Evaluation of multiple sclerosis patients through structural biomarkers of diffusion tensor magnetic imaging and correlation with clinical features

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ABSTRACT

Introduction: Diffusion tensor imaging (DTI) is an imaging technique with quantity measuring capability which enables to overcome limitations of conventional magnetic resonance imaging (MRI) and provides beneficial information concerning microscopic structures. This study aims to evaluate pathological changes in the brain tissue of multiple sclerosis (MS) patients using mean diffusivity (MD) and fractional anisotropy (FA) values in DTI technique.

Methods: A total of 45 patients with a definite diagnosis of MS with attacks relapse and 20 healthy individuals were underwent both conventional MRI and DTI. In order to evaluate progression of the neural damages in these patients, expanded disability status scale (EDSS) was recorded. The location of MS plaques and normal appearing white matter (NAWM) was determined by MRI and brain sequences were studied axial T_2W, axial T2W-FLAIR, sagittal T_2W-FLAIR and coronal T_2W.

Results: The mean of the variable MD from MS plaques (Mean=4.3±1.01) compared to of the variable MD from NWM (mean=2.1±1.1) has significant difference (P=0.00001). Moreover, mean of the FA plaques (Mean=0.24±0.05) showed significant (P=0.00001) compared to NWM (Mean=0.55±0.56). In addition, mean of FA from the NAWM of the patients (Mean=0.42±0.11) was significantly different from NWM (P=0.00001). MD values of NAWM of the patients demonstrated significant association with EDSS of the patients (P=0.004).

Conclusion: The important point in conventional MRI is that high density lesions which demand long echo time only offer an inconsiderable sign of the disease. As a result, in completing evaluation of the damages to tissue surrounding the plaques it is suggested that advanced imaging techniques such as DTI are carried out as a routine procedure in MS patients.

KEY WORDS: Diffusion tensor magnetic resonance imaging, Multiple sclerosis, Cellular Imaging, Imaging biomarker, Neuroimaging.

1. INTRODUCTION

Multiple sclerosis (MS) is a chronic disease related to the central nervous system (CNS) in which myelin membrane is destroyed and axonal damages occur. Moreover, symptoms may disappear completely between the attacks; however, permanent neurological problems often occur (Yurtsever, 2008). The multifocal lesions in the brain and the spinal cord manifest along with relapsed inflammation and gliosis (Milo and Miller, 2014). The main cause of MS is not completely known, however, evidence implies to sudden immune system attacks due to T cells sensitivity to myelin oligodendrocyte glycoproteins (MOG) (Yurtsever, 2008). The disease usually begins between the ages of 20 and 50 and is twice as common in women as in men and its prevalence is more dominant in whites comparing to other races (Milo and Miller, 2014). The common symptoms of MS are consisting of visual problems, sensory disturbances, fatigue, depression, weakness, physical, balance and perceptual deficits (Milo and Miller, 2014). According to its duration and severity, 4 types of the disease are noted.

Type 1: Relapsing-remitting multiple sclerosis (RRMS) which assigned majority of the patients. They experience the MS attacks following remissions; however, the disease does not progress in course of time. Type 2: Primary progressive multiple sclerosis (PPMS) which consists a small percentage of the patients. They show slow progression in the disease without the attacks or remissions. Type 3: Secondary progressive multiple sclerosis (SPMS) with rapid progression in the disease and it is probable that patients experience the attacks with or without recovery or remission; and the type 4: Relapsing progressive multiple sclerosis (RPMS) in which the disease deteriorates progressively in a constant way. The patients suffer from the attacks or relapse (Caramia, 2002).

