Using relaxation, magnetization transfer and diffusion to characterise multiple sclerosis lesion pathology

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Introduction

Multiple sclerosis (MS) lesions which appear hypointense on T_1-weighted images are thought to represent areas of more permanent tissue damage with severe axonal loss and increased extracellular water [1,2,3]; however, it is difficult to confirm this destruction due to the lack of pathological specificity of conventional MRI [4]. From T_2 relaxation, a new Long-T_2 fraction (200-800ms, LT_2F) has been discovered in some MS lesions and is believed to indicate increased extracellular spaces and/or edema [5]. Diffusion tensor imaging (DTI) measures are also affected by myelin and axon integrity. The trace ($\lambda_1+\lambda_2+\lambda_3$, TR) reflects the magnitude of diffusion, while fractional anisotropy (FA) is thought to be dominated by axonal membranes and only modulated by myelination [6]. Dpar (λ_1) and Dperp ($(\lambda_1+\lambda_3)/2$) are hypothesised to reflect axon and myelin integrity, respectively [7]. Based on the above description, lesions can be classified into: (1) enhancing, (2) isointense T_1, (3) isointense T_1 with LT_2F, (4) hypointense T_1 and (5) hypointense T_1 with LT_2F. The purpose of this study was to investigate how water content (WC), myelin water fraction (MWF), T_1, geometric mean T_2 (GMT_2), LT_2F, magnetization transfer ratio (MTR), FA, diffusion trace (Tr), Dperp and Dpar varied with lesion subtype. The long term goal of this project is to understand how the various MR parameters relate to specific lesion pathologies.

Methods

MRI procedures: Twenty subjects with clinically definite MS (14 RR/5SP/1B; 15F/5M; median EDSS = 2.5 (range 1.0-8.0); mean age = 38yrs (range 23-54yrs); mean disease duration = 10.5yrs (range 1-35yrs)) were scanned on a GE Signa 1.5 T MR scanner. MR studies included localisers, FLAIR (TR=10s,TE=145ms), an axial single-slice 48-echo modified T_2 relaxation sequence with variable TR [8,9] (TR=2120-3800ms, 1st 32 echoes TE=10ms, last 16 echoes TE=50ms, 4 averages, matrix 256x128), an axial single-slice fast gradient echo (GE) with inversion recovery preparation (TE=8ms, 1 average, 14 TIs from 0.1-3s) for the T_1 measurement, a 3D-GE MT sequence with and without a 2000 Hz off-resonance sinc saturation pulse (TR=106ms, TE=5ms, flip 12^O), DTI with a single shot pulsed-field gradient EPI sequence (3 b-values between 0 and 1600s/mm^2 in 7 directions) and 4 averages, a proton-density and T_2-weighted scan (TR=2500ms, TE=30/90ms) and a post Gadolinium-DTPA enhanced T_1-weighted spin echo scan (TR=550ms, TE=8ms). All exams used a field of view of 22cm and slice thickness of 5mm. Water standards were placed within the slice.

Data Analysis: Lesions and contralateral normal appearing white matter (cNAWM) regions were outlined on the 1st echo of the T_2 sequence and mapped onto the registered T_1, diffusion and MT images. The T_1 relaxation data was fit to a single exponential. T_2 relaxation distributions were calculated from the 48-echo sequence using a regularised non-negative least-squares algorithm [10]. WC was defined as the total area under the T_2 distribution, MWF as area from 0-40ms and LT_2F as the area from 200-800ms, normalised to the water standards and corrected for T_1 relaxation. GMT_2 was calculated on a log scale between 40-200ms [10]. MTR was calculated by $MTR = (M_o - M_t)/M_o \times 100\%$ where M_o and M_t are images without and with the MT pulse, respectively.

Statistics: Statistical analysis was carried out using a two-tailed Student's t-test with a p value of <0.05 considered significant. All errors are expressed as standard deviations.

