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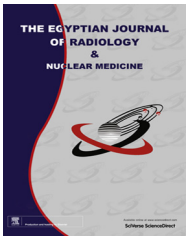

ORIGINAL ARTICLE

Diffusion tensor imaging for characterizing white matter changes in multiple sclerosis

Rasha Elshafey [a,c,*], **Omar Hassanien** [a,c], **Mohamed Khalil** [b,c]

[a] *Radiodiagnosis Department, Tanta University Hospital, Egypt*
[b] *Neuropsychiatry Department, Tanta University Hospital, Egypt*
[c] *Faculty of Medicine, Tanta University, Elgharbia, Egypt*

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KEYWORDS

Diffusion tensor imaging;
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Abstract *Purpose:* To investigate the diagnostic values of quantitative diffusion tensor imaging parameters in detecting abnormalities in white matter of MS patients and correlate this with lesion load and clinical disability as prognostic factors.
Patients and methods: Diffusion tensor imaging (DTI) was performed in 45 consecutive MS patients and 20 age-matched healthy control volunteers from March 2011 to November 2013. Mean diffusivity (MD), volume ratio (VR) and the fractional anisotropy (FA) were measured in normal appearing white matter (NAWM) and in different types of focal MS lesions during both activity and remission and compared with normal white matter (NWM) of the control group. Evaluation of lesion load was done by the semiautomated method. Clinical assessment of MS was established using the Kurtzke expanded disability status scale (EDSS) and the Kurtzke functional system score.
Results: Significant increase of MD and decrease of FA and VR from normal appearing white matter of the patients to MRI detected active lesions and the least is inactive plaques comparing with NWM of the control group (*P* value 0.003 for MD, 0.013 for FA, and 0.014 for VR). Correlation and significant difference between {(increase in MD) and (decrease in FA and VR)} and lesion load (strongest in parietal lobes) and also Kurtzke expanded disability status scale (EDSS) and Kurtzke functional system score (KFS-p).

Abbreviations: EPI, echo-planar imaging; MD, mean diffusivity; VR, volume ratio; FR, fractional anisotropy; MRI, magnetic resonance imaging; MS, multiple sclerosis; NAWM, normal appearing white matter; NWM, normal white matter; EDSS, Kurtzke expanded disability status scale; KFS-p, Kurtzke functional system score

* Corresponding author at: Radiodiagnosis Department, Tanta University Hospital, Mehala, Gharbia, Egypt. Tel.: +20 40 2211164, mobile: +20 01008806711.
E-mail addresses: drrashaelshafey@yahoo.co.uk (R. Elshafey), omr.hasanian@med.tanta.edu.eg (O. Hassanien), khalilneuro@gmail.com (M. Khalil).

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Conclusion: DTI–MRI quantitative parameters are good predictors of tissue damage not only in MRI-defined lesions but also in NAWM as a result of Wallerian degeneration and are helpful as diagnostic and prognostic tools.

1. Introduction

Multiple sclerosis (MS) is one of the common chronic demyelinating diseases of the white matter. It is considered the most common cause of non-traumatic disability in young and middle-aged adults. According to statistics, more than 400,000 persons in the United States and 2 million people worldwide are affected. MS is characterized by relapsing remitting (RR) clinical course in approximately 85% of patients with episodic onset of symptoms followed by residual deficits or by a full recovery especially in the early stage of the disease (1). The exact etiology and underlying mechanism of evolution of the disease are still not fully understood, however several experimental evidences support the auto-immune pathogenesis (2). Magnetic resonance imaging (MRI) is an important tool, not only in the diagnosis of multiple sclerosis (MS) but also for its follow up regarding the activity of the disease and responses to therapeutic trials (3).

