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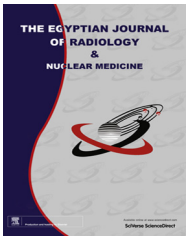

ORIGINAL ARTICLE

Applications of MR fiber tractography imaging in multiple sclerosis

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KEYWORDS

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Abstract *Aim of the study:* To evaluate role of fiber tractography in the assessment of white matter (WM) fiber tract affection in patient with multiple sclerosis (MS).
Patient and methods: Using fiber tractography, WM tract fibers were evaluated in 12 patients with MS and 8 healthy controls in correlation with motor disability in variants of MS, ages range 35–50 years, mean 40.9 ± 5.2. MRI imaging was obtained by using 1.5 T whole-body scanner. Fiber tractography was acquired after routine sequences. Data postprocessing and fiber tracking method were applied including fractional anisotropy (FA) and mean diffusivity (MD) for three regions.
Results: Bilateral WM tract fiber affection was detected in 7 patients, however only 3 showed left sided lesion and 2 patients on right side. WM tract fiber was decreased in all patients; FA and MD for patients were significantly lowered compared to control on all regions (mean values of control $FA = 1.07 \pm 0.34$, $MD = 1.27 \pm 0.36$, with $P < 0.05$ for all differences).
Conclusion: Fiber tractography is a promising non-invasive method for assessing the WM tract affection in patients with MS. It provides an accurate characterization of tissue injury including demyelination and axonal injury.
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1. Introduction

Multiple Sclerosis (MS) is a chronic inflammatory-demyelinating and neurodegenerative disease of the central nervous system (CNS) and is considered as the most common cause of non-traumatic disability in young and middle-age adults (1)). The clinical course of MS is extremely variable; about 85% of cases present with a clinically isolated syndrome involving the optic nerve, brainstem, or spinal cord In these patients,

Abbreviations: DTI, diffusion tensor imaging; FA, fractional anisotropy; FT, fiber tractography; FLAIR, fluid-attenuated inversion-recovery; IC, internal capsule; MD, mean diffusivity; MS, multiple sclerosis; NAWM, normal appearing white matter; ROI, region of interest; RRMS, relapsing-remitting MS; PPMS, primary progressive MS; WM, white matter.

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symptoms and signs typically evolve over a period of several days, stabilize, and then often improve, resulting in a relapsing-remitting (RR) course (2). Persistent signs of CNS dysfunction may develop after a relapse, and the disease may progress between relapses secondary progressive (SPMS). About 15% of patients have primary progressive (PPMS) which is distinguished by a steady progression from the clinical onset, without clear-cut relapses (3). At the initial stage, lesions are typically thin and appear to be linear (Dawson's fingers), these are probably associated with the inflammatory changes around the long axis of the medullary vein that create the dilated periventricular space. Corpus callosum, subcortical region, brain stem, U-fibers, optic nerves, and visual pathway are also regions where lesions are frequently located (4).

The observation that fiber tract loss in the corticospinal tract is associated with distal upstream lesions supports the concept of wallerian degeneration and axonal transection in MS disease (5). Fiber tractography plays a vital role not only in the identification of tracts of interest, but also in the quantification of the degree of axonal loss and demyelination (6). Demyelinating plaques cause destruction of white matter (WM) fibers which are manifested in diffusion tensor imaging (DTI) as increased diffusivity of water molecules (7,8). This can be demonstrated by comparing indices such as the mean diffusivity (MD) and fractional anisotropy (FA) (9). These indices have been successfully applied to study abnormalities in patients with MS by showing reduced FA (increased MD) in MS lesions and the normal appearing WM (NAWM) (10,11). DTI fiber tracking algorithms can be divided into deterministic and probabilistic methods; fiber assignment by continuous tracking is a deterministic method (12,13). FA change gradient has been demonstrated, with lower values being observed close to the plaques and higher values far from the plaques (14,15).

Analysis of tractography results typically involves two approaches; one can measure tract-specific values such as, FA, and mean diffusivity (MD). This approach has found correlation with clinical measures of disability in MS and with functional MRI measures of transcallosal inhibition. The second approach essentially counts streamlines generated by the tractography algorithm. However, this counting approach and the related tract volumetric study demonstrate a relatively high variability and a reduced sensitivity (16,17). Abnormalities in MD and FA in NAWM, cortex, and deep gray matter nuclei are present with the earliest stages of MS and become more pronounced with increasing the disease duration and neurologic impairment (18).

