

# Correlation of Metabolic and Diffusivity Markers in Multiple Sclerosis using MR Spectroscopic Imaging and DTI

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## Introduction

If Multiple Sclerosis (MS) is known as a chronic disease characterized by inflammation, axonal damage, demyelination and remyelination processes, the various clinical evolutions, such as primary progressive (PP) or secondary progressive (SP) period that follows a relapsing-remitting (RR) phase of inflammation, suggest that neurogenerative processes are present in MS (1). If conventional MRI provides information on lesion load localized in white matter and reflecting the inflammatory phase of the disease, these measurements are poorly correlated with the clinical status of the patient. Therefore, molecular techniques like MR spectroscopic imaging (MRSI), magnetization transfer and diffusion tensor imaging (DTI) were developed to provide more sensitive and specific biomarkers that better characterize and evaluate the progression of the disease (2). In this work, both MRSI and DTI were used first, to characterize the alterations in white matter of MS patients with different clinical forms and second, to investigate the potential correlations between the metabolic and diffusivity changes along with the patient disability status.

## Methods

This study includes 30 patients (21 women, 9 men, age =  $40.8 \pm 7.2$  y) of different clinical forms: 10 Relapsing Remitting (RR), 10 Secondary Progressive (SP) and 10 Primary Progressive (PP) patients ( $44.3 \pm 3.8$  y) and 10 control subjects (age =  $34 \pm 13$  y). All patients were diagnosed with definite MS according to McDonald's criteria and their expanded disability status scale ratings (EDSS) measured. MR exams were performed on a 1.5 T Siemens Sonata system including a millimetric 3D MPR T1-weighted sequence. MRSI acquisition consisted in one slice placed above the corpus callosum along AC-PC axis, and selected by a PRESS sequence (TR = 1500 ms, TE = 135 ms) using a VOI of  $10 \times 10 \times 1.5$  cm<sup>3</sup> and  $24 \times 24$  phase-encoding scheme over a FOV of  $240 \times 240$  mm<sup>2</sup>. DTI protocol included a spin-echo EPI sequence (TR=3800 ms, TE=96 ms) with  $96 \times 96$  phase-encoding over a FOV of  $240 \times 240$  mm<sup>2</sup> and 51 axial slices of 2.5 mm thickness. DTI images were acquired in 24 directions with b values of 0 and 1000 s/mm<sup>2</sup>, and processed using MedINRIA software (3). Diffusion parameters such as (FA, ADC) and both axial ( $\lambda_a$ ) and radial ( $\lambda_r$ ) diffusivities (mm<sup>2</sup>) were measured from selected ROIs and their histograms were analyzed. For correlation purpose between metabolic ratios and diffusion parameters, two identical ROIs were manually selected on MRSI and DTI images in left and right semioval WM regions (Fig.1).

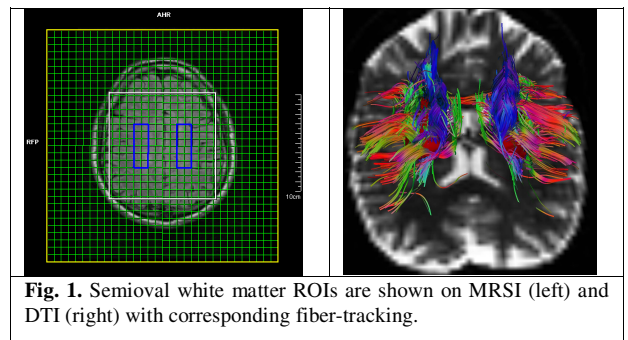


Fig. 1. Semioval white matter ROIs are shown on MRSI (left) and DTI (right) with corresponding fiber-tracking.

## Results

As reported in Table 1, a significant decrease of the NAA/Cr ratios was observed in SP and PP patients compared to controls and in PP compared to RR patients. A significant increase of the Cho/NAA ratios was shown in PP compared to RR patients and controls. From DTI measurements, FA values decreased significantly while ADC,  $\lambda_a$  and  $\lambda_r$  values increased significantly in SP and PP patients. A stronger increase of the radial component was also observed (RR: 5.9% in  $\lambda_r$  vs. 3.5% in  $\lambda_a$ ; SP: 12% in  $\lambda_r$  vs. 6.3% in  $\lambda_a$ ; PP: 12.9% in  $\lambda_r$  vs. 6.6% in  $\lambda_a$ ).

