Cognitive Impairment and Diffusion Tensor Imaging of the Normal Appearing White Matter in Multiple Sclerosis Patients

RANDA S. DEIF, M.D.*; OMAR A. AL-SRAFY, M.D.*; MOHAMMED EL-TOKHY, M.D.**; GEHAN M. RAMZY, M.D.*; DALIA M. LABIB, M.D.* and SHAIMAA SHAHEEN, M.Sc.*

The Departments of Neurology* and Radio Diagnosis**, Faculty of Medicine, Cairo University, Egypt

Abstract

Background: Cognitive impairment is a common complaint of Multiple Sclerosis (MS) patients either in earlier or later stages of the disease. Diffusion Tensor Imaging (DTI) provides a measure of white matter pathology, including demyelination and axonal loss.

Objective: To detect the damage of Normal Appearing White Matter (NAWM) in different brain region using DTI and find a relation between it and cognitive impairment in patients with Relapsing Remitting Multiple Sclerosis (RRMS) and Secondary Progressive Multiple Sclerosis (SPMS).

Methods: This study done on forty Egyptian patients meeting modified McDonald criteria for MS (20 patients RRMS and 20 SPMS) and 20 healthy control. Cognitive function tests have been done for MS patients and control, magnetic resonance imaging (MRI, 1.5T GE) that included DTI sequences of the brain have been done only for MS patients. Fractional Anisotropy (FA) and Mean Diffusivity (MD) of NAWM were obtained.

Results: A significant difference was found between patients and control in most of cognitive function tests. Cognitive impairment was present in 29 patients (72.5%). Significant difference was found between RRMS and SPMS in cognitive function test and DT-MRI brain results (for corpus callosum and temporal lobe) being severe in SPMS patients. DTI indices of NAWM founded to be correlated with poorer performance in cognitive tests.

Conclusion: The microstructural change of normal-appearing white matter of the brain has an important role in the pathogenesis of cognitive impairment in addition to lesion and brain atrophy in MS patients.

Key Words: Cognitive impairment – Multiple sclerosis – DTI – NAWM.

Introduction

MULTIPLE sclerosis is an inflammatory disease of the central nervous system with a wide range of clinical manifestations i.e. motor, sensory, sphincteric, coordination, and cognitive symptoms [1,2]. Cognitive dysfunction in Multiple Sclerosis (MS) has prevalence rates ranging from 35% to 60% [3] and relates to severity of disability as well as duration of disease [4].

The mechanisms of cognitive impairment in multiple sclerosis have not been understood, one of these mechanism is disconnection which may occur between important cortical and subcortical areas either at the level of interconnecting white matter or in cortical relays within association cortex. Presence of multiple plaques could explain the affection of different cognitive domains in multiple sclerosis as a series of disconnection affecting multiple regions [5].

Conventional MRI has been known for several decades in diagnosis of MS. It has been used for diagnosis of cognitive impairment in MS by detection of brain atrophy. Diffusion tensor imaging is an effective technique to quantify white matter demyelination and axonal loss in the brain and spinal cord of patients with MS in vivo [6]. The assessment of the microstructural changes of white and grey matter may help understanding mechanisms responsible for irreversible disability including cognitive impairment [7,8].

Aim of this study was to detect the damage of Normal Appearing White Matter (NAWM) in different brain region using DTI and find a relation between it and cognitive impairment in patients with RRMS and SPMS.

Subjects and Methods

This was a case control study conducted on 40 patients with definite multiple sclerosis according to the McDonald's criteria and its revision 2010 [9,10] with age from 20 to 48 years. Patients were...
patients in a 1.5 Tesla whole body MR system proved by Cairo University Hospitals Research Ethics Committee and written consents were obtained from patients. Multiple sclerosis patients had not experienced relapse or required steroid treatment for at least 2 months prior to inclusion, and none were on immunomodulatory therapy. Participants did not have any other significant neurological, medical, psychiatric or cognitive disorder. The study was approved by Cairo University Hospitals Research Ethics Committee and written consents were obtained from patients.

