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Diffusion Tensor Imaging as a Promising Radiological Biomarker of Disability, Disease Load, and Activity in Multiple Sclerosis

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Abstract

Background: The recent MRI brain techniques are potential biomarkers of MS lesion activity and disability. This study aimed to determine the cutoff values of Diffusion Tensor Imaging parameters correlated to the disease activity in multiple sclerosis (MS). This study included fifty MS cases and thirty age and sex-matched healthy controls were included. Axial fast spin-echo T1, T2, and 3D high-resolution T2 FLAIR images were carried out for all patients. Also delayed post-Gadolinium T1 images were obtained in MS cases for assessment of plaque activity. Diffusion Tensor Imaging (DTI) was obtained to assess the white matter tract, disease burden, and activity.

Results: MS patients reported a significant rise of the mean diffusivity and to a less significant decrease of fractional anisotropy of major white matter tracts. The analysis of DTI indices of normal-appearing white matter (NAWM) of MS group and expanded disability status scale (EDSS) score and disease load showed a significant correlation with apparent diffusion coefficient and fractional anisotropy values. The cutoff values of DTI indices that predict the disease activity in MS were fractional anisotropy ≤ 0.23, apparent diffusion coefficient ≥ 1.31, axial diffusivity ≥ 1.63, and Radial diffusivity ≥ 1.05.

Conclusions: Diffusion tensor imaging provides a powerful noninvasive tool to study complex brain tissue architecture and evaluate the severity of the disease in MS patients which is well correlated to the disease activity. Diffusion tensor imaging is a promising radiological biomarker of disability, disease load and activity in multiple sclerosis.

Keywords: MRI; multiple sclerosis; diffusion tensor imaging; tractography; white matter tracts.

Abbreviations

AD: Axial Diffusivity; ADC: Apparent Diffusion Coefficient; AF: Arcuate Fasciculus; CC: Corpus Callosum; CST: Corticospinal Tract; DTI: Diffusion Tensor Imaging; DWI: Diffusion-Weighted Imaging; DAWM: Dirty-Appearing / Diffuse Abnormal White Matter; EDSS: Expanded Disability Status Scale; ET: Echo Time; FA: Fractional Anisotropy; FACT: Fiber Assignment By Continuous Tracking; FLAIR: Fluid Attenuated Inversion Recovery; FSE: Fast Spin-Echo; IFOF: Inferior Fronto-Occipital Fasciculus; ILF: Inferior Longitudinal Fasciculus; Gd: Gadolinium; MRI: Magnetic Resonance Imaging; MD: Mean Diffusivity; MS: Multiple Sclerosis; NAWM: Normal-Appearing White Matter; NWM: Normal White Matter; RD: Radial Diffusivity; ROI: Region Of Interest; SFOF: Superior Frontal-Occipital Fasciculus; UF: Uncinate Fasciculus; WM: White Matter.

Background

Diffusion Tensor Imaging (DTI) advent has initiated a new era in the analysis of brain anatomy and connectivity as it added a powerful tool capable of reproducing white matter (WM) tract information, rather than classic imaging techniques, as conventional and / or functional MRI [1-3]. On the bases of DTI, tractography is able to reconstruct 3D trajectories of the tracts [4], and to study the anatomy of the white matter of the brain [5]. The introduction of NAWM term refers to what looks normal on conventional MRI, yet hides subtle, diffuse damage, visible with more sensitive quantitative techniques. It is of principal importance to detect microstructural damage of NAWM in MS patients, since it may contribute to the prognosis and course of the disease [6, 7]. In vivo data on brain tissue microstructure and architecture is often provided by diffusion DTI. It also offers valuable parameters associated with tissue

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damage that is not observable in T2 and FLAIR imaging, such as fractional anisotropy (FA) and mean diffusivity (MD) [8].

