Relationship Between Frontal White Matter Integrity And Fatigue In Relapsing Remitting Multiple Sclerosis: A DTI Pilot Study

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Citation

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Abstract

Background and Purpose: Though it's a frequent disabling symptom among Multiple sclerosis (MS) patients; the mechanism of fatigue in MS is not fully understood. The aim of this study is to identify the relationship between frontal white matter (WM) integrity and fatigue in patients with Relapsing Remitting Multiple Sclerosis (RRMS) using Diffusion Tensor Imaging (DTI). Methods: A case control study; that included 33 patients with RRMS and 13 healthy control subjects. Patients were subjected to medical and neuropsychological evaluation including: Expanded Disability Status Scale (EDSS), Fatigue Severity Scale (FSS), and Beck's Depression Inventory. Patients were grouped according to FSS into fatigued (FSS ≥ 4; n=15) and non-fatigued (FSS < 4; n=18) subgroups. Using DTI, Fractional anisotropy (FA) was measured to determine frontal WM integrity. Results: FSS scores correlated significantly with FA values measured in right (p 0.001, r = – 0.581) and left (p 0.001, r = – 0.738) frontal WM. This correlation remained significant after controlling for age, sex, EDSS, and disease duration. FSS scores correlated with age (p < 0.025, r =0.391), and disease duration (p = 0.015, r = 0.418), but not with EDSS (p = 0.154, r =0.254). Compared with healthy controls, all MS patients showed lower FA values (p 0.001). Conclusion: Our results support the central mechanism hypothesis of MS related fatigue which is likely to be related to disruption of the complex frontal WM networks. MS related fatigue may be more severe in older patients and with longer disease duration.

INTRODUCTION:

Fatigue is frequently encountered among Multiple Sclerosis (MS) patients, affecting almost 80% of MS patients and for many fatigue is the most disabling symptom (1). The mechanism of fatigue in MS is not fully understood and different factors are supposed to contribute to fatigue. Presumed mechanisms include immune and endocrine dysregulation, central nervous system mechanisms, as well as secondary factors like sleep disturbance and depression (2,3).

Few investigators have addressed the correlation of fatigue in MS with alterations in specific anatomical areas (4,5). Frontal White Matter (WM) dysfunction is thought to be able to generate fatigue through the disruption of the complex frontal circuits including: fronto-striatal, fronto-frontal, fronto-occipital, and fronto-limbic pathways. This may cause impairment of volitional drive to the descending motor pathways which in turn lead to fatigue perception.

In MS research, Diffusion Tensor Imaging (DTI) has demonstrated a high degree of specificity and sensitivity in detecting WM integrity using Fractional Anisotropy (FA) (6). FA is a unit-less DTI-based index ranging from 0 to 1 that is highest in compact WM tracts and decreases with WM damage and architectural disorganization.

In the current study, a validated measure of subjective fatigue (i.e., Fatigue Severity Scale) and a quantitative analysis of WM integrity (i.e., DTI) were adopted to assess the relationship between fatigue severity and frontal WM integrity in patients with MS.

MATERIALS AND METHODS

Study population

In this case control study, we prospectively recruited 33 patients during the time period from October 2013 to June 2014. Only patients with Relapsing Remitting Multiple Sclerosis (RRMS) were included. Patients were diagnosed according to revised McDonald Criteria (7). Age- and sex-

matched healthy controls were also recruited for DTI analysis. All cases were subjected to thorough medical and neurological evaluation, quantification of disability using the Expanded Disability Status Scale (EDSS) (8), Mini-Mental State Examination (MMSE) (9), evaluation of depression using Beck Depression Inventory (BDI) (10,11) fatigue assessment using the fatigue severity scale (FSS) (12) and neuroradiological examination. Exclusion criteria were; history of neurological disorder other than MS, evidence of another medical condition that can cause fatigue, clinical relapse in last month prior to study, history of alcohol or drug abuse, history of psychiatric disorders or use of antidepressant or antipsychotic drugs, BDI Score more than 18, MMSE score less than 24, and steroid therapy in last month prior to study.