We aimed to study the role of MR fiber tractography in the assessment of WM fiber tract in patients with different grades of MS compared to matched healthy control.

2. Patients and methods

This study was approved by the ethics committee of Mansoura University Hospital and a written informed consent was taken from all patients. MRI was performed between February 2013 and March 2014. Patient group includes 12 cases with different clinical grades of MS (9 females and 3 males); mean age was 49.5 years (range 35–50 years). They were clinically classified into 10 RRMS and two PPMS. Eight healthy individuals of matched age (5 females and 3 males) were enrolled as a control group.

Based on history taking and neurologic examination the clinically diagnosed MS cases were subjected firstly to conventional MRI followed by MR tractography.

2.1. MRI protocol

MR imaging was performed on a 1.5 T whole-body scanner (Achieva, Philips Medical System, Best, Netherlands). All patients underwent routine pulse sequences, including axial fast spin echo T1, T2 and FLAIR images & coronal T2 and sagittal T1 images: T1-weighted sequences (5 mm slice thickness , no interslice gap, repetition time 450 ms, echo time 15 ms) T2 weighted sequences (repetition time 3963 ms, echo time 110 ms) and FLAIR (repetition time 6000 ms and echo time 120 ms and inversion time 1800 ms).

2.2. MRI processing

The processing of Fiber-Tracking Method Anisotropy at each voxel was calculated and color maps were created. A two

Table 1 Demographic characteristics of the studied patients.

Total number	12
Age (mean ± SD)	49.5 ± 5.2
Female/male	9/3
Symptoms:	
Weakness of UL & LL	6 (50%)
Fatigue	6 (50%)
Visual problems	3 (25%)
Numbness of face	1 (8.3%)
Side of the lesion	
	Bilateral = 7
	Left = 3
	Right = 2
Location of the lesions	
	Periventricular WM = 7
	Corona radiate = 2
	Internal capsule = 1
	Frontal region = 1
	Superior cerebellar peduncle = 1

UL – upper limb and LL – lower limb.

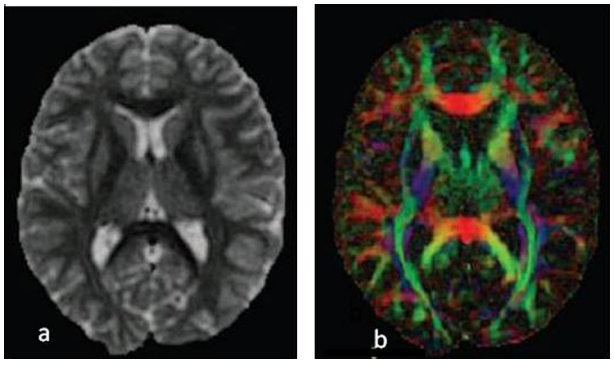

Fig. 1 Images in 37 years old female healthy control subject (a) conventional MRI T2WI shows normal periventricular WM (b) color map to identify specific WM tracts with red–green–blue color (red fibers with lateral orientation: green antero-posterior: blue, craniocaudal).