**All patients and control groups were subjected to the following:**

1. Full history taking, complete general and neurological examinations. Evaluation of disability using the Expanded Disability Status Scale (EDSS) [12], evaluation of fatigue using the Fatigue Severity Scale (FSS) [13]. Patients who obtained an FSS score of >4 were considered fatigued, whereas those with an FSS score ≤4 were considered non-fatigued.

2. Neuropsychological assessment: The following cognitive domains were assessed: A) Global intellectual functions. B) Specific cognitive functions. Global intellectual function tests were MMSE, MMME. Specific psychometric tests were Paired Associate Learning Test (PALT) for verbal memory; Benton Visual Retention Test (BVRT) for visual memory and visuospatial function; Paced Auditory Serial Addition Test (PASAT) for working memory and speed of information processing assessment; Trail Making Tests: TMT A applied for sustained attention. TMTB and Wisconsin Card Sorting Test (WCST) for executive function.

Radiological assessment was performed to MS patients in a 1.5 Tesla whole body MR system (Intera® scanner, Phillips Medical systems, Best, the Netherlands) using a bird cage head coil suited for MRI. 1) conventional Magnetic Resonance Imaging (MRI) brain was performed using the following techniques: T1 weighted images, T2 weighted images and fluid attenuated inversion recovery FLAIR pulse sequences. Barkhof criteria [14] was used to fulfill radiological criteria for definite multiple sclerosis according to McDonald’s.

The Diffusion Tensor Imaging (DTI) sequence employed a gradient pulse in twelve different directions, with 5mm section thickness and 1.5mm interval, Field of View (FOV) of 230mm, matrix of 128 X 128mm and six excitations. The images were transferred and post-processed in an independent workstation using the software DTI task card to determine the Fractional Anisotropy (FA) and Mean Diffusivity (MD). FA reflects the prevalence of diffusivity along one direction and can provide information about the integrity of WM tracts. FA is a scalar value ranging from 0 to 1 that is highest in compact WM tracts, decreases in the GM, and approaches zero in the CSF. The lower FA values the more axonal loss and severe demyelination. MD measures overall water motion without any directionality. MD is a quantitative metric of water diffusion; the higher the MD value, the higher the diffusivity which indicates an active demyelinating lesion. The method used for DTI measurement was analysis of Region of Interest (ROI). DTI was done on Normally Apparent White Matter (NAWM) (the region outside the visible lesions by conventional MRI) of the following regions: Frontal, temporal, occipital, parietal and corpus callosum.

**Statistical method:**

Data were statistically described in terms of mean ± standard deviation (±SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using student t-test for independent samples. For comparing categorical data, Chi square (χ²) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between various variables was done using Pearson moment correlation equation for linear relation in normally distributed variables and Spearman rank correlation equation for non-normal variables. p-values less than or equal to 0.05 were considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

**Results**

The demographic data of the subjects are summarized in (Table 1). Patients and controls did not differ as regard age, sex and educational level.

1. **Comparative results:**

All MS patients performed significantly poorer than the controls in global cognitive functions,
memory, attention and executive function \( (p<0.05) \). Twenty nine of the MS patients have cognitive impairment (defined as impairment in two or more tests).

Secondary progressive patients showed lower performance than relapsing remitting patients in PASAT \( (p<0.001) \), BVRT \( (p=0.02) \), PALT \( (p=0.02) \) and TMT A \( (p<0.001) \) as presented in (Table 2).

Secondary progressive patients showed lower FA value of NAWM than relapsing remitting patients in temporal and corpus callosum region \( (p=0.01, p=0.01 \) respectively) and relapsing remitting patients showed higher MD value of NAWM than secondary progressive patients in occipital region \( (p=0.004) \) as presented in (Table 3).

