Correlations between Measures of Multiple Sclerosis Pathology Derived from T2, T1, Magnetization Transfer and Diffusion Tensor MR Imaging

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Introduction

In multiple sclerosis (MS), conventional magnetic resonance (MR) imaging lacks specificity to the heterogeneous pathological substrates of MS lesions [1], and does not detect subtle abnormalities in the normal-appearing white matter (NAWM) [2]. Magnetisation transfer (MT) and diffusion tensor (DT) MR imaging, may go some way towards overcoming these limitations by providing quantitative indices with increased specificity to the most destructive aspects of MS [3-5]. In this study, we assessed the correlations between MT and DT MR imaging-derived metrics and those between these quantities and measures derived from conventional MR, to investigate the amount of independent information about tissue damage provided by each of the techniques.

Methods

We studied 34 patients with relapsing-remitting MS. Their mean age was 34.8 years, the median duration of the disease was 6.5 years and the median Expanded Disability Status Scale (EDSS) score was 1.5. Using a 1.5 Tesla magnet and in a single session, the following scans of the brain were performed: a) dual-echo turbo spin echo (TSE) (TR/TE/acquisitions=3300/16-98/1, echo train length=5); b) T1-weighted conventional spin echo (CSE) (TR/TE/acquisitions=768/15/2); c) gradient-echo (GE) (TR/TE/acquisitions= 600/12/2, flip angle = 20º), with and without an off-resonance RF saturation pulse (offset frequency = 1.5 kHz, Gaussian envelope duration = 16.4 ms, flip angle = 500º); d) pulsed-gradient spin-echo echo-planar pulse sequence (inter-echo spacing=0.8, TE=123), with diffusion gradients applied in 8 non-collinear directions. For TSE, CSE and GE scans, 24 contiguous, 5-mm thick axial slices were acquired with 256x256 matrix and 250x250 mm field of view (FOV). For DT-MR scans, 10 contiguous, 5-mm thick axial slices with 128x128 matrix and 250x250 mm FOV were acquired, with the second-last caudal slice positioned to match exactly the central slice of the other sets. T2 hyperintense and T1 hypointense lesion volumes (LV) were measured using a semi-automated technique based on local thresholding [6]. Brain volume was measured from T1-weighted images, using a seed growing technique for brain parenchyma segmentation. From the two GE images, with and without the saturation pulse, MT ratio (MTR) maps were derived pixel-by-pixel. From the DW scans, after correction for eddy current-induced distortion, the diffusion tensor was calculated assuming a mono-exponential relationship between the signal intensity and the elements of the tensor matrix. Mean diffusivity (MD) and fractional anisotropy (FA) values were derived for every pixel. MTR, MD and FA maps were coregistered to the dual-echo images. T2 lesion outlines were automatically transferred onto the coregistered images and the average lesion MTR, MD and FA, weighted by lesion area, were calculated. Normalized histograms of MTR, MD and FA maps were created as previously described [4]. MTR and MD histograms were derived from the whole of the brain tissue (BT), from the normal-appearing brain tissue (NABT), from the normal-appearing white (NAWM) and gray matter (NAGM). FA histograms were derived only from the BT. For all the histograms, the average MTR, MD and FA values were calculated. To obtain the MTR and MD histograms of NABT, T2 lesion outlines were automatically transferred onto the coregistered MTR and MD maps and then nulled out. The segmentation of NAWM and NAGM from NABT-MTR and NABT-MD maps was obtained using a technique based on FA thresholding [7]. For statistical analysis, given the high number of tests performed, only p values < or =0.01 were considered significant.

Results

No significant correlation was found between any of the MTR and FA histogram-derived metrics and T2/T1 LV or brain volume. Significance trends were found when correlating T2 and T1 LV with the MTR histogram peak heights (r values from -0.37 to -0.41, p values from 0.03 to 0.02). All the BT and NABT MD histogram-derived metrics were significantly correlated with T2 and T1 LV (Table), whereas they were not significantly correlated with brain volume. No significant correlations were found between the corresponding quantities of MTR, MD and FA histograms. Significance trends were found only when correlating the average BT MD with BT FA (r=-0.39, p=0.02) and the peak positions of the BT MD and BT MTR histograms (r=-0.34, p=0.05). Average lesion MTR, MD and FA were not significantly correlated between them. None of the MR quantities was significantly correlated with patients' EDSS score. However, significance trends were observed when correlating EDSS with T1 lesion volume (r=0.36, p=0.04), the peak height of the BT MTR (r=0.40, p=0.02), and of the NABT MTR (r=0.37, p=0.03) histograms.

Discussion

The lack of correlation between MTR and DT MR metrics in the brain tissue might be the result of the complex relationship between destructive and reparative mechanisms occurring within and outside T2-visible MS lesions. That DT histogram metrics are strongly correlated with T2 and T1 lesion volumes, whereas quantities derived from MTR histograms are only modestly correlated with them, suggests that MT MR is more sensitive to subtle MS pathology occurring in the NAWM, whereas DT MR findings are more influenced by MS macroscopic pathology. That we did not find any correlation between brain volume and quantities derived from MT and DT MR imaging in patients with a mildly disabling disease phenotype suggests that brain atrophy measurement might be not sensitive to the most subtle aspects of MS pathology. Although preliminary and warranting further investigation in the more advanced phases of the disease, our results suggest that the application of different MR techniques with variable sensitivity to the heterogeneous pathological aspects of MS might contribute to a better understanding of MS pathophysiology and call for a multiparametric MR approach in the study of patients with MS.

References

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Correlations between MD histogram metrics and T2/T1 LV

	T2 LV		T1 LV	
	r	p	r	p
BT MD	0.78	<0.001	0.71	<0.001
BT MD peak height	-0.68	<0.001	-0.65	<0.001
BT MD peak position	0.58	<0.001	0.53	<0.001
NABT MD	0.77	<0.001	0.70	<0.001
NABT MD peak heigh	-0.65	<0.001	-0.63	<0.001
NABT peak position	0.57	<0.001	0.52	<0.001