Diffusion Tensor Eigenvalues Demonstrate Inherent Differences between MS Lesion Subtypes

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Introduction

Multiple sclerosis (MS) lesions which appear hypointense on T_1-weighted images may be the result of increased extracellular water from edema for the more acute hypointense lesions; whereas the chronic hypointense lesions may represent areas of more permanent tissue damage with severe axonal loss and increased extracellular water [1,2,3]. However, it is difficult to distinguish edema from tissue destruction due to the lack of pathological specificity of conventional MRI [4]. Diffusion tensor imaging (DTI) measures the kinetics of water molecules and can be influenced by the presence of both myelin and axons. It can be formulated in terms of mean diffusivity ($<D>= (\lambda_1+\lambda_2+\lambda_3)/3$) which reflects the magnitude of diffusion, fractional anisotropy ($FA = \sqrt{\frac{1}{2}}\frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2}}{\sqrt{\lambda_1^2+\lambda_2^2+\lambda_3^2}}$) thought to be dominated by axonal membranes and only modulated by myelination [5], or more specifically by the axial and radial elements of the water diffusion tensor, D_{par} (λ_1) and D_{perp} ($(\lambda_2+\lambda_3)/2$), hypothesised to reflect axon and myelin integrity, respectively [6]. The purpose of this study was to investigate differences in diffusion metrics in acute enhancing, isointense T_1 and hypointense T_1 lesions.

Methods

MRI procedures: Twenty subjects with clinically definite MS (15 RR/5SP; 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 experiments included localisers, FLAIR (TR=10s,TE=145ms), DTI with a single shot pulsed-field gradient EPI sequence (3 b-values between 0 and 1600s/mm^2 in 7 directions, 4 slices) 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.

Data Analysis: Lesions and contralateral normal appearing white matter (cNAWM) regions were outlined on the PD/T_2 images and mapped onto the non-diffusion weighted (b=0) image of the DTI data using inhouse software whereby the ROIs were moved by single pixel shifts up or down, right or left to match the ROI position on the PD/T_2 image. The diffusion tensor was calculated for each ROI and the eigenvalues λ_1, λ_2, and λ_3 (from largest to smallest, respectively) were obtained. <D>, FA, D_{par} and D_{perp} were then calculated.

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 247 lesions and 198 cNAWM areas were examined in the 20 MS subjects. There were 17 enhancing lesions, 151 isointense T_1 lesions and 79 hypointense T_1 lesions. Results for all the diffusion metrics are shown in Table 1. All 3 lesion types showed a mean increase in eigenvalues and calculated diffusion metrics that were significantly different when compared to regions of cNAWM ($p<0.005$). Hypointense T_1 lesions showed the largest increase in diffusivities followed by enhancing lesions and then isointense T_1 lesions. Enhancing lesions were significantly different from isointense (except for λ_1) and hypointense T_1 lesions (except for FA). The diffusion metrics were all significantly different between isointense and hypointense T_1 lesions ($p<0.0001$).

Table 1 - Mean (standard deviation) MR parameter for each lesions category and NAWM.

	$\lambda_1 = D_{par}$ ($\mu m^2/ms$)	λ_2 ($\mu m^2/ms$)	λ_3 ($\mu m^2/ms$)	D_{perp} ($\mu m^2/ms$)	<D> ($\mu m^2/ms$)	FA
cNAWM	1.08 (0.19)	0.69 (0.13)	0.42 (0.15)	0.55 (0.11)	0.73 (0.08)	0.44 (0.15)
Enhancing Lesions	1.30 [a] (0.20)	0.98 [a] (0.14)	0.77 [a] (0.18)	0.88 [a] (0.16)	1.02 [a] (0.16)	0.26 [a] (0.08)
Isointense	1.23 [a] (0.21)	0.86 [a] (0.19)	0.58 [a] (0.24)	0.72 [a] (0.19)	0.89 [a] (0.17)	0.36 [a] (0.15)
Hypointense Lesions	1.47 [a] (0.24)	1.20 [a] (0.28)	0.97 [a] (0.30)	1.08 [a] (0.28)	1.21 [a] (0.26)	0.22 [a] (0.09)
p-value: enh vs iso	0.18	0.01	0.002	0.002	0.003	0.01
p-value: enh vs hypo	0.009	0.002	0.01	0.005	0.004	0.08
p-value: iso vs hypo	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

[a]$p<0.0005$, n.s.=non-significant compared to cNAWM

Discussion

The finding that hypointense T_1 lesions have a lower FA and higher <D> than isointense T_1 and enhancing lesions is in agreement with previous studies [7,8]. While mean diffusivity and fractional anisotropy seem to be more sensitive to tissue abnormality than conventional imaging, they still lack specificity. To our knowledge, this is the first study to report eigenvalues for different types of MS lesions. Previous studies on eigenvalues in multiple sclerosis tissue have been limited to NAWM where results were similar to this study [9]. Our increased eigenvalues in acute enhancing lesions and hypointense T_1 lesions support the histopathological results of more extracellular water from edema in acute lesions and larger extracellular spaces and greater tissue destruction allowing freer diffusion from the more chronic lesions. Recent animal studies, which measure the eigenvalues of the diffusion tensor and relate the results to histology, suggest that radial diffusivity is related to myelination whereas axial diffusivity may be sensitive to axonal damage [6], thus the eigenvalues may be more specific to different pathology. However, interpretation of diffusion eigenvalue results is not always straightforward; two recent studies on injured rat spinal cord showed that Dpar and Dperp were not directly correlated with histopathological staining [10] and that Dperp was not correlated with myelin thickness, however was related to axonal density [11].

Conclusions

Lesions showed a mean increase in all eigenvalues when compared to regions of contralateral NAWM. The largest increase in diffusivities was observed in hypointense T_1 lesions (λ_1=36%, λ_2=74%, λ_3=131%), followed by enhancing lesions (λ_1=20%, λ_2=42%, λ_3=83%) and then isointense T_1 lesions (λ_1=14%, λ_2=25%, λ_3=38%). The changes in <D> and especially FA were driven by the larger changes in the smaller eigenvalues rather than the primary eigenvalue.

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