### II- Correlative results:

No statistically significant correlation was found between cognitive function tests and age of MS patients.

A statistically significant negative correlation was found between EDSS and poor performance in some cognitive function tests as following: MMMSE \( (r=-0.42; p=0.006) \), PASAT \( (r=-0.4; p=0.01) \), Benton \( (r=0.4; p=0.009) \), PALT total \( (r=-0.42; p=0.006) \). EDSS was positively correlated with poor performance in TMT A \( (r=0.41, p=0.008) \) and TMT B \( (r=0.39, p=0.01) \).

A statistically significant positive correlation was found between disease duration and poor performance in TMT A \( (r=0.34; p=0.03) \) and TMT B \( (r=0.31; p=0.05) \) while no statistically significant correlation was observed with poor performance in other tests \( (p>0.05) \).

FA value of NAWM in frontal region was negatively correlated with poor performance in TMT A \( (r=-0.3; p=0.02) \) and Wisconsin card sorting test \( (r=-0.3; p=0.01) \) and positively correlated with poor performance in MMMSE \( (r=0.31; p=0.05) \), MMMSE \( (r=0.31; p=0.05) \), Benton visual retention \( (r=0.31; p=0.05) \), PALT \( (r=0.31; p=0.05) \), PASAT \( (r=0.31; p=0.05) \).

FA value of NAWM in temporal region was positively correlated with poor performance in PALT \( (r=0.05; p=0.002) \) and PASAT \( (r=0.03; p=0.02) \) and negatively correlated Wisconsin card sorting test \( (r=-0.37; p=0.01) \).

FA value of NAWM in corpus callosum region was positively correlated with poor performance in PASAT \( (r=0.04; p=0.004) \).

No correlation was found between FA value of NAWM in occipital, parietal lobes and poor performance in cognitive function tests \( (p>0.05) \).

The value of MD of NAWM in frontal connection was positively correlated with poor performance in Benton visual retention \( (r=0.42; p=0.006) \) and negatively correlated with poor performance in Wisconsin card sorting test \( (r=-0.45; p=0.03) \).

A negative correlation was found between MD of NAWM in temporal, parietal, corpus callosum regions and poor performance in MMSE \( (r=-0.3; p=0.05) \); \( (r=-0.3; p=0.05) \); \( (r=-0.3; p=0.05) \), respectively. A positive correlation was found between MD of occipital lobe and poor performance in Benton visual retention test \( (r=0.33; p=0.03) \).

### Table (1): Demographic and clinical parameters for MS patients and healthy controls.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients ( (n=40) )</th>
<th>RRMS ( (n=20) )</th>
<th>SPMS ( (n=20) )</th>
<th>Control ( (n=20) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (ys)</td>
<td>34.88±7.47</td>
<td>34.75±8.19</td>
<td>35.62±8.9</td>
<td>30.80±8.16</td>
</tr>
<tr>
<td>Sex M/F</td>
<td>17/23</td>
<td>10/10</td>
<td>10/10</td>
<td>9/11</td>
</tr>
<tr>
<td>Disease duration</td>
<td>6.73±5.4</td>
<td>6.85±7.33</td>
<td>6.6±2.5</td>
<td></td>
</tr>
<tr>
<td>EDSS</td>
<td>4.2±1.52</td>
<td>3.5±1.4</td>
<td>5±1.2</td>
<td></td>
</tr>
<tr>
<td>Fatigued patients</td>
<td>1.7±1.2</td>
<td>1.6±1.31</td>
<td>1.85±1.09</td>
<td></td>
</tr>
<tr>
<td>Cognitively impaired</td>
<td>29 (72.5%)</td>
<td>10 (50%)</td>
<td>19 (95%)</td>
<td></td>
</tr>
</tbody>
</table>