While gadolinium-enhancing of MS lesions is a well-established technique of evaluating disease activity, lesions representing blood-brain barrier disruption and inflammatory response are documented to develop in acutely demyelinating lesions with contrast-enhancing lesions [9], multiple quantitative MRI biomarkers can provide diagnostic data that can differentiate between MS lesions that are active or non-active. These MRI biomarkers can also get the additional advantage that the basic dichotomous characterization of the appearance of contrast enhancement does not provide insights into MS pathobiology. It is important to identify the most promising MRI biomarkers of MS lesion inflammatory activity to develop appropriate MS imaging studies by which these biomarkers can be further validated and assessed [10]. Therefore, we conducted this study to determine whether quantitative non-contrast MRI metrics would distinguish active and non-active MS brain lesions and to determine the values of quantitative DTI parameters in the evaluation of focal and diffuse WM abnormalities in MS disease and its correlation to the disease activity in multiple sclerosis.

Methods

Study design and participants

This prospective study included fifty patients (19 males and 32 females) with average age 33.6 ±9.5 years, range 17–49 years and average disease duration 6.5 ± 2.5 years) in addition to 30 age and sex-matched healthy controls (12 males and 18 females) were enrolled with average age 32 ± 10.2 years range 18–50 years). RRMS patients were diagnosed according to the revised 2010 McDonald's criteria for MS diagnosis and admitted to the neurology department in Mansoura University Hospital during the period from October 2019 to September 2020. Exclusion criteria include previous stroke, head trauma, or brain tumors, as well as other severe neurologic and/or systemic disorders. Also, old subjects > 60 years were excluded (to avoid misunderstanding with atherosclerotic white matter lesions and senile involution changes on MRI). The study was approved and accepted by the local ethics committee Institutional Research Board (IRB) and all cases provided written consent.

Diagnostic criteria

The patients underwent extensive medical and neurological assessments, including the duration of the disease and past exacerbations. McDonald's updated 2010 criteria for MS identified the diagnosis of MS. Patients were classified according to Lublin and his colleagues into relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS) [11]. Patients were clinically assessed using the Extended Disability Status Scale Score (EDSS) to measure the disabilities in patients with multiple sclerosis and monitor the progress in the degree of disability with time [12]. For all patients, magnetic resonance imaging and DTI were performed.

DTI study of patients NAWM and control NWM

Multiple bilateral seed ROIs were placed at genu, body, and splenium of CC, centrum semiovale, and periventricular white matter, anterior / posterior limbs of the internal capsule, frontal and occipital lobes as well as WM of both cerebellar hemispheres. Multiple seed ROIs were placed at the same positions in NWM of the control group. NAWM included regions that showed no abnormal signal on either T1-weighted or T2-weighted imaging. Lesions in proximity to CSF were excluded to remove the partial volume averaging effect. Symmetrical ROI positions were used in both diseased and healthy cohorts, then average FA and ADC values were calculated for comparison between average values of patients NAWM and control NWM.

Determination of brain MS disease load / burden

For full quantification of disease burden, MR volumetry was done for all cases, including both MS plaques and non-plaque (microscopic) lesions, which are manifested as patchy areas of subtle abnormal high WM signal intensities, lower than that of lesion plaques and slightly higher than that of the surrounding NAWM. These areas are mostly located at periventricular and centrum semiovale regions and are referred to as "dirty-appearing / diffuse abnormal" white matter (DAWM) [6]. Manual segmentation technique of tissues of interest was done using freehand drawing ROIs method. The application used for ROI drawing has variable drawing tools for image size scaling and brightness adjustment for viewing and ROI drawing procedures. The segmentation methods represent transforming the individual intensity scale to the standard scale to overcome the variations in the SI range of different tissues, depending on several factors including the magnetic field strength, homogeneity and data acquisition method, followed by edge detection and contouring. Segmentation was done lesion by lesion and slice by slice on T2 and FLAIR sequences on axial slices.

Lesion volume was determined twice, once for each sequence on time intervals separated by at least one week. Neuroradiological examination on MR images performed by senior neuroradiologist confirmed visible focal MS lesions, then segmentations are saved, visualized in 2D images, total surface area (SA) of the lesions was calculated. The volume is determined (by multiplying total SA x 6 representing slice thickness and inter-slice gaps). The average end results were calculated.

Assessment of individual WM tracts affection

Reconstruction of specific WM tracts was performed by using multiple ROIs approach (as discussed before). All major WM tracts were included in both cerebral hemispheres (CST, CC, AF, SFOF, IFOF, ILF, and UF). Specific DTI indices of each individual tract were calculated and assigned for statistical analyses.

