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# Role of MRI Diffusion Tensor Imaging in Assessment of Normal Appearing White Matter in Cases of Multiple Sclerosis

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## ABSTRACT

**Background:** Multiple sclerosis (MS) is an inflammatory demyelinating condition of the central nervous system (CNS) that is generally considered to be autoimmune in nature. White matter tracts are affected, including those of the cerebral hemispheres, infratentorium, and spinal cord. Several methods have been proposed, mainly using conventional MR modalities like T1, FLAIR or T2 images and enhanced MRI to delineate lesions. Conventional MR techniques cannot give detailed information about the integrity and location of WM tracts. Diffusion MRI is one of the non-conventional MRI techniques used for assessment of multiple sclerosis. The emergence of diffusion tensor imaging (DTI) is of great interest in MS. DTI probe the details of water diffusion within tissues, and could therefore reveal alterations in normal appearing white matter fibers before being visible in conventional MRI. Fractional anisotropy (FA), is the measure of the portion of the diffusion tensor that results from anisotropy (i.e, a measure of the directionality of the molecular motion of water).

**Purpose:** to evaluate the role of diffusion tensor imaging (DTI) in the examination of the brain white matter that shows normal appearance on conventional MRI sequences in patients with MS, thus assessing its ability to detect early abnormalities at diffusion level. **Methods**: the study included 50 patients; 38 females and 12 males having MS (between 20 and 40 years of age) referred from Neurologists to Radiodiagnosis Department with 10 ages' matched healthy control volunteers. Each patient included in the study was subjected to full history taking, reviewing medical sheet and MR examination including: Conventional MR examination and Diffusion Tensor imaging. Technique was performed using a standard 3 Tesla unit (Acheiva, Philips).

**Results**: the study showed that DTI can reveal normal appearing white matter affection in MS cases before visible sizable plaques can be detected by conventional MRI.

**Conclusion**: the current application of diffusion MRI to patients with MS shows that it has enhanced our understanding of the disease pathophysiology. The study reviewed here provides evidence that DTI-derived measures are more specific to the disease pathological processes and sensitive to the diffuse microscopic injury in the NAWM.

**Keywords:** Multiple sclerosis – MRI – Diffusion tensor imaging.

## INTRODUCTION

Multiple sclerosis (MS) is an inflammatory demyelinating condition of the central nervous system (CNS) that is generally considered to be autoimmune in nature. White matter tracts are affected, including those of the cerebral hemi-spheres, infratentorium, and spinal cord. MS lesions, known as plaques, may be detected anywhere in the white matter with resulting diverse clinical presentations. Continuing lesion formation in MS often leads to physical disability and, sometimes, cognitive decline [(1)].

Several methods have been proposed, mainly using conventional MR modalities like T1, FLAIR or T2 images and enhanced MRI to delineate lesions. Conventional MR techniques cannot give detailed information about the integrity and location of WM tracts. Enhanced MRI is reported as the most sensitive measure of short-term MS activity and is widely used to monitor disease evolution, either natural or modified by treatment [(2)].

Trials have shown that an early diagnosis can make a big difference to the efficacy of MS drug treatments. Non conventional MR techniques are becoming important in preclinical and clinical trials as companies move forward in developing disease modifying drugs (DMDs) [(3)].

Diffusion MRI is one of the non-conventional MRI techniques used for assessment of multiple sclerosis. The potential of diffusion MRI is based on the fact that, while diffusing, water molecules probe tissue structures at a microscopic scale [(4)].



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## PATIENTS AND METHODS

The study included 50 patients 38 females and 12 males having MS (between 20 and 40 years of age) referred from Neurologists to Radiodiagnosis Department with 10 ages' matched healthy control volunteers (between January 2016 and September 2017).

Each patient included in the study subjected to:

- Full history taking.
- Reviewing medical sheet whenever available.
- Inclusion criteria: Known cases of MS.
- Exclusion criteria: Claustrophobic patients and MS patients with another brain parenchymal pathology, e.g. brain neoplasm.
- MR examination including:

  - Conventional MR examination including T1WI, T2WI, and FLAIR in axial, sagittal and coronal planes.
  - Diffusion Tensor imaging.

Technique:

- Technique was performed using a 3 Tesla unit (Philips, Achieva).
- All the diffusion-weighted images were transferred to the workstation supplied by the manufacturer (Achieva R2.5 workstation, Philips).
- Images were post-processed using the Philips software devised for tractography. The maps obtained were:

1- FA 2D grey maps.