In order to evaluate progression of the neural damages in these patients, expanded disability status scale (EDSS) has been employed (Yurtsever, 2008). Better diagnosis of the disease demands findings of another tests such as magnetic resonance imaging (MRI) and functional evaluations (Milo and Miller, 2014). MS lesions with T_2-

weights and proton density manifest brightly during the acute phase due to inflammation existence in conventional MRI and in T_1 images with injection, the lesions are seen as signal increase. Chronic lesions also manifest as dark density in T_1 images (Neema, 2007). Normal shape of the lesions is oval perpendicular to the walls of lateral ventricles (Dawson's fingers) (Filippi, 2006). For a better observation of periventricular lesions and connections of the cerebral white matter (WM) and grey matter (GM), T_2 sequence along with fluid attenuated inversion recovery (FLAIR) is applied (Table 1). However, this sequence would be beneficial in evaluating lesions under the cerebral tentorium which located between the encephalon in the top and the cerebellum in the bottom and it is not much applicable in evaluating under the tentorium lesions (Neema, 2007). Since the conventional MRI has shortcomings in determining specificity of the disease type and also quantitative measurement of tissue damages to normal appearing brain tissue (NABT), in a less amount normal appearing white matter (NAWM) and normal appearing gray matter (NAGM), nowadays, advanced MRI techniques have developed and among them the magnetic resonance spectroscopy (MRS), diffusion weighted imaging (DWI) and its advanced type, diffusion tensor imaging (DTI) can be stated (Loevblad, 2010). This imaging is sensitive to those pathologic changes which disrupt integration and permeability of the barriers that limit water molecules movements (Bakshi, 2005). DTI is a modern and nonaggressive technique that does not require any contrast material and gets the information only by measuring water molecules movements in a predetermined direction (Onu, 2012). DTI technique which acts according to Brownian movements of the water molecules, a collection of diffusion gradients applies in several directions so that related tensor equations can be calculated (Onu, 2012). Apparent diffusion coefficient (ADC) in DWI, mean diffusivity (MD) (mm^2/s) and fractional anisotropy (FA) in DTI function as imaging biomarkers toward determination of the relation of these changes with clinical disabilities of MS patients (Onu, 2012). MD is equivalent to that ADC numerical value in DWI which was averaged in DTI and its quantity in biologic tissues ranges between 2 to 6. FA illustrates tissue integrity and extent of tissue alignment in neuronal nerves and the diffusion direction in every voxel and its value ranges between 0 and 1; so that the number 0 explains an isotropic environment, spherical diffusion without having a predominant direction and the number 1 explains an anisotropic environment (Onu, 2012). In anisotropic diffusion, diffusion of water molecules occurs in one or several dominant axis. As a result, it is impossible to describe this diffusion process only with one measurement. As this kind of diffusion represents useful information around anatomic structures of living tissues (such as axonal fibers in neuronal tissues and protein filaments in the muscles), anisotropic diffusion is mentioned of great importance (Onu, 2012). On the other hand, the more uniformity in diffusion along the nerve fibers leads to more closeness to the number 0 and it appears darker in the FA map (Onu, 2012). Moreover, giving information about the involved anticipations around NABT pathological changes through DTI technique to neurologists (as a complementary test), plays a valuable role in choosing treatment patterns for MS patients (Roosendaal, 2009). In 2012, Testaverde, evaluated MD and FA in the brain of MS patients and reported significant differences in white matter (WM) of normal appearing brain tissues (NABT) from the patients compared to healthy groups in which FA parameter was shown to be more sensitive than MD parameter. Ibrahim (2011), studied FA and MD parameters from corpus callosum (CC) of MS patients by DTI and reported significant decrease in FA and significant increase in MD values. These researchers repeated the study after physical therapy and physiotherapy and found that FA and MD values markedly increased and decreased, respectively; (Ibrahim, 2011), Liu (2012), examined a correlation between the data resulting from DTI and anticipation of acute platelet presence in normal appearing WM and reported that MD elevation in the fifth month before lesion manifestation in T1 images with injection can predict acute platelet manifestation in these areas. In 2012, Senda, conducted a study on GM and WM of MS patients employing DTI technique and demonstrated that extended MD changes in NAWM are in a direct correlation with period and severity of the disease as well as EDSS of the patients. As a result, MD parameter has a higher diagnostic value compared to the other parameters. Regarding the studies around DTI in MS diagnosis to provide the possibility to evaluate its relation with EDSS values in the patients, and exploring their sensitivity and characteristics in distinct geographical regions, it seems that the patient's symptoms' manifestation in different regions is different depending on race and living area. On the other hand, according to the existing reports, MS prevalence in Iran has shown a significant growth; as a consequence, the aim of the present study was to evaluate pathological changes in the brain tissue from MS patients using FA and MD values in DTI technique.