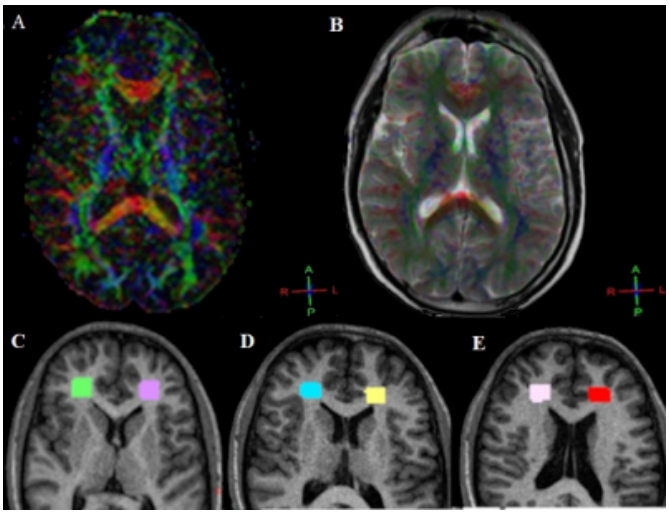
All subjects gave informed consent and the study follows the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Neuro-radiological Assessment and Analysis

Neuro-radiological assessment composed of brain Magnetic Resonance Imaging (MRI) and Diffusion Tensor Imaging (DTI). MRI was performed using a 1.5 Tesla Phillips Intera® scanner at the Magnetic Resonance Unit. T1-weighted images (axial, sagittal), T2- weighted images (axial, coronal) and Fluid attenuated inversion recovery (FLAIR) sequences. DTI technique was performed while patient is in supine position, using a standard 1.5 Tesla unit. The sequences obtained were axial, sagittal and coronal T1W, T2W, FLAIR and diffusion tensor, which consisted of a single shot, spin-echo echo planar sequence in 25 encoding directions and a diffusion weighting factor of 800 s/mm2. [T1WI: TR 450, TE 15, matrix 80 x 81, FOV 230 X177, slice thickness 5 mm. T2WI: TR 3612, TE 100, matrix 208 x 127, FOV 230 X 177, slice thickness 5 mm. FLAIR : TR 6000, TE 120, matrix 240 x 111, FOV 230 X 184, slice thickness 5 mm. DTI : TR 10951, TE 67, matrix 128 x128, FOV 224 X 224 mm, number of excitations 2, slice thickness: 2.0/00 and flip angle 90 degrees]. All the diffusion-weighted images were transferred to the workstation supplied by the manufacturer. Images were post-processed using the Philips software. Directionally encoded color FA maps were obtained then fused with T2 weighted or with T1 3D Fast Field Echo (3DFFE) images. Red, green and blue colors represent right-left, anterior-posterior and superior-inferior directions, respectively. FA was measured (through application of multiple color coded regions of interest in the frontal WM of both cerebral hemispheres in 3 consecutive levels (Figure 1). Mean FA was calculated and used for statistical analysis. All voxels were considered significant only if they were included in clusters composed of at least 30 voxels. We also excluded voxels including gray matter or CSF spaces.

Figure 1

Example of directionally-encoded color Diffusion Tensor Imaging map (A) which was obtained then fused T2 weighted image (B). Fractional Anisotropy was obtained through application of multiple color regions of interest in the frontal white matter of both cerebral hemispheres in 3 consecutive levels (C,D,and E)



Statistical analysis

Pre-coded data were entered on the computer using "Microsoft Office Excel Software" program (2016) for windows. Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Data were summarized using mean, standard deviation, median and interquartile range for quantitative variables and frequency and percentage for qualitative ones. Comparison between groups was performed using independent sample t-test for quantitative variables and Chi square test or Fisher's exact test for qualitative ones. Pearson correlation coefficients were calculated to signify the association between different quantitative variables. P values less than 0.05 were considered statistically significant, and less than 0.01 were considered highly significant.

