Diffusion Tensor Imaging in Multiple Sclerosis: Comparison of Radial and Axial Diffusivity Markers in Different Clinical Forms

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Introduction: Conventional magnetic resonance imaging (MRI) is important in the assessment of multiple sclerosis (MS) but it suffers from a lack of specificity and is unable to detect subtle changes in the normal-appearing white matter (1). Thus, surrogate markers of pathological processes occurring in MS such as demyelination and/or neurodegeneration are needed to evaluate the progression rate of the disease in each patient, and ultimately, to provide early diagnosis of the clinical form to adapt the therapy to each patient. Therefore, the goal of this project is to perform a longitudinal study of 100 patients being followed every six months during 3 years, by conventional MRI, diffusion tensor imaging (DTI) and spectroscopic imaging. DTI provides information about altered tissue organization through several parameters such as apparent diffusion coefficient (ADC) and fractional anisotropy (FA) which have been shown to increase for ADC and to decrease for FA in different brain regions and lesions of MS patients (2). Therefore, we investigate in this preliminary study the role of DTI in characterizing different clinical form of MS by using new diffusion coefficients such as the axial and radial diffusivities (λ_1 and λ_2) compared to FA and ADC.

Methods: This work includes 35 patients of different clinical forms: 6 Clinical Isolated Syndrome (CIS) (mean age ± SD, 39.1 ± 6.7 y), 9 Primary Progressive (PP) (41.7 ± 7.8 y), 8 Relapsing Remitting (RR) (31.7 ± 6.3) and 12 Secondary Progressive (SP) patients (41.6 ± 4.6 y) and 10 control subjects (37.0 ± 10.8). All patients were diagnosed with definite MS according to McDonald's criteria and their expended disability status scale ratings (EDSS) measured. The MRI protocol was performed on a 1.5 Tesla Siemens Sonata system and included MPR 3D T1w sagittal millimetric images with and without gadolinium injection (TR=1880ms, TE=4 ms), Turbo Spin Echo (TSE) PD- and T2-weighted axial slices of 3 mm thickness (TR=3000 ms, TE=12 ms, 85 ms) and an axial FLAIR image with 3 mm slice thickness. DTI protocol included a spin-echo EPI sequence of 128x128 phase-encoding over a FOV of 320x320 (TR=3800 ms, TE=96 ms) and 51 axial slices of 2.5 mm thickness. Diffusion weighted images were obtained in 24 directions with b values of 0 and 1000 s/mm^2. DT images were processed using MedINRIA software (http://www-sop.inria.fr/asclepios/software/MedINRIA/index.php). After co-registration of T1s images to DT images, five ROIs (Fig. 1) were manually delimited on T1s images: the genu (red), splenium (green) and center (dark blue) of the *Corpus Callosum* (CC), and the caudate (light blue) and lenticular nuclei (purple) as grey nuclei (GN). A whole brain segmentation of white (WM) and grey (GM) matter was performed using BrainVisa (http://brainvisa.info/index_f.html) to provide ROIs of WM and GM. Diffusion parameters (FA, ADC, λ_1 and λ_2) were calculated and analyzed from these ROIs.

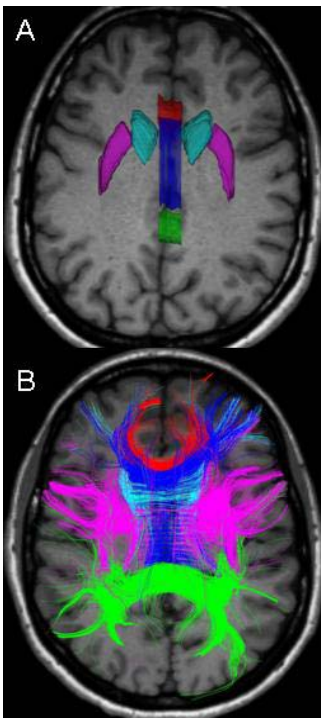

Fig. 1: ROIs delimited on the T1 in an axial view (A) and the correspondent fibers (B).

