Quantification of Neurodegeneration in Amyotrophic Lateral Sclerosis (ALS) using DTI and Iron Mapping

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1. Introduction

DTI based techniques such as fiber-tracking and tract based spatial statistics (TBSS) [1] have revealed disease related brain tissue changes in amyotrophic lateral sclerosis (ALS) [2-3] which previously remained undetected by conventional MRI. Iron mapping holds promise to assess additional components of neurodegeneration [4], but has rarely been used in this context [5]. We therefore wished to test whether iron accumulation might confer information on pathophysiologic changes related to ALS complementary to regional DTI, focussing on the corticospinal tract (CST) and on deep gray matter structures.

2. Subjects and Methods

Fifteen patients with definite or probable ALS (mean age 60.1yrs, SD 8.8yrs, range 42-82yrs) and an age- and gender-matched cohort of 15 healthy controls (mean age 60.8yrs SD 8.1yrs) underwent clinical examination and MRI at 3T (TimTrio, Siemens Healthcare, Erlangen, Germany). Structural imaging included a FLAIR sequence and a 3D MPRAGE sequence with 1mm isotropic resolution (TR/TE/TI/FA=1.9s/2.19ms/0.9s/9°). A spoiled FLASH sequence (TR/FA=86ms/20°) with 12 equally spaced echoes (echo spacing= 4.92ms) was used for the estimation of R_2^* as an indicator for iron deposition. DTI data were acquired with a diffusion weighted SE-EPI sequence (TR/TE/FA=6.7s/95ms/90°), where the diffusion sensitizing gradients were applied in 12 independent directions (b=1000s/mm). Diffusion data were analysed with TBSS [1] and the non-linear transformations matrices for the DTI datasets, calculated by TBSS were also used for transforming the R_2^* dataset. In contrast to voxel-based analyses (VBA) this approach also incorporated structural information of white matter tracts (WMT) and therefore allowed a more precise identification of iron deposition in WMT. The skeleton generated by TBSS was modified to obtain a mask including the central part of the CST. Based on the high resolution 3D scan, several deep gray-matter structures and the brainstem were defined fully automated [6]. R_2^* was calculated from the multiecho data [7] and then was evaluated in the predefined regions. ANOVA and multiple regression analyses were used to explore the impact of aging and clinical disease duration on regional iron deposition and on DTI characteristics.
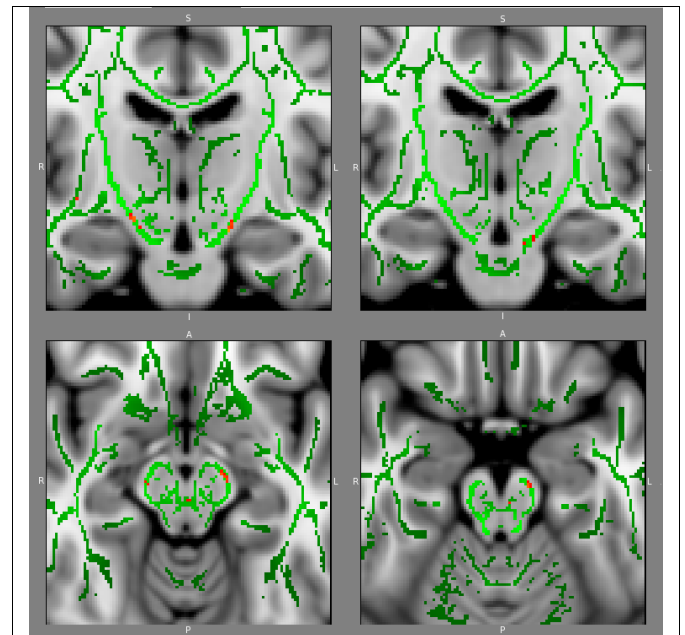

Figure 1: TBSS Skeleton of WMT (green) where significantly decreased FA (left panel) and increased R2* (right panel) values in ALS patients compared to age- and sex-matched controls in the mesencephalic CST are shown in red (p<0.05). Note the anatomical overlap.

3. Results

Upon TBSS analysis, patients demonstrated lower FA values and higher R_2^* values compared to controls in the mesencephalic CST (Figure 1). The CST analysis showed that the magnitude of the R_2^* increase in patients exceeded that of the decrease in FA (Table 1). Regarding iron deposition in the predefined gray matter and brain stem regions, there were no significant differences between patients and controls, and within patients, no effect of disease duration was observed. However, in both groups, there was a strong correlation between age and iron deposition in the caudate, globus pallidus and putamen (Table 2).

	Mean R_2^* [s^{-1}]	SD R_2^* [s^{-1}]	Mean FA [arb.u.]	SD FA [arb.u.]
Controls	26.28	1.68	0.703	0.025
ALS Pat.	27.86	1.87	0.687	0.027

Table 1: Mean R2* and FA in the segmented CST.

	R	p	R_2^* Regression
Caudate	0.486	0.002	22.2+0.108*Age
Globus pallidus	0.375	0.024	31.6+0.067*Age
Putamen	0.708	<0.001	20.8+0.157*Age

Table 2: Effect of age on iron deposition (R_2^*) in selected deep gray matter structures.

4. Discussion/Conclusion

Extending previous reports using DTI in ALS, our observation of a regionally specific increased iron deposition along the CST provides evidence that R_2^* assessments might also allow depicting tissue changes relevant to ALS. Our findings further, signal a somewhat increased sensitivity of R_2^* over DTI. However, longitudinal studies are warranted to determine whether these changes are primary, secondary or independent to the DTI changes.

References:

[1] Smith SM, 2006, NeuroImage, 31:1487-1505, [2] Ciccarelli O, 2008, HBM, (Eprint), [3] Sage CA, 2007, NeuroImage, 34:486-99, [4] Berg D, 2006, Topics MRI,17:5-17, [5] Oba H, 1993, Rad.,189:843-6, [6] Patenaude B, 2007, Proc.HBM 2007, [7] Haacke EM, 2005, MRI, 23:1-25