| EDSS : Expanded Disability Status Scale. |
| F : Female |
| M : Male |

### Table (2): Comparison between performance of RMMS and SPMS in psychometric tests.

<table>
<thead>
<tr>
<th>Psychometric test</th>
<th>RRMS Mean ± SD</th>
<th>SPMS Mean ± SD</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognitive function:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMMSE</td>
<td>27.8±4.09</td>
<td>26.6±1.98</td>
<td>0.08</td>
</tr>
<tr>
<td>MMMSE</td>
<td>87.9±6.65</td>
<td>84.6±8.1</td>
<td>0.16</td>
</tr>
<tr>
<td>Memory tests:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PASAT</td>
<td>40.5±24.3</td>
<td>11.42</td>
<td>&lt;0.001 **</td>
</tr>
<tr>
<td>BVRT</td>
<td>17.5±3.22</td>
<td>14.6±4.06</td>
<td>0.02*</td>
</tr>
<tr>
<td>PALT total</td>
<td>12.9±3.69</td>
<td>10.4±2.84</td>
<td>0.02*</td>
</tr>
<tr>
<td>PALT (compatible pairs)</td>
<td>8.23±1.11</td>
<td>7.6±1.14</td>
<td>&lt;0.08</td>
</tr>
<tr>
<td>PALT (incompatible pairs)</td>
<td>4.68±2.95</td>
<td>2.8±2.19</td>
<td>0.04*</td>
</tr>
<tr>
<td>Executive function test:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST (total errors)</td>
<td>29.5±11.4</td>
<td>35.6±13.3</td>
<td>0.21</td>
</tr>
<tr>
<td>WCST (preservative errors)</td>
<td>21.6±10.3</td>
<td>24.7±15.2</td>
<td>0.72</td>
</tr>
<tr>
<td>WCST (non preservative errors)</td>
<td>8.15±8.5</td>
<td>10.6±7.75</td>
<td>0.07</td>
</tr>
<tr>
<td>Attention test:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMT A</td>
<td>1.08±0.67</td>
<td>1.92±0.97</td>
<td>&lt;0.001 **</td>
</tr>
<tr>
<td>TMT B</td>
<td>3.47±1.91</td>
<td>4.28±1.46</td>
<td>0.17</td>
</tr>
</tbody>
</table>

\* : Significant at \( p \)-value <0.05.  
** : Highly significant at \( p \)-value <0.001.
Discussion

In this study all MS patients had poor performance in all cognitive function tests when compared to control subjects and the prevalence of cognitive impairment among MS patients was 72.5% (50% of RRMS and 95% of SPMS). There were more impairment with increased EDSS. Our results are in agreement with Amato et al., [15] who reported that cognitive impairment are not confined to later stages of the MS but it can present in early stages as in RRMS. Also, we found SPMS patients had significant poorer performance in cognitive function tests than RRMS patient which was going with previous studies [16-18].

For many years, conventional MRI plays an important role in early diagnosis of MS and monitoring its response to current treatments. According to Janardhan et al., [19] conventional MRI shows multiple plaques which are corresponding to histopathologic changes in the white matter of MS patients. Moreover, many studies confirmed that; in MS; tissue damage is not limited to the plaques [20,21] but subtle changes are known to occur in the NAWM including diffuse astrocytic hyperplasia, patchy edema, perivascular infiltration, gliosis, abnormally thin myelin, and axonal loss [22]. Recently DTI appeared to be more sensitive than conventional MR imaging in the detection of occult tissue damage outside the plaques through accurate information about water diffusion within tissues. The quantitative parameters of DTI are Fractional Anisotropy (FA) and Mean Diffusivity (MD) [23].

In the current study, comparative results showed statistically significant difference in FA values of NAWM of corpus callosum and temporal lobe being more impaired in SPMS than in RRMS. Previous studies by Preziosa et al., [24] and Braley et al., [25] showed significantly reduction of FA values in SPMS patients than other types of MS (RRMS, CIS, PPMS) in NAWM of corpus callosum and temporal lobe. For DTI assessment, the first study used Voxel Based Morphometry (VBM), while the second study used analysis of ROI method as in our study.