Table.1. Summary of main pulse sequences in the conventional and advanced MRI techniques and applications for evaluation and detection of brain changes in MS patients.

	Sequences	Applications
Conventional MRI techniques	Proton density (PD) weighted imaging or fast spin echo T2-weighted.	The better detection of white matter lesion and changes in posterior fossa with PD-weighted Imaging
	Noncontrast T1-weighted imaging	Demonstration of white matter lesion hypointensity associated with axonal loss in more chronic plaques

	Contrast-enhanced T1-weighted imaging	White matter lesion enhancement suggesting breakdown of blood-brain barrier and acute inflammation
	FLAIR, axial and sagittal planes	Suppression of cerebrospinal fluid (CSF) with improved detection of periventricular white matter lesions
Advanced MR techniques	Magnetization transfer imaging	Detection of damage to macromolecules, including myelin
	Diffusion tensor imaging	Detection of damage to highly organized white matter tracts
	Diffusion tensor tractography	Detection of damage to specific functional units in the brain
	MR proton spectroscopy	Detection of metabolite changers in both acute and chronic white matter lesions as well as in surrounding gray and white matter
	Functional MR imaging	Detection of alterations in cortical activation suggesting brain plasticity
	MR perfusion imaging	Detections of focal as well as global alterations in cerebral blood flow and volume

2. METHOD AND MATERIALS

Patients and Ethics: In this study, a total of 45 patients with a definite diagnosis of MS who were referred to neurologists due to relapse of their attacks, were referred to MRI Center of Chamran Hospital and underwent DTI scan and routine brain imaging. In the present evaluation, from the total 45 patients, 33 (73.3%) were women and 12 were men (26.7%) with an age average of 36.2±6.3. Also, the median disease duration in patients was 14.7 (1.8-27.6) years. On the whole, 39 patients suffered from relapsing-remitting multiple sclerosis (RRMS) and 6 from secondary progressive multiple sclerosis (SPMS) (Table 2). Moreover, 20 volunteer healthy individuals with an age average of 32.9±4.9 were also included in this study. The EDSS of the patients which were determined according to neurological tests and functional system, recorded by a neurologist and ranked for statistical analysis. Necessity of performing this study in acquiring the resulting data for precise diagnosis of involving areas and quality of treatment design were described completely to the patients. In addition, a written informed consent was taken from the patient and respecting to their privacy of personal information emphasized. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation national and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

Table.2. Demographic and clinical characteristics of MS patients with specific location lesions using DTI. EDSS of the patients ranged from 3 to 7

Total number		45
Age (mean±SD)		36.2 ± 6.3
Sex (Female/male)		33 (73.3%)/12 (26.7%)
Visual problems		19 (42.22%)
Numbness of face		7 (15.55%)
Side of the lesion	Bilateral	16 (35.55%)
	Left	9 (20%)
	Right	20 (44.44%)
Location of the lesions (%)	CC† (Body)	11 (24.44%)
	CC (Genu)	5 (11.12%)
	CC (Splenium)	2 (4.44%)
	Supratentorial WM‡	9 (20%)
	Infratentorial WM	3 (6.66%)
	Corona radiate	5 (11.12%)
	Internal capsule	7 (15.56%)
	Frontal region	3 (6.66%)
EDSS$^+$ (Female/male)		4.3/2.1
Lesion count (SD) (Female/male)		3.8 (0.9)/ 3.5 (0.7)
Disease type (%) (RRMS$^\#$/SPMS*)		39 (86.66%)/6 (13.34%)