RESULTS

Patient characteristics

Thirty-three MS patients were included in this study. Their

age ranged from 16 to 48 years, with a mean age of 33.55 ± 9.54 Standard Deviation (SD). There were twenty-two males (66.7%) and eleven females (33.3%). The duration of illness ranged from 1-12 years with mean disease duration 5.36 ± 3.62 SD. The EDSS ranged from 1-5 with mean of 3.21 ± 1.8 SD. Scores of FSS ranged from 1.2 to 6 with a mean score of 3.38 ±1.25. Fifteen patients had FSS score ≥ 4 (fatigued subgroup) and eighteen patients had score 4 FSS score (non-fatigued subgroup). Thirteen age and sex matched healthy controls were also recruited for MRI analysis. Mean FA of right frontal WM was 0.42 ± 0.07 for MS patients and 0.51 ± 0.04 for healthy controls. Mean FA of left frontal WM was 0.43 ± 0.07 for MS patients and 0.53 ±0.07 for healthy controls. Compared to healthy controls, MS patients had decreased mean FA values in all of the explored regions of interest (p 0.001).

Comparison between fatigued and non-fatigued MS patients

There was statistically significant difference between the two subgroups regarding age, disease duration, disability, and measured FA but no significant differences found regarding sex (Table 1).

Table 1

Comparison between fatigued and non-fatigued multiple sclerosis patients regarding patient characteristics and mean fractional anisotropy values; MS, Multiple Sclerosis; EDSS, Expanded Disability Status Scale; FSS, Internal Carotid Artery; FA, Fractional Anisotropy; WM, White Matter.

Characteristic		Fatigued MS (n=15)	Non-fatigued MS (n=18)	P value
Age years (SD)		39.60 (5.6)	28.50 (9.28)	< 0.001
Female sex no. (%)		6 (40)	5 (27.8)	0.5
Disease Duration years (SD)		7 (3.91)	4 (2.79)	0.02
EDSS score (SD)		3.67 (1.01)	2.67 (1.14)	0.013
FSS score (SD)		4.52 (0.58)	2.44 (0.76)	< 0.001
Mean FA (SD)	Right frontal WM	0.38 (0.07)	0.45 (0.05)	0.002
	Left frontal WM	0.38 (0.05)	0.47 (0.06)	< 0.001

Correlative analysis

Statistical analysis revealed a significant negative correlation between FSS scores and mean FA values in right frontal WM (p 0.001, r = – 0.581) and left frontal WM (p 0.001, r = – 0.738). Using a partial correlation approach the correlation between FSS scores and mean FA values remained significant after controlling for age, sex, disease duration and EDSS (Figure 2,3). Fatigue severity showed a significant positive correlation with age (p < 0.025, r =0.391), and disease duration (p = 0.015, r = 0.418), but not with disability as measured by EDSS (p = 0.154, r =0.254).

Figure 2

Relationship between of fatigue severity scores and mean fractional anisotropy values in right frontal white matter.