Assessment of focal plaque activity

For each MS patient, conventional MRI including T1 post-Gd images was examined slice by slice in the whole brain, for characterization of plaque age and pattern of enhancement to identify active and inactive lesions. Active plaques show ho-

mogeneous or peripheral contrast enhancement with possible associated mild perifocal edema, whereas inactive plaques show iso-signal on T1WIs, with no significant enhancement. Chronic plaques showing a marked low signal on T1WI; representing black holes were excluded from the study. 20 active plaques and 20 inactive plaques were recruited in the study from 15 RRMS patients (11 female and 4 male). B0, DWI, ADC, FA and FA color maps were generated. Seed ROI was placed over each plaque, average DTI indices (FA, ADC, RD and AD) were calculated for statistical analyses and differentiation between active and inactive plaques on bases of DTI qualitative metrics were assessed.

Statistical analysis

Statistical analysis was performed for the collected data by utilizing SPSS program (Statistical Package for Social Sciences) for Windows V 18. For comparing the patients and control groups t-test was used for comparison of quantitative data. Pearson correlation was used to assess the relationship between DTI indices of NAWM of MS group and EDSS score, also to assess the relationship between DTI indices of NAWM of MS group and disease load. To determine the cutoff values for DTI indices that were associated with high sensitivity and specificity for disease activity in MS patients a receiver operating characteristic (ROC) curve was performed. P-value of 0.05 is considered significant.

Table 1: *Demographic and clinical data of MS patients and controls.*

	MS patients	**C**ontrols	**P value**
	(N = 50)	**(N = 30)**	
Age (Y)			
Mean ± SD	33.6 ± 9.5	32 ± 10.2	0.79
Min-Max	17 - 49	18 - 50	
Sex			
Male	19 (38%)	12 (40%)	0.85
Female	31 (62%)	18 (60%)	
MS subtypes			
RRMS	35 (70%)	N.A.	N.A.
SPMS	13 (26%)		
PPMS	2 (4%)		
Disease duration (Y)			
Mean ± SD	6.5 ± 2.5	N.A.	N.A.
Min-Max	(1-15)		
EDSS			
Mean ± SD	3.5 ± 2.5	N.A.	N.A.
Min-Max	3 (0-8)		
Relapse number			
	4 (1-15)	N.A.	N.A.

Relapsing Remitting; PP: Primary Progressive; SP: Secondary Progressive; RR: NA: not applicable; EDSS: Extended Disability Status Scale score

Results

This study included 50 patients (19 males and 31 females) with mean age 33.6 ±9.5 years, and mean disease duration 6.5 ± 2.5 years and 30 age and sex-matched healthy controls (12 males and 18 females) with mean age 32 ± 10.2 years (**Table 1**).

DTI study of NAWM and individual WM tracts

For the study of NAWM and individual WM tracts, DTI quantitative metrics (FA and ADC) were used to characterize intrinsic damage of each individual main white matter tract, and analysis the topographic damage in MS patients (**Figure 1**). Also, **figure 2** demonstrated a significant reduction of FA and an increase in ADC values of the CC (representing NAWM) noted in the suspected MS cases as compared to the controls (**Figure 2**). The mean values of FA and ADC of NAWM in MS patients were 0.44 ± 0.031 and 0.90 ± 0.042 (× 10−3 mm2/s) and in control group were 0.52 ± 0.047 & 0.79 ± 0.048 (× 10−3 mm2/s) (p = 0.003 in ADC and p=0.012 in FA). The comparison between DTI indices of each individual tract in MS patients and control group detected a variable extent of diffuse MD and FA changes among all included major WM tracts, with CC showing highest intrinsic damage followed by CF, SFO and AF then IFO and CST (**Table 2**).