2- Directionally-encoded color FA maps and fused FLAIR/DTI maps.

**The study was done after approval of ethical board of Ain Shams University.**

## RESULTS

The study included 38 female patients and 12 male patients between 20 and 40 years old. Comparison with FA of healthy volunteers' white matter regions was made. *p*-value for FA results was 0.013. Pie charts were done for ratio of cases showing one or more normal appearing white matter region of FA reduction. 84% of the cases showed at least one region of NAWM FA reduction.

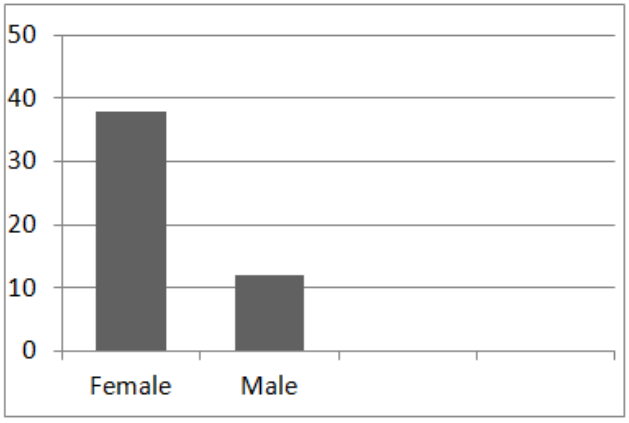


Fig. (1): Female to male ratio of the study cases.

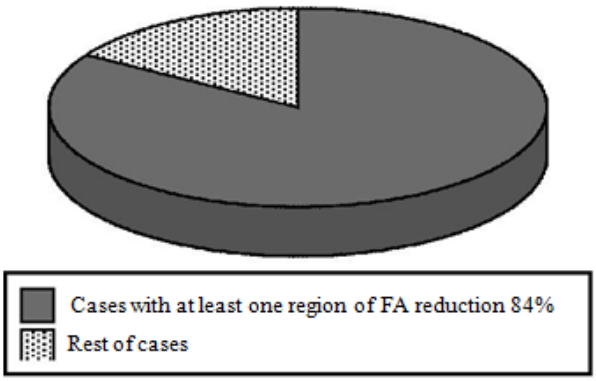


Fig. (2): Ratio of cases with at least one region of reduced FA.

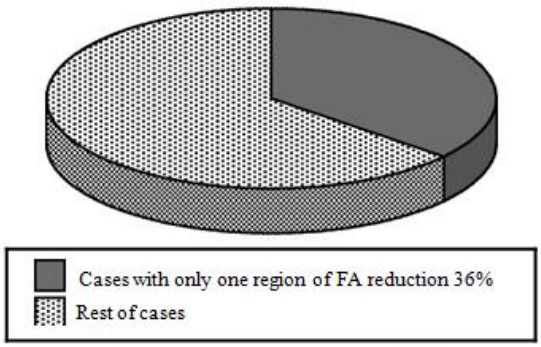


Fig. (3): Ratio of cases with only one region of FA reduction.

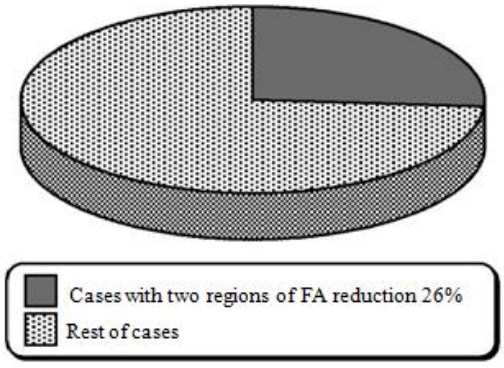


Fig. (4): Ratio of cases with two regions of reduced FA.