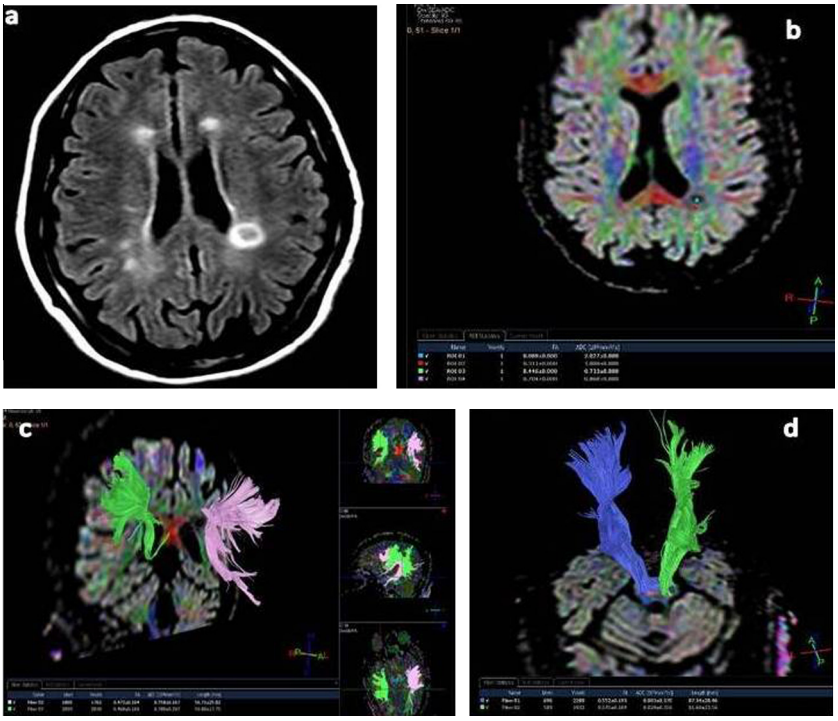

Fig. 2 Images in 35 years old female RRMS patient; (a) axial view FLAIR MRI (9000/90/2000; matrix, 288 × 288; FOV, 230 × 230 mm; section thickness, 5 mm) shows bilateral peri-ventricular WM lesions (the largest one on left side shows black holes). Suggestive of multifocal white matter disease. (b) ROIs for the evaluation of tracts in MS white matter lesions. (c and d) Fiber tractography; shows reduced number of fibers when they traverse white matter lesions and cross-sectional area of the CST (green) on the affected side (FA at fibers measures 0.43 while MD 0.90).

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, cranio-caudal). The procedure for mapping neural connection started through multiple fiber tracking of 3 arbitrary ROIs. We determined ROIs on axial slices of the color vector map for all patients where the CST measures, including cerebral peduncle (CP), posterior limb of the internal capsule (IC), centrum semiovale and subjacent to primary motor cortex (MC). 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 (19). This technique can be used to analyze the displacement of fibers as well as to detect Wallerian degeneration (20).

3. Results

Demographic characteristics of the studied patients including the symptoms, side and site of lesions, were shown in Table 1.

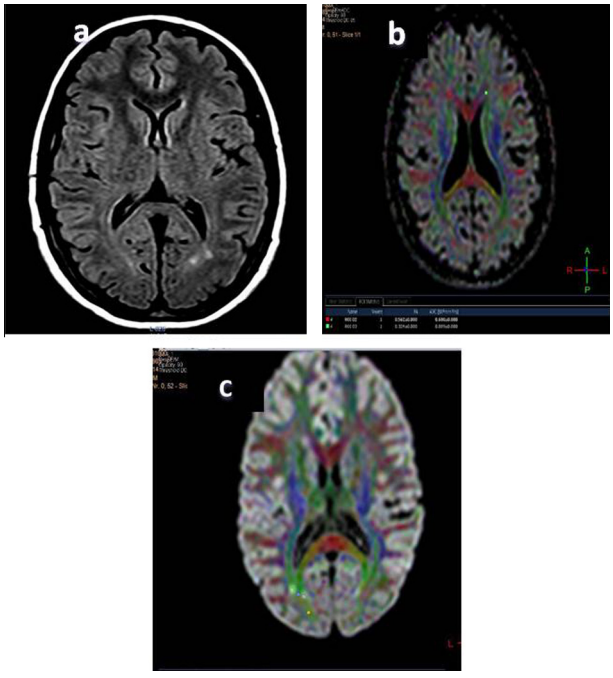

Fig. 3 Female patient (37 years) (a) FLAIR MRI shows multiple hyperintense lesions in periventricular WM (b and c) color-encoded maps (red, left to right; blue, cranial to caudal; green, anterior to posterior.