Conventional MR images of patients with MS show multiple focal abnormalities especially on T2 and FLAIR sequences, which correspond to the histopathological changes in the white matter (WM) lesions, however it is less sensitive to the associated diffuse damage in normal appearing white matter (NAWM) and gray matter (NAGM) (4). Also the limitations of the expanded disability status scale (EDSS) and Kurtzke functional system score (KFS-p), which is heavily weighted toward ambulatory dysfunction (5,6).

On the other hand, diffusion tensor imaging (DTI) provides in vivo information about brain tissue microstructure and architecture. It also provides quantitative parameters like fractional anisotropy (FA) and mean diffusivity (MD), correlated with tissue damage that is not detectable in T2 and FLAIR imaging (7–10).

The aim of this work is to study the diagnostic values of quantitative diffusion tensor imaging parameters (MD, FA and VR) in detecting abnormalities in focal lesions of MS with evaluation of underlying pathology of NAWM in comparison with NWM of the control group as prognostic factors.

2. Materials and methods

The study was approved by the Research Ethics Committee (REC) of our hospital and a written informed consent was obtained from all subjects prior to study entry.

From March 2011 to November 2013, forty five consecutive MS patients referred to the Department of radiodiagnosis from Neuropsychiatry Department prospectively participated in this study, (18 male and 27 female) with an age range of 27–59 years, a mean age of 41.3 ± 7.2 years, the median disease duration was 11 years (range: 4–31). Twenty age-matched healthy volunteers were included as control subjects with an age range of 26–49 years and a mean age of 39.8 ± 5.6 years (6 male and 14 female). The neurological impairments were evaluated in accordance to Kurtzke expanded disability status scale (EDSS) and Kurtzke functional system score as a more specific estimate of motor impairment (5,6).

Exclusion criteria were history of stroke, brain trauma or tumours, other major neurologic and/or systemic diseases, or age older than 60 years (to avoid confounding with atherosclerotic changes and age related involutional changes on MR images).

Twenty eight patients had been given interferon beta (23 patients on interferon beta-1b and 5 on interferon beta-1a), 17 patients had been given oral corticosteroids (10 mg per day).

All individuals of the study were subjected to: full history taking, thorough clinical and neurological examinations and routine laboratory investigations in the form of: CBC, liver and kidney function tests, fasting and 2 h postprandial blood glucose, ESR, LDH, CRP, CSF analysis (26 patients) with a 2 year follow up for all patients.

2.1. Image acquisition and postprocessing

Images were acquired by using a 1.5-T General Electric scanner (GE Medical Systems, Milwaukee) with a neurovascular coil.

Sedation was needed for 10 patients (for uncooperative patients and abnormal movements).

All patients were examined in the supine position using a neurovascular coil with the head maintained in a neutral position. Routine axial spin echo T2-weighted images (repetition time [TR] 2000 ms, echo time [TE] 20/100 ms; matrix size 256 × 256; field of view [FOV] 240 mm; slices thickness 5 mm), FLAIR (TR 8000 ms, TE 50/158 ms; matrix size 256 × 256; FOV 240 mm; slice thickness 5 mm, inversion time, 2200 ms). Axial T1-weighted MR images (TR = 600 ms, TE = 10 ms, axial slices 5 mm) were acquired pre- and postadministration of 0.1 mmol/kg Gd-DTPA for all patients.

Diffusion weighted images (DWI) in 25 directions to obtain diffusion tensor images (DTI) using pulsed gradient, echo-planar imaging (repetition time [TR]/echo time [TE], 12,000/78; matrix, 128 × 128; field of view, 240 × 240 mm; slices 4 mm; *b* values, 0, 1000 s/mm^2.

Data were processed at workstation (Sun workstation (Sun Microsystems, Mountain View, CA using 4.6 ready view software package).

By collecting data from FLAIR images, T2 WI, Diffusion WI 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. The diffusion tensor quantitative parameters, fractional anisotropy (FA), volume ratio (VR) and mean diffusivity (MD), were calculated for active, inactive plaques (if present), corpus callosum and NAWM (infratentorial, supra-

tentorial and internal capsule) and compared with the results obtained from the matched control group.