Results

A total of 107 lesions and 90 cNAWM areas were examined in the 20 MS subjects. These were divided into enhancing lesions, isointense T_1 lesions with and without an LT_2F and hypointense T_1 lesions with and without an LT_2F. Results for all the MR parameters are shown in the Table. cNAWM was significantly different from all lesions except for WC and MWF in enhancing lesions and MWF in isointense lesions with no LT_2F. Hypointense lesions with LT_2F were significantly different from all other regions for T_1, MTR, Dpar, Dperp and Tr.

Regions of Interest	WC (%)	MWF (%)	GMT_2 (ms)	T_1 (s)	MTR (%)	Dpar ($\mu m^2/ms$)	Dperp ($\mu m^2/ms$)	Tr ($\mu m^2/ms$)	FA
hypointense w/ LT_2F	83.2	1.8	137	1.24	18.0	1.57	1.22	4.02	0.19
N=17	(4.5)	(2.1)	(54)	(0.24)	(4.2)	(0.28)	(0.34)	(0.93)	(0.10)
hypointense	80.0	3.4	134	0.99	23.1	1.25	0.92	3.04	0.20
N=8	(2.7)	(1.6)	(15)	(0.12)	(2.5)	(0.17)	(0.19)	(0.50)	(0.10)
isointense w/ LT_2F	80.6	4.0	116	0.97	23.3	1.28	0.87	3.03	0.28
N=8	(5.1)	(2.9)	(19)	(0.16)	(4.7)	(0.37)	(0.29)	(0.87)	(0.19)
isointense	78.1	3.5	111	0.90	25.9	1.21	0.72	2.63	0.36
N=69	(4.6)	(2.4)	(18)	(0.14)	(2.6)	(0.20)	(0.19)	(0.51)	(0.15)
enhancing	75.7	3.7	132	0.99	23.3	1.26	0.81	2.88	0.29
N=5	(1.3)	(1.1)	(14)	(0.16)	(2.6)	(0.14)	(0.10)	(0.31)	(0.07)
cNAWM	73.4	5.8	90	0.78	28.1	1.03	0.55	2.07	0.43
N=90	(3.1)	(3.2)	(8)	(0.07)	(1.9)	(0.14)	(0.11)	(0.31)	(0.13)

Table: MR parameters (WC: water content, MWF: myelin water fraction, GMT_2: geometric mean T_2, T_1, MTR: magnetization transfer ratio, Δπαρ: λ_1, Dperp: $(\lambda_1+\lambda_3)/2$, Tr: diffusion trace $(\lambda_1+\lambda_2+\lambda_3)$ and FA: fractional anisotropy) for each lesion type and contralateral NAWM (cNAWM). Standard deviations are shown in parentheses.

Discussion

Lesions with an LT_2F were different from lesions without and therefore longer T_2 times may be representative of different pathology. Initial investigation of the LT_2F linked it to regions with increased water such as extracellular edema [5]. Interestingly, hypointense T_1 lesions, which are believed to be area of severe tissue destruction, did not all show an LT_2F, although the frequency of having an LT_2F was higher in hypointense than isointense lesions. Black holes with LT_2F were the most abnormal lesions compared to cNAWM for all measured MR parameters. Parameters from isointense T_1 lesions with no LT_2F were most often the least different from cNAWM. These lesions are expected to have less tissue destruction than black holes and have less extracellular edema than lesions with an LT_2F. When comparing lesions (either isointense or hypointense T_1) with and without an LT_2F, MR parameters from lesions with an LT_2F were the most different from cNAWM. MR parameters from black holes and isointense T_1 lesions with an LT_2F were similar except for T_2 and FA. Active lesions, as determined by enhancement, had values ranking close to cNAWM for some parameters (WC, MWF, Dperp, FA) and ranked close to black holes with LT_2F for other parameters (T_2, T_1, Dpar) indicating that certain parameters are more affected by early stage lesions than others.

Conclusions

Long-T_2 fraction and T_1-weighting separated lesions indicating that the LT_2F has a use in determining lesion pathology. Different parameters gave independent information about lesions.

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