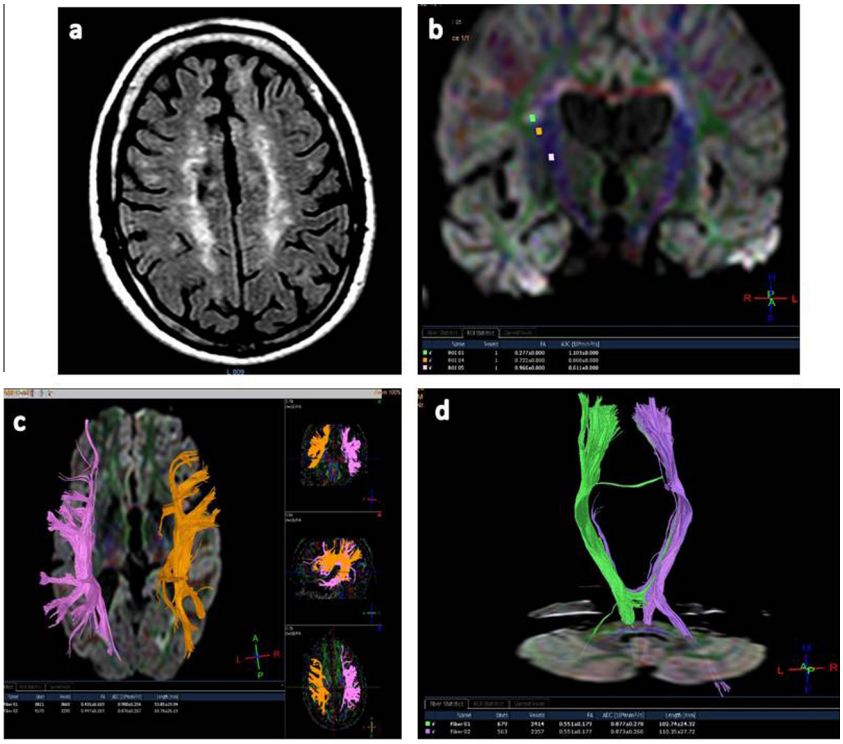

Fig. 4 Male patient (49 years) (a) axial view FLAIR shows bilateral hyperintense lesions in periventricular WM. (b) Color-coded WM fiber maps of ROIs show: FA at ROI 1measures 0.27 while MD 1.10 (c and d). Three-dimensional fiber tracts on CST on both sides generated on the basis of fractional anisotropy(FA measures 0.55 while MD 0.87).

On conventional MRI, 7 patients had bilateral multiple periventricular perpendicular plaques T2 hyperintensities, while 3 patients had left sided and 2 right sided lesions. Normal anatomical tractography was first established on the healthy controls to provide a base line for qualitative analysis of WM tract fibers (Fig. 1). The most common location of MS plaques was periventricular in 7 patients (Figs. 2–4), followed by two cases in corona radiate, one case in anterior limb of IC and one case in superior cerebellar peduncle. The last one was found in left frontal region (Fig. 5).

FA and MD values were explored and analyzed using SPSS version 16 for windows; data were parametric; mean and standard deviation were used for measurement of the central tendency and dispersion. Analysis of difference between patients and control regarding FA and MD revealed statistically significant lower values in MS patients compared to control when assessed for all regions (mean values of control for $FA = 1.07 \pm 0.34$, for $MD = 1.27 \pm 0.36$, with $P < 0.05$ for all differences (Table 2). Lowering of FA values of corticospinal tract fibers was shown in Fig. 2.

4. Discussion

MS is a disabling neurological disease characterized by inflammatory demyelinating lesions within the WM of the brain and spinal cord. Moreover MS involves demyelination and neuroaxonal loss within the GM and normally appearing WM (21). In the current work, we applied MR tractography for the assessment of the corticospinal tracts affected in patients MS compared to the healthy control.

The main findings in the present work was the statistically significant reduction of FA (Fibers directionality/axonal loss), and increase of MD (amount of water diffusion/myelin loss) in all MS patients compared to the healthy control; a finding which is in agreement with other work which concludes that FA decrement correlated with the disease severity while MD values were not uniformly increased as in our work, this difference may be related to the smaller sample size or the limited range of disease severity in our work (22,23). MD is higher in plaques than in NAWM, and higher in NAWM than in healthy WM (24).

Fatigue was found in half of the cases while the other half had weakness of upper and lower limbs. Fatigue is very common and disabling in MS with a close relationship to depressive symptomatology (25).

Atrophy is seen in all stages of MS including the early stages and in a progressive manner. The rate of brain atrophy is higher in MS (0.6–1.0% annually) than in the normal aging process (0.1–0.3% annually) Inflammatory injury in MS causes both demyelination and axonal loss. The end result of this injury was loss of tissue and lastly brain atrophy (26). In the current study five patients have been diagnosed with brain atrophy as evidenced by enlarged ventricles and reduced size of the corpus callosum; four were diffuse brain atrophy while only one patient had brain atrophy restricted to cerebral cortex being the milder form disease (RRMS).