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 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 $<20\,mm^2$ or in proximity to CSF were excluded to eliminate partial volume artifact and exclude nonspecific lesions. The lesion load was assessed quantitatively by estimating the total volume of the white matter lesions using a semiautomated local thresholding technique by tracing their outlines manually, and the software was preset not to exceed the outlines of the region of interest by assigning the MR numbers of the tissues subject of study, a quantification process was run which rendered the volume of the structure in focus, using a 3D Slicer version 4.2.2-1 software which is a multiplatform, free and open source software package for visualization and medical image computing developed by the Harvard university and approved for medical research (http://www.slicer.org/).

Imaging data were reviewed by two radiologists (with more than five years of experience) blinded to the patients clinical pictures; and then they nearly reached a consensus opinion.

2.2. Statistical analysis

Statistical presentation and analysis of the present study were conducted, using the mean and standard deviation by SPSS V.16. Analysis of variance [ANOVA] tests and Tukey's test were used to determine the significance between 2 groups: According to the computer program SPSS for Windows. ANOVA test was used for comparison among different times in the same group in quantitative data. P value <0.05 was considered significant.

Correlations were made among MD, FA, and VR and lesion loads and disability scores by using the Spearman rank correlation test.

3. Results

The present study includes forty five MS patients and twenty matched (age and sex) control volunteers.

The clinical course was categorized as 23 cases of relapsing–remitting multiple sclerosis (RRMS) and 12 cases of secondary progressive, 7 primary progressive and 3 progressive relapsing multiple sclerosis, According to the United States National Multiple Sclerosis Society (11). 18 patients had active plaques and 27 patients had inactive plaques.

Mean Quantitative DTI parameters assessment of NAWM and plaques in specific locations in MS patients and control group was shown in Table 1.

All patients in the study showed significant increase of the MD while decrease of FA and VR of normal appearing white matter and plaques compared with normal white matter of the controls (P value 0.003 for MD, 0.013 for FA, and 0.014 for VR). Inactive plaques showed more changes in DTI parameters than active ones. However no statistical difference was seen among active and inactive groups (P value 0.07). (Figs. 1–3).

Table 1 Mean quantitative DTI assessment of NAWM and plaques in specific location in MS patients and the control group.

Specific regions	FA (control)	FA (patient)			MD×10^{-3}mm^2/s (control)	MD (×10^{-3} mm^2/s) (patient)			VR (control)	VR (patient)		
		Plaque		NAWM		Plaque		NAWM		Plaque		NAWM
		A	I			A	I			A	I	
CC (body)	0.65	0.6	0.38	0.63	0.34	0.46	0.49	0.39	0.35	0.19	0.16	0.24
CC (genu)	0.74	0.69	0.47	0.7	0.31	0.41	0.44	0.36	0.352	0.23	0.21	0.27
CC (splenium)	0.72	0.63	0.43	0.67	0.36	0.48	0.52	0.41	0.38	0.19	0.14	0.29
Internal capsule	0.69	0.55	0.47	0.65	0.29	0.35	0.39	0.32	0.361	0.27	0.19	0.3
Supratentorial WM	0.45	0.32	0.29	0.39	0.279	0.402	0.42	0.35	0.31	0.23	0.19	0.26
Infratentorial WM	0.53	0.35	0.3	0.41	0.281	0.38	0.403	0.33	0.3	0.22	0.17	0.28

NB: We use a personal calculator for conversion of numbers with base **e** into their equivalent numbers with base **10**.
A = active plaques, I = inactive plaques.

By comparing statistical significance of DTI parameters in corpus callosal regions, MS patients showed lower FA and VR with higher MD in each callosal region compared with NWM, however statistical significance was detected only in the splenium (*P* value 0.024) (Table 2).

By analysis of DTI parameters in NAWM, increased MD was more widely detected in the periventricular region, especially in the frontal and occipital lobes more than changes in FA and VR (Figs. 2 and 3).