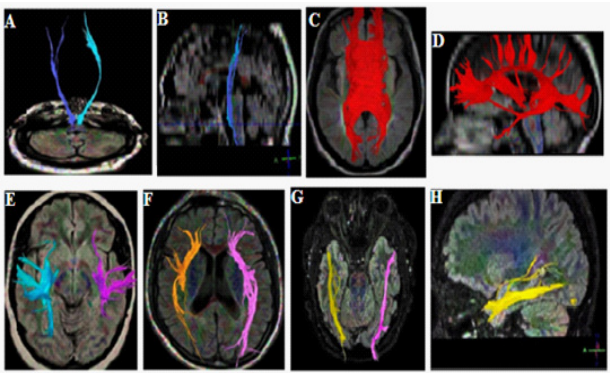

Figure 1: *Diffuse WM tracts atrophy in MS patient.*

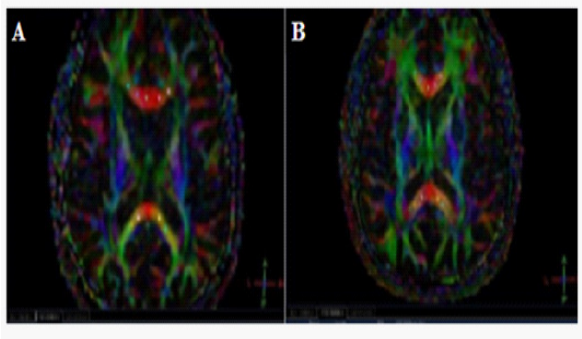

Figure 2: *34 years old female patient has recurrent attacks of upper and lower limb weakness, gait disturbance and decreased visual acuity over 2 months duration diagnosed as clinically isolated syndrome suggestive of MS. Multiple seed ROI at genu and splenium of the CC of A) suspected MS case and B) age matched control subject with computing of DTI metrics for comparison. (Patient average CC FA was 0.582, ADC 1.256 × 10-3 mm2/s and control average CC FA was 0.710 and ADC 0.827 × 10-3 mm2/s). Significant reduction of FA and increase in ADC values of the CC (representing NAWM) noted in suspected MS case as compared to the control subject.*

47 years old female patient with long history of MS and high disease load showing: (A-H) Diffusion tensor representation of the major white matter tracts (CST, CC, Arcuate, IFO, ILF respectively) reveal diffuse atrophy of the WM tracts with decreased fiber density.

Table 2: *Comparison of DTI indices individual major WM tracts between MS patients & healthy control group.*

Average Tract	Fractional anisotropy (FA)			Axial diffusivity (ADC)		
	MS patients N = 50	Control N = 30	P	MS patients N = 50	Control N = 30	P
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Total	0.44 ± 0.031	0.52 ± 0.047	0.012*	0.90 ± 0.042	0.79 ± 0.048	0.003*
CC	0.55 ± 0.031	0.6 ± 0.029	<0.001*	0.87 ± 0.075	0.92 ± 0.034	<0.001*
CST	0.51 ± 0.035	0.54 ± 0.022	0.009*	0.82 ± 0.052	0.94 ± 0.043	0.005*
Cingulate	0.38 ± 0.039	0.42 ± 0.024	0.001*	0.83 ± 0.038	0.9 ± 0.028	0.003*
SFOF	0.36 ± 0.044	0.41 ± 0.026	0.001*	0.93 ± 0.036	0.82 ±0.027	0.001*
Arcuate	0.39 ± 0.031	0.42 ± 0.032	0.009*	0.82 ± 0.037	0.79 ± 0.019	0.001*
IFOF	0.42 ± 0.035	0.44 ± 0.033	0.037*	0.90 ± 0.055	0.85 ± 0.019	0.002*
UF	0.39 ± 0.038	0.44 ± 0.034	0.001*	0.92 ± 0.045	0.88 ± 0.041	0.002*
Uncinate	0.38 ± 0.04	0.39 ± 0.035	0.3	0.91 ± 0.063	0.87 ± 0.032	0.46

CC: Corpus callosum
CST: Corticospinal tract
IFOF: Inferior fronto-occipital fasciculus
SFOF: Superior frontal-occipital fasciculus
UF: Uncinate fasciculus

Table 3: *Correlation between FA & ADC of NAWM in MS patients with EDSS and disease load.*

	EDSS	Disease Load
NAWM FA	r = 0.36 p = 0.023*	r = 0.362 P = 0.042*
NAWM ADC	r = 0.589 p < 0.001*	r = 0.489 p = 0.03*