Imaging Parameters: In order to evaluate the location of MS plaques and NAWM, a tissue with abnormal manifestations without density change in conventional MRI, imaging was carried out with routine brain sequences such as axial with the sequences T_2W and T2W-FLAIR, sagittal with the sequence T_2W-FLAIR and coronal with the sequence T_2. Moreover, in order to performed software processing for normalizing DTI images, 3-dimensional imaging T_1 MPRage was also performed. For the imaging, 1.5 tesla (T) MRI scanner (Avanto, Siemens Co.,

Germany) with 8-channel head coil was employed. T1-weighed sequences with magnetization transfer (MT) before and after intravenous administration of gadolinium (repetition time (TR) = 635 ms, echo time (TE) = 9.4 ms, field of view (FOV) = 240 mm, matrix=256×256 mm and 5-mm section thickness with 35% of interval). T_2W-FLAIR images with TR=9950 ms, TE=100 ms, FOV=220 mm, matrix=256×256 mm and 5-mm thickness section with 35% of interval) were prepared. In addition, T_2W images with TR=4410 ms, TE=98 ms, FOV=240 mm, matrix=320×320 and 3-mm section thickness with 30% of interval and T_1 MPRage images with TR=2300ms and TE=4.71ms with 176 slices of 1 mm thickness were prepared. For evaluating FA and MD values, DTI sequence employed a gradient pulse in six different directions, with two b factor (b-value), 0 and 1000, TR=1200ms, TE=90ms, matrix of 128×128 mm, FOV of 230 mm, with 68 slices of 5-mm section thickness and 1.5 mm interval were prepared. The used sequence was single-shot spin-echo planar imaging (SE-EPI) and diffusion gradients were applied in 6 directions which had been acquired with the related processing.

Images analysis: After getting the desired data and images, a primary processing was needed for the final evaluation and analysis. In the first step, in order to correct artifacts related to eddy current distortions, FSL software was employed (Figure 1). Following corrections of DTI data, the data was normalized according to the standard patterns using SPM software (Version 8).
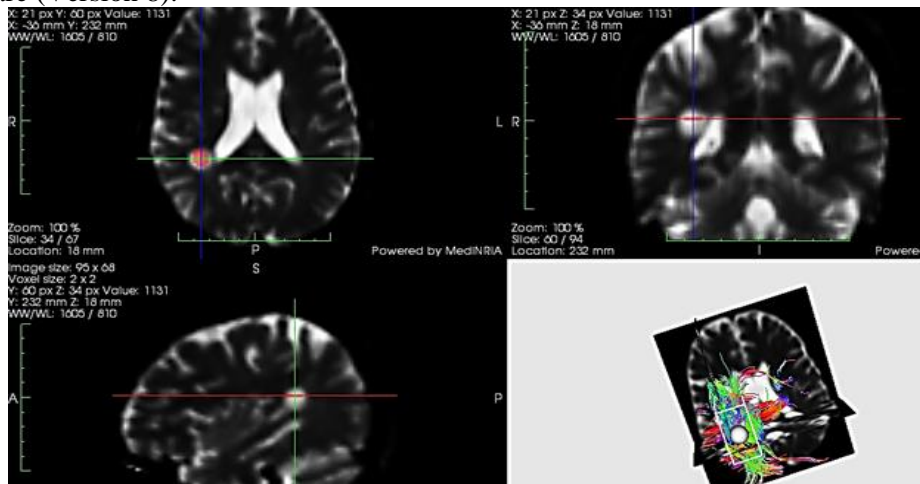

Figure.1. DTI image of a 41-year old male patient with a 12-years history of the disease. The EDSS grading equals to 7; the intersection of the lines in the image illustrates MS plaques in the surrounding area of the posterior horn of lateral ventricle from the right brain hemisphere.