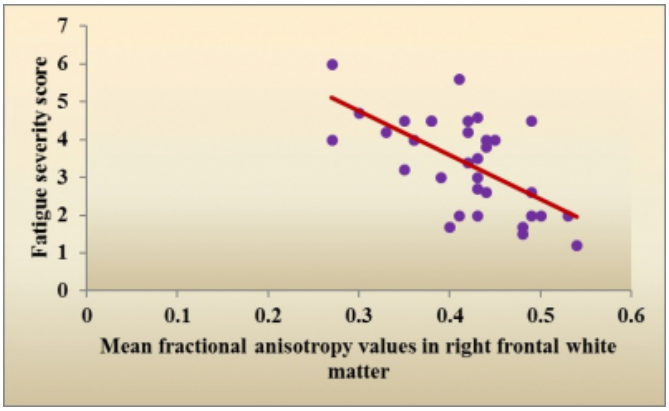
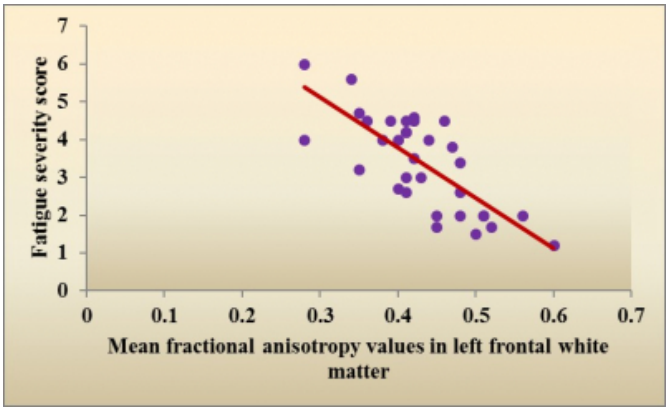


Figure 3

Relationship between of fatigue Severity scores and mean fractional anisotropy values in left frontal white matter.



DISCUSSION

Our study showed a significant correlation between fatigue severity scores and frontal lobe WM integrity as determined by FA. This correlation remained significant after controlling for age, sex, disease duration, and EDSS using a partial correlation approach. In consistence to our results; Pardini and colleagues found that fatigue severity correlated with reduced left frontal WM integrity in patients with RRMS (13). Gobbi et al. found reduced FA of the right anterior thalamic radiation in fatigued non depressed MS patients compared to non-fatigued patients (14). In contrast to our findings, Codella et al did not find any significant difference between fatigued and non-fatigued RRMS patients regarding FA of the frontal WM (15). However in

this later study; no rating scale was implied to exclude concomitant depression, only patients with low disability (EDSS ≤ 1) were included, and also the range of disease duration of their study population varied widely (1 – 40 years).

Frontal white matter damage is thought to be able to generate fatigue through the disruption of the complex frontal neural circuits. Frontal neural circuits have been related to effort-based and reward-based decision making and motivation via the interaction of anterior cingulate, medial prefrontal, orbitofrontal cortices. Therefore, loss of interaction between these cortices may lead to fatigue perception (16,17).

In our study, fatigue severity scores showed a significant positive correlation with age and disease duration. This agree with findings by previous studies (18,19). However, others failed to demonstrate any association between age and fatigue among patients with MS (20,21). We did not find any significant correlation between fatigue severity and neurologic disability as determined by the EDSS, which is consistent with other publications (22,23). However, other investigators have reported an association between physical disability and fatigue (19,24). This discrepancy may be related to relatively small sample size in our study, It can be also due to inclusion of different MS phenotypes in the last two studies. Mills and colleagues concluded that fatigue was worse in those with progressive MS phenotype (21). Our study could not find differences regarding distribution of both sexes among fatigued and non-fatigued subgroups. This is in agreement with several previous studies who found no differences in fatigue related to gender among MS patients (18,21,26). However, Tedeschi and colleagues observed that females had lower fatigue scores than males (4). They attributed their finding to disease specific pathology as females in their study had less degeneration and smaller T1 lesion volume than males.

In the current study, all MS patients showed lower Fractional Anisotropy (FA) values when compared with healthy controls. Similar results could be seen in recent studies (14,25). This finding points to the importance of diffusion studies in detection of subtle brain damage not detected by conventional MRI studies.

Our study was not without limitations. The limitations of the current study should be considered when interpreting the results. Our study was a pilot study with a relatively small sample size. Biases may have influenced our assessment of fatigue severity as we used a self-report assessment scale.

CONCLUSION

Our study showed that fatigue severity in RRMS patients was correlated to frontal WM integrity measured by DTI. Future studies, integrating structural and functional imaging, are warranted for better understanding of pathophysiology of fatigue in MS. Age and disease duration were positively correlated with fatigue severity among our study population.

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