Diffusion tensor imaging in bulbar and limb-onset amyotrophic lateral sclerosis

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Purpose: Bulbar onset amyotrophic lateral sclerosis (ALS-B) has a worse prognosis than limb onset (ALS-L)[1]. This could simply mean that when precisely the same pathological process strikes muscles that are more critical for survival, patients succumb more rapidly. Alternatively it could indicate that those with ALS-B have a biologically more aggressive variant. Past studies addressing this issue have been confounded by poor matching of groups on clinical severity variables that could have explained any observed differences[2-4]. This study, therefore, aimed to address the question using diffusion tensor imaging (DTI) and groups that were precisely matched for power, sex and clinical severity measures. **Methods:** 14 non-demented patients with ALS-B were identified from a prospective ALS study. A far larger pool of ALS-L patients was available enabling selection of 14 ALS-L cases matched for sex distribution (10M/4F per group). For comparison, a group of 29 controls subjects (23M/6F) were recruited and screened to exclude neurological illness and cognitive deficits. The ALS-L group were further selected to be precisely matched for disease severity on the amyotrophic lateral sclerosis functional rating (ALSFR-R) scale (mean scores: ALS-B=39.7, ALS-L=39.1, p=0.79) and for cognitive ability using the Montreal Cognitive Assessment (scores: ALS-B=25.8, ALS-L= 26.7, p=0.27). The mean symptom duration was shorter for the ALS-B cohort, 16.1±9.8 compared to 23.2±19.2 months for ALS-L, although this was not statistically significant (p=0.23). Imaging: Experiments were performed on a Siemens Verio 3T system equipped with a 32 channel RF head coil. Diffusion tensor imaging was carried out using twice refocused, single shot, echo planar imaging acquisition using the following parameters: TR/TE=12700/81ms; matrix, 128x128; 72 contiguous slices; isotropic resolution of 2x2x2 mm^3; receiver bandwidth of 1628 Hz/pixel; echo spacing of 0.72 ms; GRAPPA acceleration factor of 3 with 57 reference lines. The tensor was computed using 30 non-collinear diffusion directions (b=1000 s/mm^2) and one scan without diffusion weighting. A T2-weighted axial FLASH sequence was acquired during the same session using the following parameters: TR/TE=620/19.90 ms; 24 slices; slice thickness=5mm; matrix = 256x256; and an in-plane resolution of 0.9x0.9 mm^2. These images were used to ensure vascular pathology was not significant in any subject. Image Analysis: FMRIB software was used to correct for motion, eddy currents, fit the diffusion tensor and generate the parametric maps[5]. TBSS was used to perform whole brain, cluster-based, statistical analyses at white matter tract centres[6] with threshold free cluster enhancement enabled[7]. Statistical comparisons contrasted the control group to each of the ALS groups for changes in fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (λ_1). Regional data analysis: A region of interest (ROI) comprising both left and right corticospinal tracts (CST) was delineated in standard space, using the FMRIB58_FA template. Mean quantitative values resulting from the intersection of the ROI with the mean skeleton mask were computed. A Lilliefors test was applied to assess whether ROI data were normally distributed. RD values within the ALS-B cohort were not normally distributed at alpha = 0.05. Hence, for consistency, non-parametric Mann-Whitney U-tests were used to compare all unpaired DTI-derived values from independent sample groups (controls, ALS-B, ALS-L). Results are given at three levels of statistical significance: * p< 0.05, ** p<1e-2, *** p<1e-3). **Results:** TBSS analysis of ALS-B cohort (Top row, Fig. 1). At p<0.05 corrected for multiple comparisons, bilateral and confluent changes along the CST were found for FA. RD showed less extensive statistical differences, mainly restricted to the CST at the thalamic level. No differences were detected for MD or λ_1 in these whole brain analyses. TBSS analysis of ALS-L cohort. The group comparison between ALS-L and controls (corrected p<0.05) showed no significant differences, however, reducing the significance threshold to uncorrected p<0.05 found FA and RD differences in CST (Bottom row, Fig. 1). ROI- results (Fig. 2). Significant changes in FA were found in the contrast of controls with either ALS group, although differences between controls and ALS-B were more significant (p<1e-3). MD changes were statistically significant between controls and ALS-B (p<0.01) and also between ALS-B and ALS-L (p<0.05). RD changes were significant between ALS-B and controls (p<1e-3); ALS-L and ALS-B (p<0.05); and ALS-L and controls (p<0.05). λ_1 changes were significant between ALS-L and controls only (p<0.05). **Discussion:** Results showed extensive bilateral FA and RD differences along the CST between ALS-B and controls; a similar distribution was seen for ALS-L at a less stringent TBSS threshold (p<0.05 uncorrected). ROI analyses also showed more significant changes in ALS-B than ALS-L when each was compared to controls; in the case of MD and RD values reached statistical significance in the direct contrast of the two patient groups. **Conclusion:** Considering that both groups of patients were matched according to cognition, disease severity, sex and power, the results suggest that ALS-B alters the structural integrity of white matter tracts more rapidly than ALS-L, which would explain why patients suffering from ALS-B have worse prognosis and shorter life expectancy. This hypothesis is reinforced when symptoms duration are taken into consideration given that ALS-L subjects presented symptoms for a slightly longer, although not statistically significant, period of time.

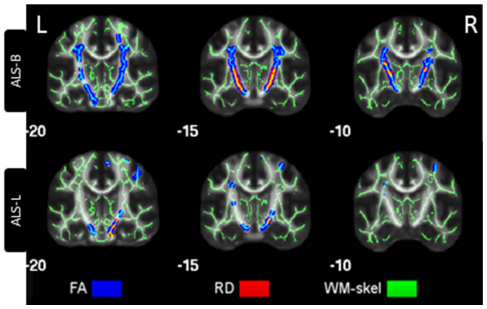

Figure 1: TBSS results. Top row, ALS-B vs. controls, p(corrected)<0.05. Bottom row, ALS-L vs. controls, p(uncorrected)<0.05.

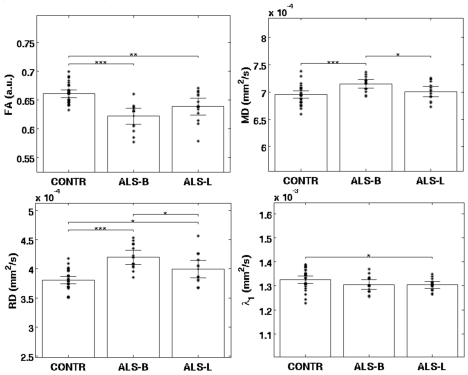

Figure 2: ROI results-. In all columns each of the scattered dots represents the mean value of each metric for each subject within its respective group. Whiskers indicate the 95% confidence interval and bar plot represents the group means. (* p<0.05, ** p<1e-2, ***p<1e-3).

References: [1]Roche et al, Brain, 2012;135:847-852. [2]Ellis et al, Neurology 1999;53:1051-1058. [3]Prell et al, Clin Neurol and Neurosurg, 2013;115:1281-1287. [4]van der Graaf et al, Brain, 2011;134:1211-1228. [5]Smith et al, Neuroimage, 2004;23 Suppl 1:S208-219. [6]Smith et al, Neuroimage, 2006;31:1487-1505. [7]Smith et al, Neuroimage, 2009;44:83-98