After normalizing the DTI data, final processing and analyzing were performed to find FA and MD values in MS plaques and NAWM in the specific regions include the carpus callosum (CC) parts (body, genu, and splenium), Supratentorial WM (centrum semiovale), Infratentorial WM, corona radiate (radial crest), Internal capsule, and Frontal region (Figure 2) and NWM using MedINRIA software (Table 3). FA and MD values corresponding to the MS plaques location in the related cortex were acquired in NWM. Since, the lowest MD value was higher than the highest value in the healthy individuals and also the highest FA value of the patients was lower than the lowest value in the healthy individuals; the data from NWM was averaged and employed in comparison and statistical evaluation between the patients and the normal group. By collecting data from FLAIR images, T2 WI, DWI and T1 with contrast images using high contrast resolution images, slice by slice for the whole brain for each patient, the lesion contour, size, intensity, extensions and pattern of enhancement were recorded to identify active, inactive lesions and NAWM. Lesion load is quantified by comparing conventional spin-echo scans especially FALIR images consecutively in a random order and then side-by-side by two expert and unaware radiologists, lesions on each sequence were counted and marked. Only hyperintense areas which were considered lesions by both the raters with high confidence were counted as lesions. Lesions of area <15 mm^2 or in proximity to CSF were excluded to eliminate partial volume artifact and exclude nonspecific lesions.
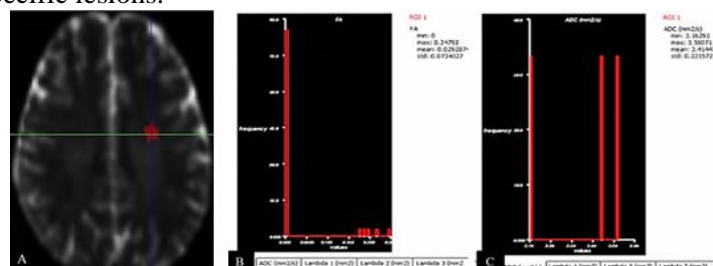

Figure.2. ROI tracing in NAWM. (A) Frontal lobe WM in the affected hemisphere of the patient. (B) FA value analysis and (C) MD value in MS plaques recorded by MedINRIA software

The processing of Fiber-Tracking Method Anisotropy at each voxel was calculated and color maps were created. A two dimensional visualization approach was used to identify specific WM tracts. In this approach, image brightness represents fractional anisotropy with a red–green–blue color scheme indicating tract orientation (red revealing fibers with lateral orientation, green, anterior-posterior; and blue, craniocaudal). The procedure for mapping neural connection started through multiple fibers tracking of 3 arbitrary ROIs. We determined ROIs on axial slices of the color vector map for all patients where the corticospinal tract (CST) measures, including cerebral peduncle (CP), posterior limb of the internal capsule (IC), centrum semiovale and motor cortex which not shows in images. DTI metrics of FA, MD, were measured in each ROI after superimposing each subject's own CST tractography mask on their DTI maps. Values were then compared between MS patients and controls. All fibers were identified on axial, sagittal and coronal slices of directional color-coded maps. FT in which 3D pathways of white matter tracts are reconstructed from continuous trajectories, this method delimits major tracts of WM in vivo: after the selection of one, or more than one, seed region of interest (ROI) nervous pathways are reconstructed by tracking along the principal direction of the fibers passing through the ROI (Mori and Van Zijl, 2002) This technique can be used to analyze the displacement of fibers as well as to detect Wallerian degeneration (Pagani, 2007) (Figure 3).

Table.3. The averaged values of MD and FA resulting from MS plaques and NAWM in specific location in MS patients and the control group.