We noticed lowering of FA values of corticospinal tract fibers (Fig. 2). Localization of this finding could help in clinical context; patients with PPMS had a correlation between superior cerebellar peduncle FA on the one hand and upper limb function and walking ability on the other hand (3).

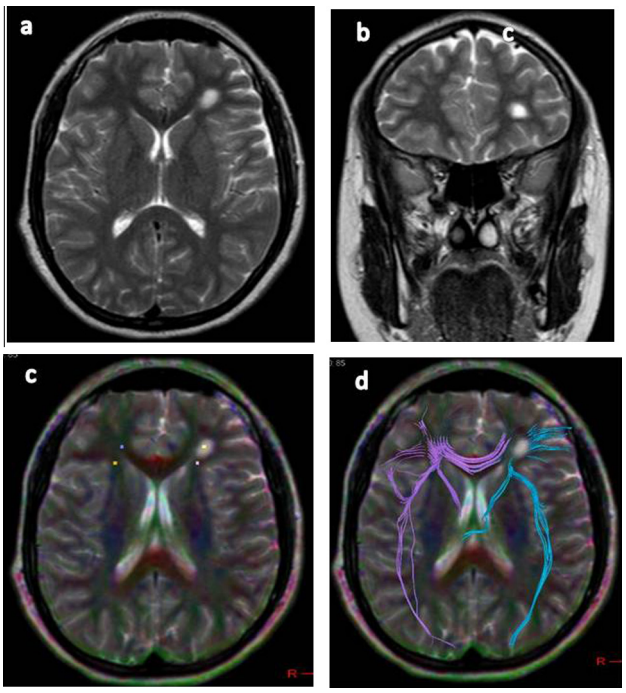

Fig. 5 Images in female patient (42 years) complained from fatigue and weakness of UL & LL (a) axial T2 WI: hyperintense plaque in left frontal region, (b) coronal T2 WI, (c) axial T2 Color-coded WM fiber maps of ROIs in normal(right) and affected side (left), (d) tractography shows decreased fibers in the left frontal region.

Table 2 Qualitative analysis of fractional anisotropy (FA) and mean diffusivity (MD) in patients with MS.

	Patients mean ± SD	Control mean ± SD	*T* value	*P*
Fractional anisotropy (FA)				
ROI 1	0.35 ± 0.17	1.07 ± 0.34	6.21	< 0.001
ROI 2	0.49 ± 0.17		4.52	0.002
ROI 3	0.49 ± 0.23		4.14	0.002
Mean diffusivity (MD)				
ROI 1	0.68 ± 0.25	1.27 ± 0.36	3.23	0.005
ROI 2	0.74 ± 0.34		3.34	0.004
ROI 3	0.65 ± 0.19		4.43	< 0.001

P is significant if less than 0.05.

A limitation of our study was the decreased number of cases; therefore a future work using such quantitative assessment (FA and MD) and applied on a large scale of patients has to be contemplated comparing these results with other studies.

Acute Disseminated Encephalomyelitis (ADEM) is another important differential diagnosis of MS. This is a monophasic, immune-mediated demyelinating disease which often presents in children following an infection or vaccination. Follow-up to these patients, the course of disease regress and the patient complete resolution while MS patients develop new lesions or stationary course (27). In this study we exclude one patient diagnosed ADEM as regards age of the patient and course of the disease which regress and complete resolution after course of treatment. Therefore, long term follow-up studies will be valuable to clarify the relationship between altered WM anatomy and progression of the MS.

In conclusion, FT proved to be a promising method for assessing the WM tract affection in patients with MS. It can provide a noninvasive modality which can accurately assess the extent of injury of WM fibers by quantitative analysis. Our study shows that the FA values were low in WM fibers disrupted by the lesions and significantly correlated with the extent of disease severity. Advances in imaging are providing a more accurate characterization of tissue injury including demyelination and axonal injury, therefore we strongly recommend the integration of FT in the diagnostic work up of demyelinating disorders as well as their follow-up.

Conflict of interest

They declared that there were No conflict of interests and No fund had been received from anybody.

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