**P value significant < 0.05*
r: Pearson correlation coefficient
ADC: Apparent diffusion co-efficient
FA: Fractional anisotropy
NAWM: Normal-appearing white matter

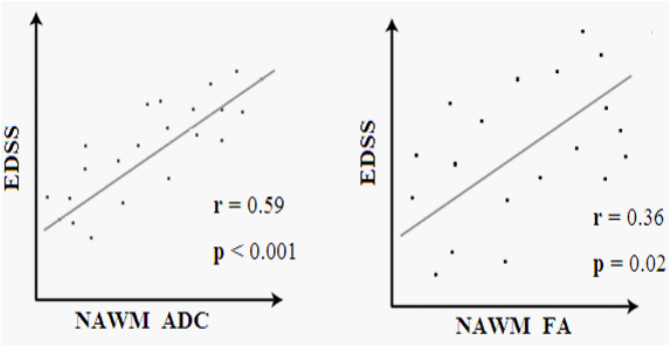

Figure 3(a): *Correlation between FA & ADC of NAWM in MS patients and EDSS.*

Correlation between DTI indices of NAWM with EDSS and disease load (**Table 3**) The correlation between DTI indices of NAWM of MS group and EDSS score detected significant correlation with ADC values (r = 0.59 and p < 0.001), and a moderate correlation was found with FA values (r = 0.36 and P=0.02) (Figure 3 a). On correlation between DTI indices of NAWM of MS group and disease load, modest yet significant correlation was found with ADC values (r = 0.49 and p = 0.03) and FA values (r = 0.36 and p = 0.04) (**Figure 3 b**). (**Figure 4**) showed a 3-D representation of the disease load and the utility of DTI for qualitative and quantitative assessment of the effect of chronic high MS disease load on WM tracts.

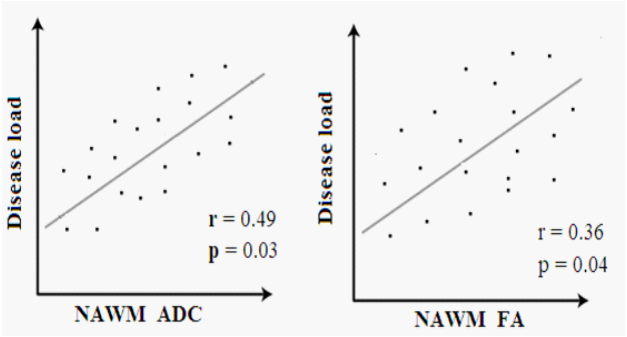

Figure 3(b): *Correlation between FA & ADC of NAWM in MS patients and disease load.*

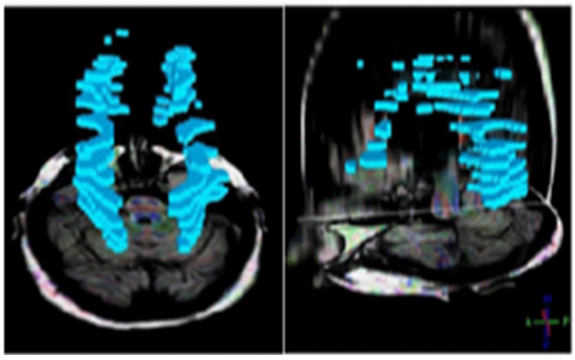

Figure 4: *MS disease load on WM tracts.*

3D representation showed the disease load (plaques and DAWM). This case reveals the utility of DTI for qualitative and quantitative assessment the effect of chronic high MS disease load on WM tracts.

DTI study of MS plaques activity

The comparison between DTI indices of inactive and active plaques, were significantly different in all DTI indices (P value <0.05) (**Table 4**).