Regions of brain	FA$^+$			MD* (mm^2/s)		
	Control	Patients		Control	Patients	
		Plaque	NAWM$^\#$		Plaque	NAWM
CC† (Body)	0.54	0.36	0.4	0.37	0.48	0.42
CC (Genu)	0.78	0.6	0.59	0.34	0.45	0.39
CC (Splenium)	0.71	0.53	0.56	0.42	0.54	0.47
Supratentorial WM‡	0.81	0.64	0.72	0.3	0.49	0.36
Infratentorial WM	0.59	0.37	0.45	0.27	0.4	0.33
Corona radiate	0.83	0.61	0.68	0.37	0.51	0.43
Internal capsule	0.52	0.34	0.39	0.32	0.42	0.36
Frontal region	0.76	0.58	0.62	0.4	0.51	0.46

Statistical Analysis: Statistical analysis was carried out using SPSS (Version 20) and $P < 0.05$ considered as significant difference. At first, normality of the variables was evaluated according to Shapiro–Wilk test. Analysis of variance (ANOVA) tests and Tukey's test were used to determine the significance between groups. In order to present descriptive statistic from averaged descriptive statistics, mean and standard deviation (SD) were employed. Also, to illustrate the data, histogram graph was used. Since, statistical analysis does not suffice normalizing the variables and such tests do not possess enough power to completely evaluate normalization, P value graph was used as well. Due to lack of normality in all the variables, a non-parametric test, Mann-Whitney, was performed. Correlations between MD and FA, and lesion loads and disability scores were made by using the Spearman rank correlation test. P value < 0.001 was considered significant.
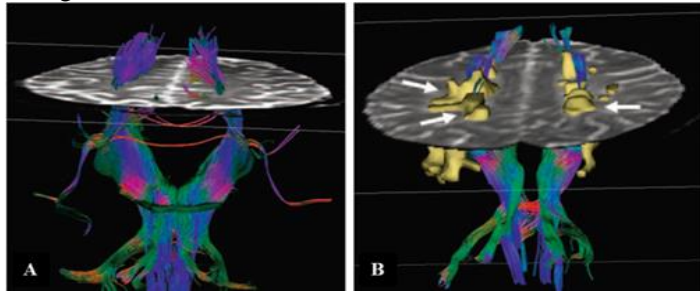

Figure.3. Diffusion tensor tractography in a healthy volunteer control (A) and a patient with MS (B). images shows reduced number of fibers and fiber tract disruption caused by the transection of lesions.

3. RESULTS

The Mann-Whitney test demonstrated that mean of the variable MD from MS plaques (Mean=4.3±1.01) compared to of the variable MD from NWM (mean=2.1±1.1) has significant difference (P=0.00001). Moreover, mean of the FA plaques (Mean=0.24±0.05) showed significance (P=0.00001) compared to NWM (Mean=0.55±0.56). In addition, mean of FA from the NAWM of the patients (Mean=0.42±0.11) was significantly different from NWM (P=0.00001). Furthermore, mean of MD in NAWM of the patients (Mean=3.25±0.93) showed significant difference compared to NWM of healthy individuals (P=0.00001). Regarding the graphs related to mean comparison of FA and MD values between healthy and patient groups, MD values in NAWM of the patients were higher than NWM of the healthy individuals, however; they showed lower values than MS plaques of the patients. The FA values also were lower in NAWM of the patients compared to NWM of the healthy individuals, nevertheless;

they were higher than the FA values of MS plaques from the patients. On the other hand, MD values of NAWM of the patients demonstrated significant association with EDSS of the patients (P=0.004). Also, FA value in NAWM of the patients showed significant association with EDSS of the patients (P=0.001). Conversely, data analysis of EDSS and MS plaques with NAWM proved no significant difference between MD and FA values (Figures 4, 5 and 6).
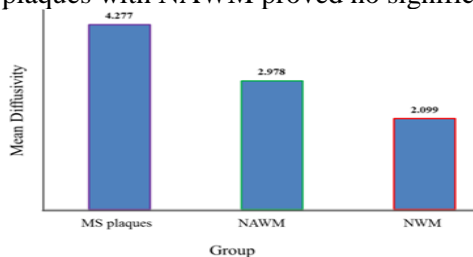