Infratentorial region (especially in the occipital lobes) showed significant decreased FA especially in the white matter adjacent to the ventricles (*P* value 0.031) (Table 3).

There were correlations and significant difference between increase in MD and decrease in FA and VR and lesion load. The strongest correlations were found between FA, VR and MD and LLs in the parietal lobes (*P* value 0.04 for MD, 0.036 for FA, and 0.041 for VR.).

Our statistic showed more significance of MD in the detection of widespread MS lesions and subsequently the LL than done by FA and VR, reflecting more extension of the axonal and peri-axonal pathology.

Correlation and significant difference between (increase in MD) and (decrease in FA and VR) and EDSS AND Kurtzke functional system score (KFS-p), strongest values in Kurtzke functional system score (KFS-p) (*P* value 0.046 for MD, 0.03 for FA, and 0.048 for VR.). This correlation was of benefit in treatment trials and assessment of quality of life and as prognostic values.

4. Discussion

Multiple sclerosis (MS) is an immune-mediated, inflammatory demyelinating disease of the central nervous system. It is characterized histopathologically by demyelination, axonal injury, inflammation, gliosis and remyelination (12–13).

For many years, conventional MRI (including T2-weighted, FLAIR, pre- and post-contrast T1-weighted scans) plays an important role in early diagnosis of MS and monitoring its response to current treatments and upcoming experimental agents (14).

According to Janardhan et al. (15) conventional MRI shows multiple focal abnormalities in MS, which correspond to histopathologic lesions in the white matter.

On T2-weighted and FLAIR images, lesions appear hyperintense compared with the background, whereas on T1-weighted images (T1 WI), the MS lesions are often isointense to the normal white matter but can be hypointense if chronic tissue injury or severe inflammatory edema occurs. After IV