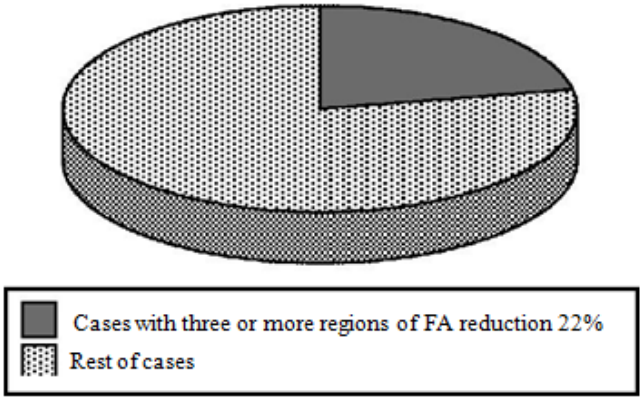


Fig. (5): Ratio of cases with three or more regions of reduced FA.

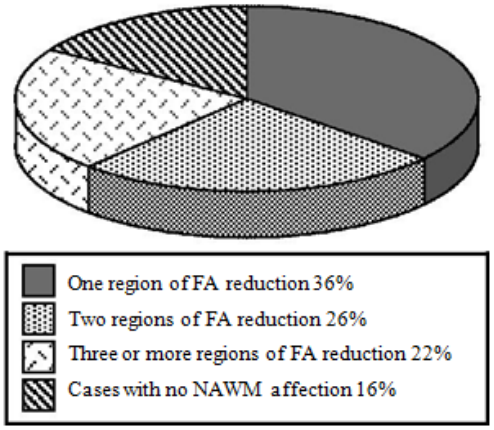


Fig. (6): Cases with FA affection in relation to total cases.

## CASES

**Case (1)**

*Clinical profile:* MS female patient of 36 years old with recurrent bouts of clinical symptoms.

***Conventional MRI findings***

Irregular patchy areas and foci (plaques) of abnormal white matter high FLAIR and T2 signal intensity are seen implicating both cerebral periventricular and subcortical regions. They are seen mostly implicating the parieto-occipital regions.

***DTI findings***

Fused FLAIR/DTI axial images revealed evident heterogeneous cartography maps colors of the sub-cortical and periventricular as well as the brain stem white matter denoting normal appearing white matter affection with parametric indices as follows

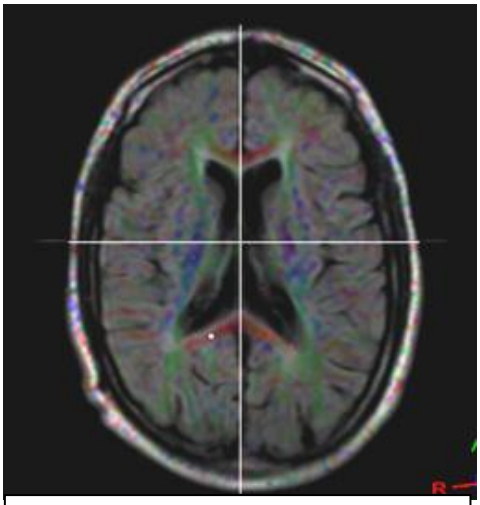

Figure 7: Case (1) fused FLAIR/DTI Axial image

| White matter region | FA | ADC | MD |
|---|---|---|---|
| Right frontal | 0.3 | 0.9 | 0.0027 |
| Left frontal | 0.4 | 0.03 | 0.0021 |
| Right parietal | 0.5 | 0.9 | 0.0027 |
| Left parietal | 0.5 | 0.7 | 0.0023 |
| Right occipital | 0.5 | 1 | 0.0022 |
| Left occipital | 0.7 | 0.7 | 0.0022 |
| Corpus callosum | 0.8 | 0.9 | 0.002 |
| Brain stem | 0.7 | 0.9 | 0.0021 |

**CASE (2)**

Clinical profile: MS female patient of 30 years old with recurrent bouts of clinical symptoms and under regular follow-up.

***Conventional MRI finding***

Irregular patchy areas (plaques) of abnormal white matter signal intensity are seen implicating both cerebral periventricular and subcortical regions. They are seen mostly implicating the right fronto-parietal region.

***DTI findings***

Fused FLAIR/DTI axial images revealed evident heterogeneous cartography maps colors of the left parietal white matter denoting normal appearing white matter affection with parametric indices as follows.