Figure.4. Comparing MD mean in the healthy and patient individuals. MD values in NAWM of the patients were higher than NAWM of healthy individuals, nevertheless; they were lower than MD values in MS plaques. P=0.00001 was considered as a significant difference.
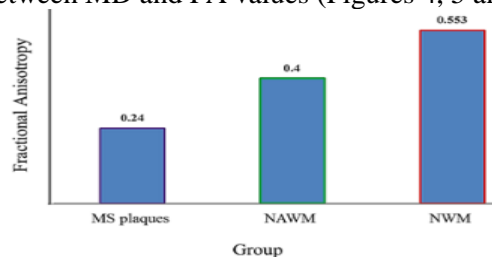
Figure.5. Comparing FA mean in the healthy and patient individuals. FA values in NAWM of the patients were lower than NAWM of healthy individualls (P=0.00001), nevertheless; they were higher than FA values in MS plaques (P=0.00001).
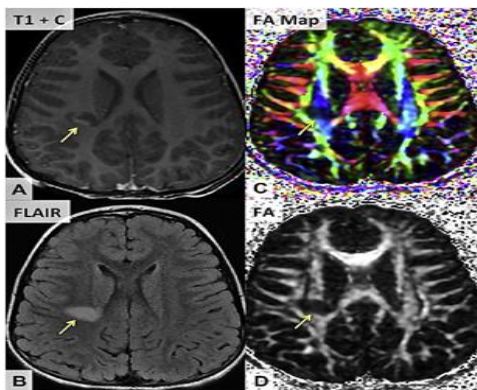

Figure.6. MR imaging shows increases in MD and reductions in FA associated with focal white matter lesions, as well as, to a lesser degree, the NAWM of patients with MS. Also, an enhancing focal white matter lesion in the right centrum semiovale on both enhanced T1-weighted and FLAIR-weighted imaging (arrows in A and B). On diffusion tensor imaging, the lesion shows a reduction in FA (arrows in C and D).

DISCUSSION

As mentioned earlier, MS disease is an autoimmune disorder which manifests with several symptoms such as inflammatory lesions, edema, myelin destruction, axonal damages, gliosis or a combination of these indications (Sijens, 2006). DTI is an imaging technique with quantity measuring capability which enables it to overcome the mentioned limitations of conventional MRI and provides beneficial information around microscopic structures (Yoshida, 2013). The first quantitative feature is ADC in DWI averaged and explains diffusion magnitude (Onu, 2012). The second feature is FA which explains the rate of unidirectional diffusion and the third is diffusion tensor tractography (DTT) which shows the main diffusion direction and has applied in nerve fibers tracing. This tool traces structure's direction in under studied environments and demands complex analyzing software (Onu, 2012). Therefore, DTI imaging technique presents little information about size and orientation of water molecules in a three dimensional space which can represent functional and microstructural disorders of the body tissues. Several studies demonstrated abnormal FA and MD changes in the MS plaques and NAWM by tracing the region of interest (ROI) (Ibrahim, 2011). In this regard, Bakshi, (2005) reported that ADC values resulting from MS lesions show enhanced diffusion rate and increased MD in the plaques in the present investigation is in accordance with Bakshi's study, however; MS plaques in our study were not separated according to their acute and chronic state and further study will be needed. In addition, Schmierer (2007), reported that FA and MD values resulting from analyzing DTI images which presents myelin content, axonal count and gliosis severity, are profoundly different between WM and NAWM lesions. In the present study, also, changes in WM lesions were higher than NAWM lesions. Evaluating WM disorders and their association with perceptual and motor disabilities, bring about helpful information around pathologic mechanisms of MS patients which can be employed in treatment of the disease (Yoshida, 2013). Using DTI technique, Yu (2008), reported that in RRMS, MD increased in NABT, NAWM and NAGM compared to its normal values especially in RRMS and FA decreased equally which is consistent in the present investigation.

