column regions of interest (ROIs) using JIM6 (Xinapse systems, www.xinapse.com) on the B0 image in the lateral and posterior columns[11] (Fig. 1A). To segment the spinal cord grey matter (GM) we created an average image of all diffusion weighted images that are approximately perpendicular to the main WM orientation (+/- 50 degrees) assumed to be along the magnet axis. We then marked the grey matter ROI using an edge finding tool (Fig. 1B). We calculated the mean and standard deviation (SD) of each DTI parameter contained within the delineated ROIs; for the lateral column ROIs we calculated an average value using the left and right masks, after testing that no significant differences in diffusion measures were present between the sides. D) Statistics: We calculated differences in DTI parameters between patients and controls using a t-test and subsequently calculated univariate correlations with disability in the MS group.
RESULTS: A) Comparison with controls: In CIS spinal cord abnormalities were detected compared to controls. In both RRMS and SPMS FA was lower than controls and both MD and RD were higher. There were no significant differences in spinal cord AD between MS and controls. Mean ± SD are provided in the table, p values are denoted as: * $p < 0.05$; † $p < 0.01$; ‡ $p < 0.001$; § $p < 0.0001$ **B)** Significant correlations with physical disability in the MS cohort (i.e. excluding CIS): The following DTI metrics were found to correlate with EDSS: posterior column FA (r=-0.32, p=0.01), MD (r=0.31, p=0.02), RD (r=0.37, p<0.01) and GM MD (r=0.36, p<0.01), RD (r=0.38, p<0.01). The TWT z-score was correlated with GM MD (r=0.37, p<0.01) and RD (r=-0.38, p<0.01). The 9-HPT z-score was correlated with lateral column MD (r=-0.33, p=0.01), RD (r=-0.28, p=0.03), posterior column FA (r=0.26, p=0.04), MD (r=-0.38, p<0.01), RD (r=-0.35, p<0.01) and GM MD (r=-0.49, p<0.01), RD (r=-0.47, p<0.01) and AD (r=-0.35, p<0.01).

Spinal cord region	DTI	Control	CIS	RRMS	SPMS
Lateral column	**FA**	0.76 ± 0.04	0.72 ± 0.05‡	0.71 ± 0.05§	0.69 ± 0.05§
(x 10^{-3} mm^2/s)	**MD**	0.91 ± 0.06	0.95 ± 0.05*	0.96 ± 0.07‡	0.98 ± 0.07§
	RD	0.39 ± 0.07	0.45 ± 0.06†	0.49 ± 0.08§	0.50 ± 0.07§
Posterior column	**FA**	0.79 ± 0.05	0.77 ± 0.05	0.73 ± 0.05§	0.71 ± 0.05§
(x 10^{-3} mm^2/s)	**MD**	0.95 ± 0.06	0.93 ± 0.05	0.96 ± 0.06	1.03 ± 0.09§
	RD	0.37 ± 0.07	0.39 ± 0.06	0.45 ± 0.08§	0.51 ± 0.09§
Grey matter	**FA**	0.56 ± 1.16	0.53 ± 0.04*	0.51 ± 0.05§	0.48 ± 0.05§
(x 10^{-3} mm^2/s)	**MD**	0.82 ± 0.04	0.84 ± 0.04	0.86 ± 0.05‡	0.91 ± 0.06§
	RD	0.53 ± 0.04	0.56 ± 0.04†	0.59 ± 0.04§	0.64 ± 0.05§

CONCLUSION: We have demonstrated spinal cord abnormalities in CIS i.e. the first phase of relapse-onset MS. In RRMS and the later progressive stage of relapse-onset MS, spinal cord DTI measures differed significantly from the healthy controls with a tendency towards greater differences in SPMS. Different DTI metrics are thought to reflect diverse pathological processes in MS, and we have shown that they can detect functionally relevant abnormalities in both central GM and major white matter tracts, as we have demonstrated correlations with disability using global and tract specific disability scales in both grey and white matter. Generally stronger correlations with disability were seen in the spinal cord GM than either white matter tracts evaluated in this study, thus suggesting a hitherto unrecognised effect of pathology in spinal cord grey matter on disability in MS.

ACKNOWLEDGEMENTS: The NMR Research Unit is supported by the MS Society of Great Britain and N.Ireland and UCLH-UCL BRC. **REFERENCES:** 1)Bot et al. Neurology 2004 2)Nijeholt et al. Brain 2001 3)Ganter et al. Neuropathol Appl Neurobiol 1999 4)Kidd et al. Neurology 1993 5)Bergers et al. Neurology 2002 6)Le Bihan NMR Biomed 1995 7)Kurtzke Neurology 1993 8)Fischer et al. Mult Scler 1999 9)Wilm et al. Magn Reson Med 2007 10)Cook et al. ISMRM abstract 2006 11)Hesseltine et al. AJNR 2006