Results: As reported in Table 1, ADC values are significantly increased in PP, RR and SP patients compared to control subjects. λ_1 and λ_2 values are also significantly increased in all MS forms and in all brain regions, with the exception of λ_1, which is only increased in WM of SP patients. We observed larger changes in λ_2 than in λ_1, in RR (λ_2= 6.03% *vs.* λ_1=4.12% compared to controls) and SP (λ_2=9.59% *vs.* λ_1=5.93%) groups. ADC, λ_1 and λ_2 values are greater in WM regions (CC) when compared with GM regions (GN). In contrast FA values are only decreased in SP patients (0.326±0.028 in CC, 0.320 ±0.022 in GN, 0.282±0.018 in WM and 0.278±0.017 in GM) compared to controls (0.369±0.012 in CC, 0.346±0.016 in GN, 0.304±0.007 in WM, 0.301±0.007 in GM).

Discussion: In almost all MS patients, ADC increased and FA decreased in different brain structures and regions, being constituted either of white matter or grey matter. First, these findings are in agreement with previous studies and demonstrate that MS is characterized by alterations not only in WM (including CC) but also in GM (including GN), confirming the neurodegenerative hypothesis of the disease (1). Of course, these alterations are more significant in SP than RR or CIS patients in relation with the severity of the disease, and as previously described (3), are probably due to axonal tract damage and tissue integrity loss as seen in histopathological studies. Second, we observed that ADC, λ_1, λ_2 values were significantly different in CC and GN ROIs, but not in global WM and GM of CIS patients. These results may be of great interest first, to early differentiate CIS patients, and second, suggest that an early neurodegenerative process occurs in primary structures such as subcortical grey nuclei and *corpus collosum*. Third, we observed a more significant and larger change in λ_2 compared to λ_1 suggesting that radial diffusivity might be a better marker of myelin integrity whereas axial diffusivity is more specific to axonal degeneration (4). Therefore, the widely reported FA decrease in MS is primarily due to an increase in the diffusivity of water transverse (λ_2) to the axon defining the functional pathway (5). In conclusion, the less significance of FA values added to the greater change in λ_2 confirm the necessity of measuring more specific parameters such as λ_2 to better understand pathological processes in MS and define new MR markers that could differentiate between MS clinical forms.

Subjects	N	CC-ADC	CC-λ_1	CC-λ_2	GN-ADC	GN-λ_1	GN-λ_2
Controls	10	2.54±0.056	1.184±0.028	0.775±0.016	2.485±0.071	1.132±0.025	0.769±0.020
CIS	6	2.721±0.074■	1.247±0.031●	0.849±0.024■	2.665±0.049■	1.205±0.017■	0.844±0.016■
PP	9	2.806±0.099■	1.276±0.036■	0.878±0.037■	2.695±0.101■	1.215±0.042■	0.854±0.034■
RR	8	2.854±0.165●	1.301±0.067●	0.888±0.056●	2.693±0.092	1.209±0.039●	0.852±0.031■
SP	12	3.047±0.286■	1.355±0.094■	0.962±0.106■	2.858±0.254■	1.246±0.065■	0.903±0.061■

Subjects	N	WM-ADC	WM-λ_1	WM-λ_2	GM-ADC	GM-λ_1	GM-λ_2
Controls	10	2.506±0.077	1.099±0.027	0.737±0.105	2.519±0.048	1.101±0.021	0.799±0.013
CIS	6	2.759±0.058	1.189±0.016	0.807±0.146	2.784±0.045	1.197±0.0127	0.897±0.015
PP	9	2.841±0.131●	1.159±0.205	0.901±0.043●	2.873±0.138●	1.229±0.051●	0.926±0.048●
RR	8	2.791±0.120●	1.206±0.049	0.896±0.043*	2.830±0.129●	1.215±0.054*	0.909±0.046●
SP	12	3.003±0.312■	1.285±0.121●	0.976±0.108■	3.033±0.315■	1.284±0.131■	0.987±0.109■

Table 1: Values (mean ± SD) of ADC (mm^2/s), λ_1 (mm^2) and λ_2 (mm^2) in the *Corpus Callosum* (CC), the grey nuclei (GN) and in the segmented white matter (WM) and grey matter (GM) (*p<0.05, ●p<0.01, ■p<0.001).

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