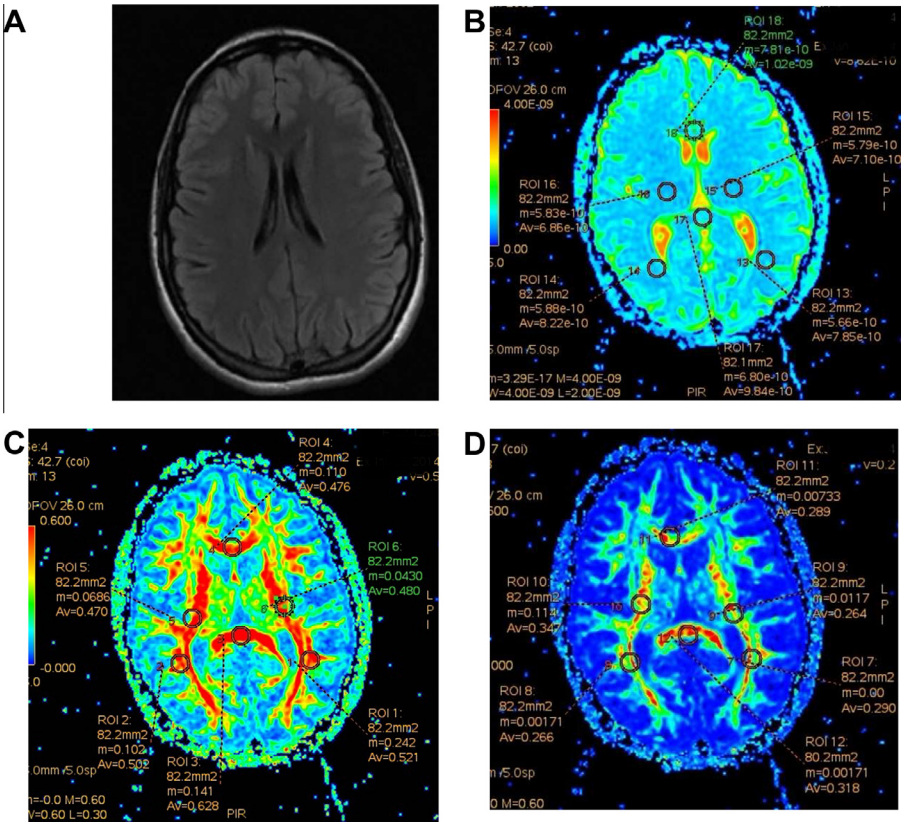

Fig. 1 DTI of a healthy volunteer. The calculated parameter maps of diffusion tensor imaging (MD, FA and VR) reflecting normal values in Multiple ROI at corpus callosum, supratentorial normal white matter, posterior limb of internal capsule. In MD map the image contrast is defined by the different diffusivity of CSF and brain parenchyma. FA and VR maps reveal proper delineation of white matter tracts with a great variation throughout the brain due to differences in fiber direction and density with proper myelin sheath of axons. Highest anisotropy is seen in the genu and splenium of the corpus callosum. The contrast between regions of low and high anisotropy is stronger in VR map than FA. (A) Axial FLAIR image. (B–D) DTI directionally encoded color (B: MD, C: FA, D: VR) map (ROIs are placed in genu, splenium of corpus callosum and NWM.