Subjects	MRSI			DTI		
	NAA/Cr	Cho/Cr	Cho/NAA	FA	$\lambda_a$	$\lambda_r$
Controls	2.13 ± 0.10	1.53 ± 0.08	0.72 ± 0.04	0.406±0.021	1.059±0.030	0.560±0.022
RR	2.01 ± 0.08	1.52 ± 0.09	0.76 ± 0.05	0.387±0.038	1.136±0.036	0.630±0.049
SP	1.82 ± 0.10#	1.44 ± 0.09	0.80 ± 0.06	0.358±0.030●	1.201±0.076#	0.712±0.084#
PP	1.78 ± 0.09#●	1.62 ± 0.10	0.92 ± 0.06●*	0.355±0.031●	1.207±0.126#	0.726±0.113#

Table 1: Values (Mean ± SD) of metabolic ratios and diffusivity parameters in semioval white matter ROIs (\*p<0.05, ●p<0.01, #p<0.001).

When correlation between metabolism and diffusivity were analyzed, the metabolic NAA/Cr ratios were significantly correlated with all diffusivity parameters such as ADC ( $R^2=0.33$ , p<0.001), FA ( $R^2=0.28$ , p<0.001),  $\lambda_a$  ( $R^2=0.35$ , p<0.001) and  $\lambda_r$  ( $R^2=0.36$ , p<0.0001), as shown in Fig. 2.

A significant correlation was found between the EDSS and the metabolic ratios of NAA/Cr ( $R^2=0.24$ , p<0.05) and Cho/NAA ( $R^2=0.23$ , p<0.05) while no correlation were found with diffusivity parameters.

## Discussion

While ADC and FA were significantly changed in SP and PP forms of MS patients as reported (4-5), the alterations in diffusivity seemed to be driven by the radial component  $\lambda_r$  of the tensor (6). This result may suggest that the increased diffusivity in radial direction to the axon axis defining the functional pathway is rather due to an increase in myelin porosity than axonal damage, at least at this stage of the disease. This mechanism might also be different in PP form where gliosis may occur earlier than in RR and SP forms. This hypothesis is further demonstrated by the increases in Cho/NAA ratios in PP form. NAA/Cr ratios decrease was correlated with axial and radial diffusivities. In contrast to diffusivity parameters, metabolic ratios (NAA/Cr and Cho/NAA) were significantly correlated with the EDSS clinical status.

## References

- 1) Compston A, et al. 4th ed. Churchill Livingstone, 2006;
- 2) Ciccarelli O, et al. J. Neurol. 2003, 250:287-292;
- 3) Toussaint N, et al. Proc. MICCAI, 2007;
- 4) Hannoun S, et al. Proc. Int. Soc. Magn. Reson. Med., 2008;
- 5) Neema M, et al. Neurotherapeutics 2007, 4:602-617;
- 6) Lowe MJ, et al. Neuroimage. 2006, 32:1127-1133.

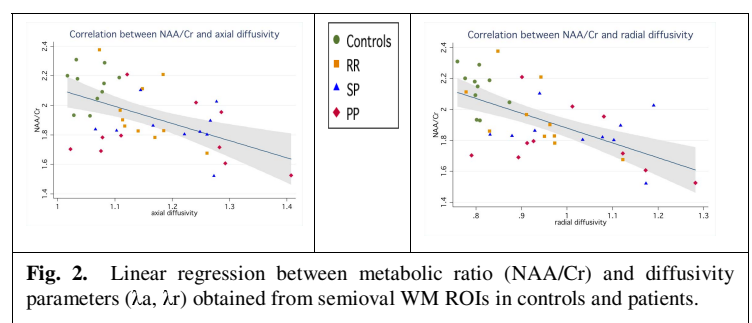


Fig. 2. Linear regression between metabolic ratio (NAA/Cr) and diffusivity parameters ( $\lambda_a$ ,  $\lambda_r$ ) obtained from semioval WM ROIs in controls and patients.