Table 4: *DTI indices values in active versus inactive plaque.*

	Inactive plaques N = 32	Active plaques N = 18	Significance
FA Mean ± SD Min-Max	0.29 ± 0.016 (0.22 – 0.34)	0.33 ± 0.036 (0.23 – 0.38)	**P < 0.05***
ADC Mean ± SD Min-Max	1.57 ± 0.08 (1.40 – 1.68)	1.05 ± 0.12 (0.83 – 1.23)	**P < 0.01***
AD Mean ± SD Min-Max	1.96 ± 0.07 (1.82 – 2.10)	1.33 ±0.07 (1.19 – 1.44)	**P < 0.01***
RD Mean ± SD Min-Max	1.35 ± 0.12 (1.09 – 1.50)	0.86 ± 0.07 (0.69 – 1.02)	**P < 0.01***

FA: Fractional anisotropy
ADC: Apparent diffusion co-efficient
AD: Axial diffusivity
RD: Radial diffusivity

(**Table 5**) showed the cutoff values of DTI indices that predict the disease activity in MS with the following values: FA ≤ 0.23, ADC ≥ 1.31, AD ≥ 1.63 and RD ≥ 1.05 with the highest sensitivity, specificity and accuracy. These results suggest the relevance of DTI utility as an additional quantitative parameter for the assessment of plaque activity (**Figure 5**).

Table 5: *Validity & cutoff values of DTI indices in active Vs inactive plaque.*

	Cut off	Sensitivity	Specificity	Accuracy
FA	≤ 0.23	92	94	97.5
ADC	≥ 1.31	95	92	96
AD	≥ 1.63	91	91	95
RD	≥ 1.05	94	90	91

FA: Fractional anisotropy
ADC: Apparent diffusion co-efficient
AD: Axial diffusivity
RD: Radial diffusivity

Conclusions

DTI study of NAWM

NAWM alterations are mostly attributed to axonal WD, microglial activation, or both entities together as reported in pathological studies. The increased MD in NAWM results from the net loss of structural barriers by both demyelination and axonal damage, while reduced FA is due to alteration of the nerve bundle's structural organization [13]. This proves that DTI by its quantitative measurements (FA and MD), permits the evaluation of extensive occult tissue injury that exists beyond the apparent focal MS plaques determined on conventional MRI and thus has important clinical potential which can contribute to disability in MS patients [14].

Kolasinski and his colleagues also found that the degree of MD changes in NAWM is more widespread than that of FA. This can be explained by the fact that MD is predominantly affected by free space and therefore its rise with vasogenic edema, myelin loss and axonal destruction whereas FA is more prone for detection of the neuronal axons and WM fibers integrity

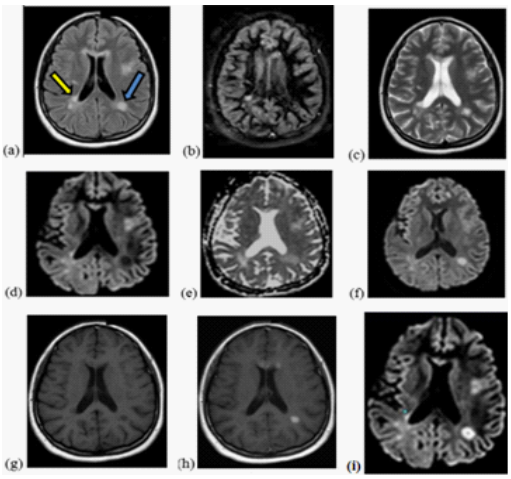

Figure 5: *Active MS plaques versus inactive plaques in 29 years old female patient with history of RRMS shows neurological signs of disease activity (a), (b) & (c) axial FLAIR, DIR & T2 images reveal presence of one sizable oval plaque (blue arrow) at the left deep periventricular parietal-occipital WM, and another smaller plaque (yellow arrow) at right deep periventricular parietal WM. (d) (e) & (f) axial FA map, DWI and ADC map reveal markedly reduced FA and restricted diffusion within the 1st plaque denoting active nature, while 2nd plaque shows no FA changes or diffusion restriction denoting non active nature. (g) & (h) axial pre and post-contrast T1 WIs reveal diffuse enhancement of the first plaque with no significant enhancement of the second plaque confirming the activity of first plaque and lack of activity in second plaque. (i) Quantitative assessment: axial 3D FLAIR with seed ROI placed at both plaques, 1st shows the following DTI metrics (FA= 0.418, ADC= 0.973 × 10-3 mm2/s, AD= 1.461, RD= 1.779) and 2nd plaque (FA= 0.047, ADC= 1.822 × 10-3 mm2/s, AD= 1.907, RD= 0.729).*

[15]. Also in this study, a significant correlation was detected between MD and FA changes and EDSS clinical score, with the highest correlation seen with MD values. Ciccarelli and his colleagues observed strong correlations between EDSS clinical score and FA in both the supratentorial and infratentorial NAWM in cases with RRMS [16]. Also, Elshafey et al., found a significant correlation between DTI indices and total EDSS and Kurtzke functional system score [17]. Another study of the relation between DTI in NAWM and EDSS scores revealed a tendency toward a correlation between EDSS and ADC, yet non-statistically significant [18].