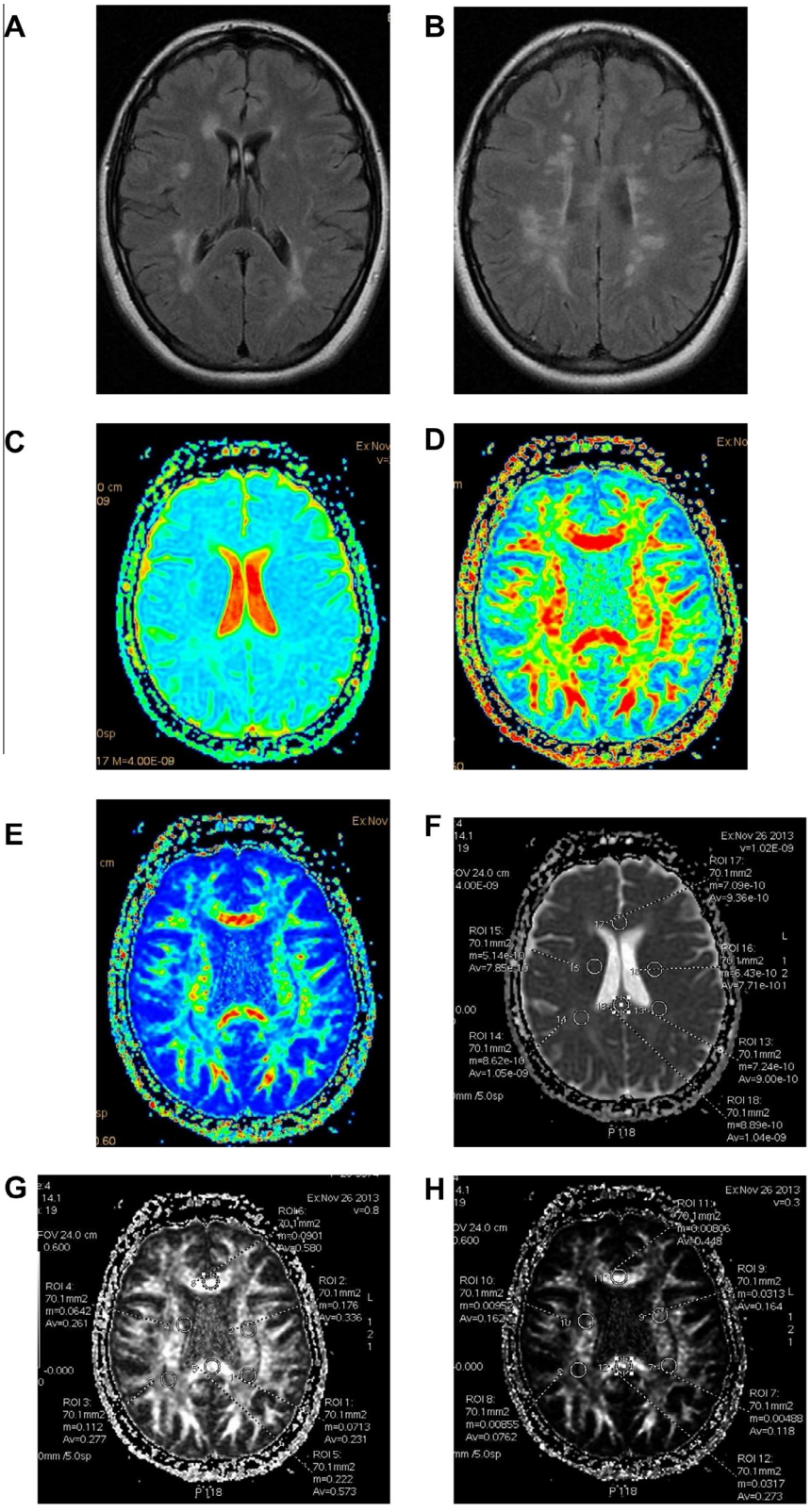

Fig. 2 Female patient aged 29 years with RRMS (4 years duration). Multiple hyperintense MS plaques are seen in FLAIR images in centrum semiovale, and anterior limb of internal capsule. MD map reveals multiple areas of increased diffusivity. FA and VR maps showing areas of decreased anisotropy which are much larger than the lesion's appearance on FLAIR images. (A and B) Axial FALIR images. (C–E) DTI directionally encoded color (B: MD, C: FA, D: VR) map. (F–H) DTI directionally encoded (E: MD, F: FA, G: VR) map (ROIs are placed in the genu and splenium of corpus callosum, MS plaques and NAWM).