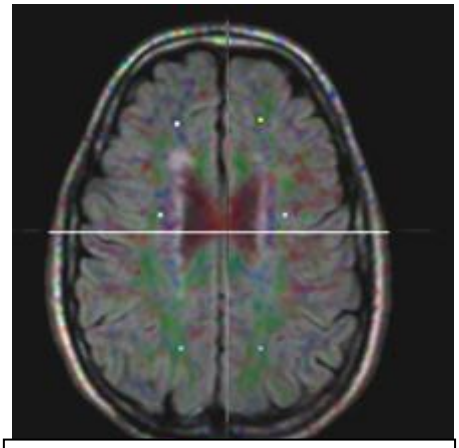

Figure 8: Case (2) fused FLAIR/DTI Axial image

| White matter region | FA | ADC | MD |
|---|---|---|---|
| Right frontal | 0.6 | 1 | 0.0022 |
| Left frontal | 0.7 | 0.6 | 0.0024 |
| Right parietal | 0.3 | 0.02 | 0.0021 |
| Left parietal | 0.3 | 0.6 | 0.0028 |
| Right occipital | 0.5 | 0.9 | 0.0022 |
| Left occipital | 0.4 | 0.9 | 0.0026 |
| Corpus callosum | 0.8 | 0.7 | 0.003 |
| Brain stem | 0.8 | 0.8 | 0.002 |

**CASE (3)**

Clinical profile: MS female patient of 22 years old with recently diagnosed MS.

***Conventional MRI finding***

Irregular patchy areas (plaques) of abnormal white matter signal intensity are seen implicating both cerebral peri ventricular, subcortical and brain stem regions. They are seen mostly implicating the left parietal region.

***DTI findings***

Fused FLAIR/DTI axial images revealed evident heterogeneous cartography maps colors of the left parieto-occipital white matter denoting normal appearing white matter affection with parametric indices as follows.

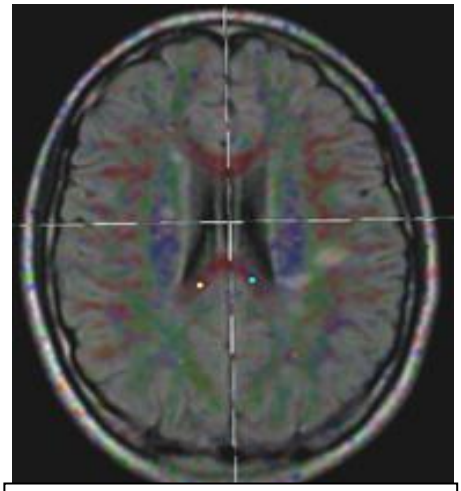

Figure 9: Case (3) fused FLAIR/DTI Axial image

| White matter region | FA | ADC | MD |
|---|---|---|---|
| Right frontal | 0.3 | 0.8 | 0.0021 |
| Left frontal | 0.4 | 0.8 | 0.0027 |
| Right parietal | 0.5 | 0.7 | 0.0025 |
| Left parietal | 0.4 | 0.7 | 0.0028 |
| Right occipital | 0.4 | 0.8 | 0.0021 |
| Left occipital | 0.5 | 0.6 | 0.003 |
| Corpus callosum | 0.8 | 1 | 0.0025 |
| Brain stem | 0.7 | 0.7 | 0.002 |

**CASE (4)**

Clinical profile: MS male patient of 24 years old with recurrent bouts of clinical symptoms.

***Conventional MRI finding***

Irregular patchy areas (plaques) of abnormal white matter signal intensity are seen implicating both cerebral peri ventricular and subcortical regions. They are seen mostly implicating the left parieto-occipital region.

*DTI findings*

Fused FLAIR/DTI axial images revealed evident heterogeneous cartography maps colors mostly of the parieto-occipital white matter denoting normal appearing white matter affection with parametric indices as follows.