As regarding the disease load, our study showed an important association between increased MD & decreased FA on one side with the global brain lesion load on the other side. Also, Ciccarelli and his colleagues found a significant correlation between disease burdens with DTI changes when the entire CC was included in the analysis. These powerful correlations indicate that the underlying pathological processes in the brain are universal and interconnected [16].

DTI study of individual WM tracts

The analyses of our findings revealed diffuse MD and FA changes among all included major WM tracts, suggesting disrupted integrity of large-scale brain connectivity, however to a variable extent, with CC showing highest intrinsic damage as expected being the largest fiber tract in the brain. These findings support the importance of assessing damage to clinically eloquent WM tracts by using DTI to obtain a more complete picture of disease-related injury in patients with MS [19]. Preziosa and his colleagues reported pronounced damage in nearly all tracts in the form of advanced FA alteration of the tracts in SPMS [20]. Another study on a pediatric MS group also revealed higher mean ADC values in all tracts and

lower means FA than those in healthy controls [21]. Shu et al. concluded that both global and local network efficiencies were expressively diminished in the MS patients compared to controls. They also found a significant correlation between the degree of lost connectivity with EDSS, disease durations, and total WM lesion load [22].

Oztruk et al. revealed significant DTI changes in the CC paralleling ours and added that spatial analysis localized the most abnormal segments to the body and isthmus, with relative sparing of the rostrum and genu [23]. Also using segmented CC diffusivity measures, Rimkus and his colleagues study have revealed increased MD and AD in the posterior mid-body and splenium. They also found a strong correlation of these indices with EDSS scores [24]. On the other hand, Yu and his colleagues study revealed lower FA values in RRMS participants compared to controls across the tract skeleton with increased MD which was dominated by increased RD with no significant change in AD [25]. Inal and his colleagues study, using the ROI method also found significantly lower ADC values of the CST in MS patients than in the control group and proposed that to be the result of cellular infiltration due to inflammation, cytotoxic edema, demyelination, or remyelination processes [26].

DTI study of focal plaque activity

Our statistical analyses revealed high significant differences of all DTI indices between active and inactive plaques. The cutoff values of focal plaque activity were FA ≤ 0.23, ADC ≥ 1.31, AD ≥ 1.63 and RD ≥ 1.05, with the highest sensitivity, specificity and accuracy. Rueda Lopes and his colleagues study revealed synchronous results to our study, on comparing acute enhancing plaques with chronic non-enhancing ones, with a significant statistical difference of mean DTI measures between both types [27].

Testaverde et al. found that inactive plaques reveal higher changes in DTI parameters than active ones when compared to DTI indices of control NWM which go with our results; however, they also show no statistically significant differences between active and inactive plaques indices, regarding FA and ADC values, which is controversial to our study. This debate can be explained by different technical aspects and heterogeneity of MS group clinical phenotypes between both studies [28]. Regarding MD, Senda et al. stated that the highest ADC values were found in T1 hypo-intensity chronic non-enhancing lesions, as they represent areas of irreversible tissue disruption, gliosis, and axonal loss [29].

Limitations of this study

The major limitations of this study were the small size sample because it was carried out in one center only and the correlation of radiological findings was not assessed in different subtypes of multiple sclerosis. Also, the study did not correlate the results with different treatment modalities.

Conclusions

We have revealed the potential role of DTI in the diagnosis of MS, its sensitivity in detecting occult damage of NAWM non-evident on conventional MRI. DTI provides a powerful non-invasive tool to study complex brain tissue architecture and evaluate the severity of the disease in MS patients which is well correlated to the disease activity. Diffusion tensor imaging is a promising radiological biomarker of disability, disease load and activity in multiple sclerosis.

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