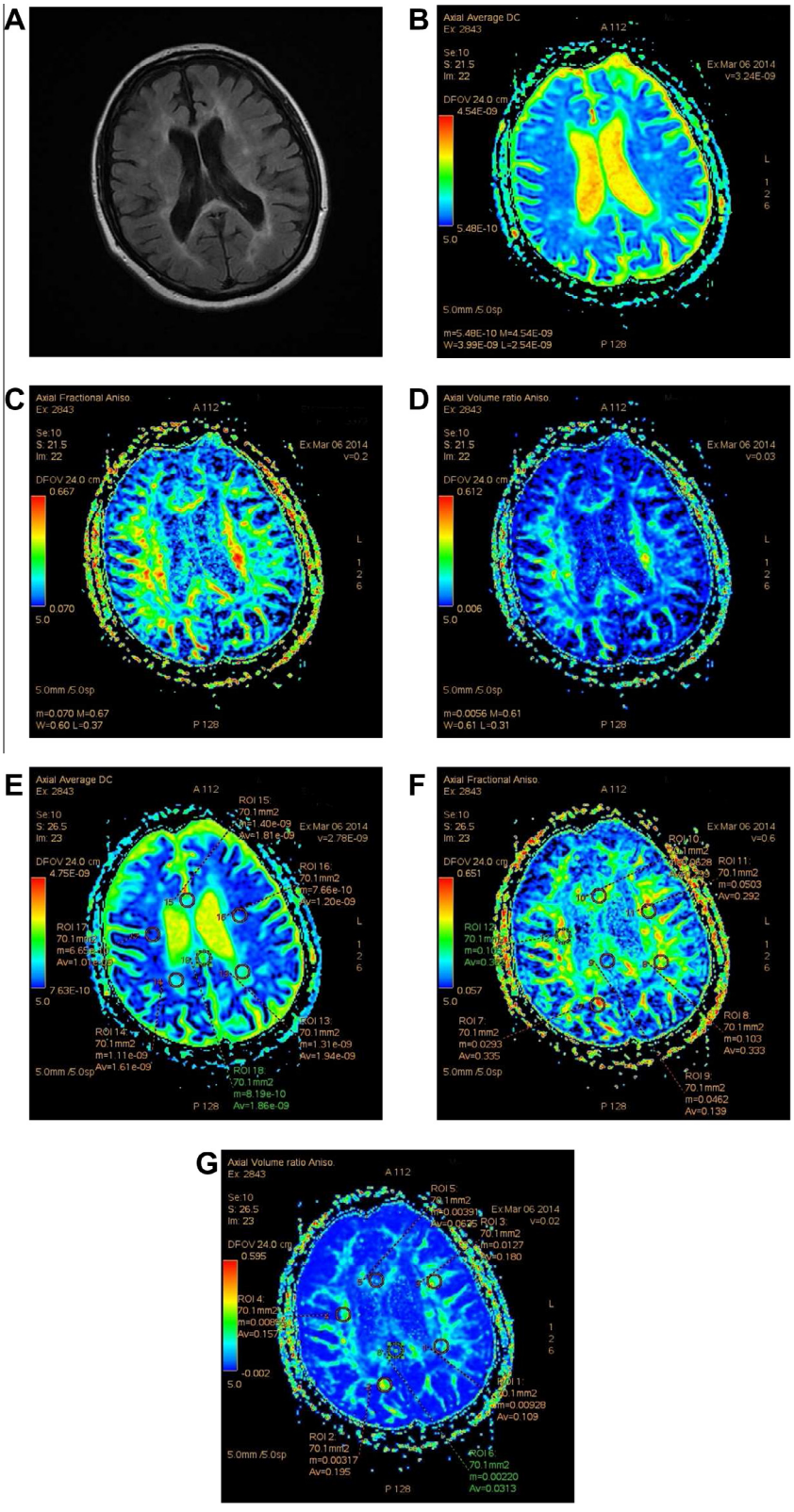

Fig. 3 Female patient aged 42 years with secondary progressive MS (7 years duration). Multiple scattered MS plaques with surrounding edema, prominent involvement of the frontal lobes denote unfavorable clinical status. MD, FA and VR maps reveal multiple areas of increased diffusivity and decreased anisotropy. Marked diffuse increase in mean MD denoting advanced stages of the disease (secondary progressive) with irreversible tissue disruption, gliosis, and axonal loss. These changes are not confined to MS plaques but also to NAWM denoting astrocytic hyperplasia, patchy edema, perivascular infiltration, demyelination and axonal loss. (A) Axial FALIR images. (B–D) DTI directionally encoded color (B: MD, C: FA, D: VR) map. (E–G) DTI directionally encoded color (E: MD, F: FA, G: VR) map (ROIs are placed in the genu and splenium of corpus callosum, MS plaques and NAWM).

Table 2 Correlation between quantitative DTI parameters and lesion load of MS plaques.

Quantitative DTI parameters	Lesion Load	
	P	*r*
MD	0.04	0.42
FA	0.036	−0.38
VR	0.041	−0.27

P significant <0.05, *r* correlation coefficient.

Table 3 Correlation between DTI parameters and overall EDSS and Kurtzke functional system score (KFS-p).

DTI parameters	Overall EDSS		(KFS-p)	
	P	*r*	*P*	*R*
FA	0.03	−0.36	0.02	−0.64
MD	0.046	+0.48	0.038	+0.67
VR	0.048	−0.45	0.041	−0.59

P significant <0.05, *r* correlation coefficient.

contrast administration the same lesions may appear hyperintense (enhancing) if they are in the acute inflammatory phase.

Many previous studies confirmed that tissue damage in multiple sclerosis (MS) is not only limited to the lesions (plaques) seen in T2 and fluid attenuated inversion recovery (FLAIR) sequences, but also involves the white and gray matter of the brain (16–20).