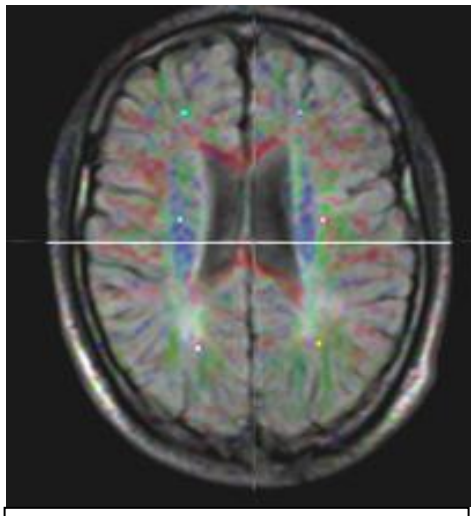

Figure 10: Case (4) fused FLAIR/DTI Axial image

| White matter region | FA | ADC | MD |
|---|---|---|---|
| Right frontal | 0.4 | 0.9 | 0.0026 |
| Left frontal | 0.2 | 0.9 | 0.003 |
| Right parietal | 0.5 | 0.7 | 0.0024 |
| Left parietal | 0.4 | 0.9 | 0.002 |
| Right occipital | 0.1 | 1 | 0.0021 |
| Left occipital | 0.4 | 0.9 | 0.0031 |
| Corpus callosum | 0.6 | 1 | 0.0027 |
| Brain stem | 0.3 | 0.9 | 0.0024 |

**DISCUSSION**

Multiple Sclerosis (MS) is a chronic inflammatory demyelinating and neurodegenerative disease of the central nervous system (CNS) and the most common cause of non-traumatic disability in young and middle-age adults. Pathologically, MS is characterized by areas of demyelinated plaques scattered throughout the CNS with a predilection for optic nerves, spinal cord, periventricular white matter (WM), corpus callosum and, as demonstrated by more recent correlative MRI-histological studies, cortical and sub-cortical gray matter (GM) [(5)].

Approximately 85% of MS patients experience a relapsing-remitting (RR) clinical course characterized by the episodic onset of symptoms followed by residual deficits or by a full recovery especially in the early stage of the disease. While within 25 years, most of untreated RRMS patients will evolve into a secondary progressive (SP) phase characterized by a chronic and steady increase of disability, 20% of RRMS patients will remain clinically stable for two decades and will be classified as benign MS (BMS). Finally, 10-15% of MS patients experience a primary progressive (PP) course since the onset in absence of relapses [(5)].

Conventional MRI (including T2-weighted, pre- and post-contrast T1-weighted scans) has had a huge impact on MS by enabling an earlier diagnosis, and by providing surrogate markers for monitoring response to current disease-modifying treatments and upcoming experimental agents. Despite its increasing role in the clinical management and scientific investigation of MS, conventional MRI is limited by low pathological specificity and low sensitivity to diffuse damage in

normal-appearing white matter (NAWM). In addition, conventional MRI shows only limited associations with clinical status [6].

Diffusion weighted MRI is a quantitative technique able to overcome these limitations by providing markers more specific to the underlying pathologic substrates of the disease and more sensitive to the full extent of 'occult' tissue damage in patients with MS.

The diffusion tensor is a mathematical description of the magnitude and directionality (anisotropy) of water molecules movement in the three-dimensional space. Since in brain white matter, the motion of water molecules can be hindered by the presence of highly organized myelin fiber tracts, water molecules move more easily parallel to tracts and are restricted in their movement perpendicular to tracts. Abnormalities in diffusivity patterns have been seen both in focal MS lesions and in NAWM [7].

Although conventional MRI is very sensitive to macroscopic lesions, it lacks sensitivity to the 'occult' microscopic pathology involving NAWM and NAGM [8].Several studies have described abnormalities of diffusion MRI metrics outside T2 lesions in NAWM and in NAGM of MS patients contributing to improve understanding of MS pathophysiology.

In our study 84% of the cases showed at least one region of NAWM FA reduction, 26% of the cases showed two regions of NAWM FA reduction. 22% showed three or more white matter regions of NAWM FA reduction.

Our study showed also that regions of maximum FA reduction of the NAWM are not always related to the largest demyelinating plaque seen. FA of NAWM are only partially correlated with the extent of focal lesions and the severity of intrinsic lesion damage suggesting that diffusivity changes in normal-appearing tissue are not the mere consequence of retrograde degeneration of axons transected in T2-visible lesions. Indeed, astrocytic hyperplasia, patchy edema, perivascular infiltration, demyelination and axonal loss may also contribute to the diffusion abnormalities of normal-appearing brain tissue [9]. Several DTI studies have shown that NAWM injury become more pronounced with increasing disease duration and clinical disability [10].processes, suggesting that DTI is likely to be sensitive to more severe pathological process [11,12].

## CONCLUSION

The current application of diffusion MRI to patients with MS shows that it has enhanced our understanding of the disease pathophysiology. The study reviewed here provides evidence that DTI-derived measures are more specific to the disease pathological processes and sensitive to the diffuse microscopic injury in the NAWM.

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