Conversely, these researchers did not acquire significant results between DTI and EDSS of the patients (Yu, 2008); nevertheless, in our study, significant results concerning DTI values were obtained. The discrepancy may be due to different statistical software in DTI analyzing. Rovira and Leon (2008), stated that cutting neural fibers in WM and permeability of axonal membranes can cause enhanced ADC and MD values resulting from DTI and DWI techniques and usually increase MD and decrease FA in MS plaques in comparison to the present data in NAWM, however; there was no significant association among MD and FA values, MS type and EDSS of the patients. In the present study, enhanced MD and reduced FA values in the plaques were compared with the values in NAWM and the result demonstrated that there is a significant association between MD and FA values in NAWM and EDSS of the patients which indicates spread and attack of the lesions to the WM around the patients' plaques. Hu (2011), evaluated quantitative changes in MD and FA values in the neural fibers of RRMS using DTI images analysis and reported that MD values in the plaques lesions are higher than NAWM and also amount of this variable in NAWM is higher than NWM. Moreover, these researchers stated that FA value in the plaques lesions is lower than its amount in NAWM and FA value in NWM is higher than NAWM (Hu, 2011), which are consistent with the results of our study. Onu (2012), investigated the lesions in both NAWM and NAGM from MS patients using DTI and reported that FA and MD values compared to normal group were high and low, respectively, which may explain lesions spread to NAWM and NAGM and had a direct association with motor disabilities and the disease period of patients. Also, in the present study, the results were similar and showed spread of the lesions to the tissue surrounding the patient's plaques and there was a direct association between these lesions and the patients' disabilities. The spread of lesions to the WM consists of astrogliosis, microglial activity, and disruption of blood - brain barrier result in entering of the pro-inflammatory T cells and monocytes to parenchyma which occurs via interactions between adhesion molecules found on the surface of lymphocytes and endothelial cells) and decrease in myelin density. Regarding prevalence of the MS lesions around the brain ventricles and the corpus callosum, examination of these regions employing DTI to identify the presence of the lesions in neural fibers seems necessary (Tavazzi, 2007; Tournier,2011; Ahmadi, 2014). Another advantages of DTI in MS patients, is illustration of the resulting data difference according to the MS type, such that in SPMS significant changes in FA and MD values can be observed compared to RRMS. Therefore, DTI may provide information about tissue microstructure and architecture including size, shape, and organization and in turn constitutes a proved and effective quantitative method for evaluating tissue integrity at a microscopic molecular level. As a consequence, DTI studies are of great importance in evaluating long term and quantitative pathologic evaluations (Onu, 2012). Unfortunately, only few imaging centers have DTI facility and due to center's problems and also load of work on the imaging systems, this technique has limited profoundly. Nowadays, researchers study on MS, searching parameters in MRI which can be beneficial in precise diagnosis of extent and severity of the lesions and clinical-imaging association as well as owing sensitivity and high repeatability.

In order to be considered as an outcome measure in clinical trials, DTI parameters must be sensitive to change over time and must be highly reproducible and the sample size of the studied cohort must be appropriate to ensure the reliability of the results. The sample size needs to be planned on the basis of the statistical methods to be adopted, of the precision of the information required, and of the number of hypotheses to be tested, and in such a way as to take in account any missing values or drop-out patients.

4. CONCLUSION

The result demonstrated that FA and MD factors of DTI as imaging biomarkers can give valuable information about condition of MS patients at cellular levels. The important point in conventional MRI is that high density lesions which demand long echo time only offer an inconsiderable sign of the disease presence. As a result, in completing evaluation of the damages to the brain tissue surrounding the plaques it is suggested that advanced imaging techniques such as DTI are carried out as a routine procedure in MS patients.

5. ACKNOWLEDGMENT

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