In this study, we found no difference between RRMS and SPMS in FA values of NAWM of prefrontal connection and parietal lobe. This is agreement with Vrenken et al., [26] who found that no difference between RRMS and SPMS in FA of NAWM of prefrontal lobe and posterior corona radiata by using the same method of analysis (ROI). On the contrary, Scanderbeg et al., [27] found that FA values of NAWM of prefrontal lobe and corona radiata were lower in patients with SPMS than in RRMS. The difference can attributed to applying different method of the DTI analysis which was Tract-Based Spatial Statistics (TBSS) to evaluate WM microstructure.

Reduction of FA values can be attributed to disruption of the integrity of myelin sheaths or nerve axons leading to the restriction of water diffusion across the fiber tract and so FA is expected to decrease [28].

In the current study, we found increased MD value of NAWM only in occipital lobe of RRMS patients more than SPMS patient with no difference between them in MD value of NAWM in other regions. Rocca et al., reported that an increase of MD value in NAWM may be occurred as a consequence of demyelinating processes which may precede the appearance of a new lesion on conventional MRI by several weeks [29].
When we investigated the relationship between injury within NAWM and cognitive performance in multiple sclerosis, we found correlation between impaired prefrontal lobe function (long term memory, attention and executive function) with decreased FA values and increased MD values of prefrontal lobe. Roca et al.,[30] in their study; using analysis of ROI; found that low FA values of fronto-subcortical fiber tracts was associated with impairment in executive function and long term memory tests. In spite of applying TBSS to map cognitively relevant tract disorganization in their studies, Roosendaal et al.,[31] and Dineen et al.,[5] found correlations between impaired attention, working memory and speed of information processing and decreased fractional anisotropy of tracts connecting prefrontal cortical regions.

In agreement with previous studies we found impairment in working memory and speed of information processing correlated with decreased FA value in corpus callosum in MS patients[31-33].

In the current study, we found that episodic and working memory were impaired with more decreased FA value of NAWM in temporal lobe of MS patients. This finding was in agreement with Fink et al., [34] who found correlation between impairment of episodic memory and the reduction in FA of temporal lobe.

In the present study, correlative studies showed that no relation between FA value of NAWM in occipital lobe and cognitive function test in MS patients which may be attributed to absence of axonal damage in occipital lobe. Visual memory was impaired with more increased MD value of NAWM of occipital lobe in MS patients which can be explained by presence of active lesion in occipital lobe. Warlop et al.,[35] found that no correlation between FA of NAWM of occipital lobe and cognitive function in MS patients using Voxel Based Morphometry (VBM) to analyses DTI. On the other hand, Catani et al.,[36] found that low FA values of tracts connecting the occipital lobe with temporal lobe (Inferior Longitudinal Fascicle (ILF) were correlated with impaired visual working memory using TBSS to analyses DTI. The difference in the results of previous studies can be explained by the difference in the study method. TBSS has higher sensitivity than ROI and VBM [6].

In the current study, correlative studies showed no relation between FA, MD values of NAWM of parietal lobe and cognitive function test in MS patients. In contrast to, Yu et al.,[37] who found that low FA values of posterior corona radiate related to impairment in visual working memory using Symbol Digit Modalities Test (SDMT) to assess visual working memory and TBSS to analyses DTI. The difference between results can be explained by the difference in methodology, we used PASAT to assess auditory working memory and no test had been done for visual working memory and ROI to analyses DTI.

Our study confirms widespread abnormalities involving NAWM lead to reduced functional connectivity between cortico-cortical or cortico-subcortical cognitive processing regions, making an important contribution to cognitive dysfunction in multiple sclerosis.

Conclusion:
The microstructural change of normal-appearing white matter of the brain has an important role in the pathogenesis of cognitive impairment in addition to lesion burden and brain atrophy in MS patients.

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