Recently DTI appeared to be more sensitive than conventional MR imaging in the detection of occult tissue damage in MS patients through accurate information about water diffusion within tissues. The DTI by its quantitative parameters fractional anisotropy (FA) and mean diffusivity (MD), allows an assessment of the more widespread tissue damage occurring outside the obvious lesions detected by conventional MR (21). MD is a quantitative metric of water diffusion without any directionality, so increase in its value reflects more diffusivity in that area. On the other hand, fractional anisotropy (FA), represents the prevalence of diffusivity along one direction. The scalar value of FA ranging from 0 to 1 with highest value in compact WM, decreases in the gray matter, and approaches zero in the CSF (22).

Forty five MS patients were included in this study who were diagnosed both clinically using Kurtzke expanded disability status scale (EDSS) and Kurtzke functional system score and by conventional MR. Another twenty healthy age matched control subjects were also included for comparison. High-resolution diffusion tensor imaging (DTI) was performed for all patients and the control subjects. For each patient the average values of MD, FA and VR for the NAWM, active and inactive plaques were calculated. These values were compared with normal white matter (NWM) of the control cases taken at the corpus callosum, internal capsule, infra-tentorial and supra-tentorial white matter. Our results showed gradual descent of the FA and VR average values with highest values seen in the NWM of the control subjects followed by NAWM of the patients then the active plaques and lastly the inactive plaques. The MD average values were in the opposite direction with the highest values seen in the inactive plaques while the least values were in the NWM of the healthy control, similar results were reported by Testaverde et al. (21).

We also agreed with Ceccarelli et al. (23) who stated that decrease of FA in MS patients is likely due to altering of the structural organization of nerve bundles even with reparative gliosis as the glial cells do not have the same organization in space as the cells that they replace.

Regarding the MD, our results were synchronized with those of Senda et al. (12) in their study. They stated that the highest increases in MD were found in T1 hypo-intensity lesions without gadolinium (Gd) enhancement, which represent the areas of irreversible tissue disruption, gliosis, and axonal loss. Our results also coincide with Kolasinski et al. (24) as they found that the extent of MD lesions in NAWM is more than that of FA lesions. We could explain these results that MD is primarily influenced by free space hence its increase with vasogenic edema , axonal and myelin loss while FA is more sensitive to the detection of the integrity of WM but not very specific in distinguishing between diseases characterized by a range of pathological processes, such as edema, inflammation, demyelination, and leukoaraiosis.

In this study we also proved a significant correlation between increase in MD and decrease in FA and VR on one side with the lesion load on the other side ($P < 0.05$), Similar findings were mentioned by Ciccarelli et al. (25) who found a significant correlation between total brain lesion load (LL) with both FA and MD when the whole corpus callosum (CC) was included in the analysis. This strong correlation indicates that the pathological mechanisms are widespread and interrelated throughout the brain.

One important limitation in our study was the presence of variable MS phenotypes with heterogeneity of the clinical variables in addition to presence of some patients with mixed disease course. Another limitation was the short time study and relative low number of the patients. Lastly some patients received medications like steroids which may influence the state of myelination in health and disease.

The use of the DTI metric study in patients with multiple sclerosis is of benefit as prognostic values, to identify early pathological changes in the normal-appearing white matter and so predict cognitive disorders, to investigate the relation between global magnetic resonance burden of disease in the pyramidal tracts and disability and so identifying patients at risk for neuropsychological (NP) impairment on the basis of MRI and would thus enhance the quality of care and life.

5. Recommendation

We recommend adding quantitative diffusion tensor imaging to the other routine sequences for diagnosis and follow up of multiple sclerosis patients. We also recommend the other Longstanding study for evaluation using diffusion tensor imaging for monitoring disease progression and treatment response.

6. Conclusion

DTI–MRI quantitative parameters are good predictors of tissue damage not only in MRI-defined lesions but also in NAWM as a result of Wallerian degeneration and are helpful as diagnostic and prognostic tools.

Conflict of interest

None.

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