SCIE DOI: 10.14744/scie.2021.57614
South. Clin. Ist. Euras. 2021;32(4):388-394

Original Article

Assessment of the Fatigue with Biochemical Data and Corpus Callosum Atrophy in Multiple Sclerosis Patients

Tülin Aktürk,[1] Hikmet Sacmacı,[2] Mustafa Erkoç[3]

[1]Department of Neurology, Kartal Dr. Lütfi Kırdar City Hospital, İstanbul, Turkey
[2]Department of Neurology, Yozgat Bozok University Faculty of Medicine, Yozgat, Turkey
[3]Department of Radiology, Yozgat Bozok University Faculty of Medicine, Yozgat, Turkey

Submitted: 26.02.2021
Accepted: 06.07.2021

Correspondence: Tülin Aktürk, Kartal Dr. Lütfi Kırdar Şehir Hastanesi, Nöroloji Anabilim Dalı, İstanbul, Turkey
E-mail: tulin_birlik@hotmail.com

Keywords: Corpus callosum atrophy; corpus callosum index; fatigue; folate; multiple sclerosis; triglycerides.

ABSTRACT

Objective: Fatigue is a common finding in patients with multiple sclerosis (MS) and its etiopathogenesis has not been fully elucidated. The aim of this study was to evaluate the relationship between fatigue and biochemical data and corpus callosum index (CCI) in brain magnetic resonance imaging (MRI).

Methods: In this cross-sectional study, 100 individuals (58 MS patients and 42 control subjects) were included. The disability of the patients was determined with the extended disability status scale (EDSS), and their fatigue was evaluated with the Fatigue Severity Scale (FSS). Biochemical data were analyzed. CCI values were calculated on brain MRI scans.

Results: There was no difference between the groups in terms of age, gender, and BMI ($p>0.05$). In MS patients, folate level and CCI values were found to be statistically significantly lower compared to the control group ($p=0.029$ and $p<0.001$, respectively). It was seen that the triglyceride value was significantly higher in the MS group, and there was no significant difference between the groups in terms of other biochemical data. It was found that there was a positive correlation between fatigue and EDSS, and a negative correlation between the CCI and folate value in the MS group. When MS patients with and without fatigue and the control group were compared,only folate levels were found to differ between the groups ($p=0.011$).

Conclusion: Our results suggest that fatigue in MS patients is associated with corpus callosum atrophy, a higher level of disability, and lower folate levels. Folate replacement therapy may reduce fatigue, even if folate levels are above the lower limit. Confirming these findings with larger patient series will contribute to a better understanding of fatigue in MS disease and the relationship between fatigue and folate.

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that occurs with a wide range of clinical findings as a result of neuroinflammation. Fatigue is commom in MS patients and affects the quality of life significantly.[1] The pathophysiology of MS-related fatigue is complex and multifactorial.[2] Although the role of the central nervous system (cerebral lesion load, cortical atrophy and activation of neural circuits), immunological factors, neuroendocrine involvement and the effect of peripheral abnormalities have been implicated in the pathophysiology,[3–7] it has not been fully clarified yet.The corpus callosum, the largest commissural fiber bundle of the brain connecting the two cerebral hemispheres, is one of the sites where MS lesions show a predilection for involvement. Atrophy is observed in the corpus callosum in MS patients with the impact of both focal lesions and distant lesions that result in Wallerian degeneration.[8] In the normal population, the corpus callosum is relatively resistant to age-related changes.[9] The Corpus callosum index measurement is a practical method to assess corpus callosum atrophy. Corpus callosum atrophy has been evaluated as a biomarker for neurodegeneration in MS disease, however, it has been reported to be an independent risk factor for disease-related fatigue.[10,11] On the other hand, identifying serum biochemical data that can be analyzed in relation to fatigue can provide insight into the causes of fatigue in MS patients. In this study, it was aimed to evaluate the relationship between fatigue, routine biochemical parameters and corpus callosum atrophy detected with corpus callosum index measurement on cerebral MRI.

MATERIALS AND METHODS

Study group

Fifty-eight consecutive patients between the ages of 18-65 who were admitted to the Neurology outpatient clinic of the Yozgat Bozok University Faulty of Medicine , and were followed-up by our center with the diagnosis of multiple sclerosis according to the 2010 McDonald criteria[12] and forty-two healthy controls were included in this study. The clinical and demographic characteristics of the patients were recorded. The disability level of the patients was evaluated by the same neurologist using the Expanded Disability Status Scale (EDSS).[13] Body mass index (BMI) was calculated (kg/m^2). The biochemical data of the patient and control groups were obtained from the hospital registry system. Patients who did not have an attack in the last month and did not receive vitamin D replacement were included in the study.

Patients with anemia, chronic infections, autoimmune diseases, cancer, diabetes, liver disease, chronic lung diseases, alcohol or any substance addictions and endocrinological disorders such as hypothyroidism that could cause unexplained fatigue were excluded from the study. Furthermore, patients with self-reported depression and those diagnosed with depression by clinical evaluation were excluded from the study. The study was conducted in accordance with the Helsinki declaration and the Yozgat Bozok University Faculty of Medicine Ethics Committee approved the study protocol (protocol number: 2017-KAEK-189_2020.05.19_07). Written informed consent was obtained from all participants.

Evaluation of fatigue

Fatigue levels of the patients were assessed using the Turkish version of the Fatigue Severity Scale (FSS).[14] This scale evaluates the overall effect of fatigue on daily activities with 9 questions. Each question is rated from 1 (strongly disagree) to 7 (strongly agree). The FSS score is calculated as the average of nine parts. We applied 4 cut-off points on the FSS scale to determine basic fatigue levels. A high score indicates that the severity of fatigue increases.[15] The reason we used the FSS scale in this study is that it provided significant findings in previous randomized clinical trials.[16] The assessment scale was performed by the same clinician with the face-to-face interview method.

Calculation of corpus callosum index on brain MR imaging

Brain MRI examinations were performed using a 1.5-channel MRI device (Philips, Philips Medical Systems, Ingenia 1.5, The Netherlands) with a 32-channel cranial coil. T1-weighted sagittal cranial MRI sections were obtained from the patients included in the study. The imaging parameters for the T1 series were 3810 ms/114 ms/1; 259x118 matrix, 800-cm field of view (FOV), 130 kHz bandwidth, 13 echo train length and 5 mm section thickness. MRI sections were evaluated in sagittal plans in the T1-weighted series. Corpus callosum index value measurements were performed as previously described by Yaldizli et al.[17] All measurements were performed by the same radiologist.

Statistical analysis

The data were analyzed with SPSS (Version 18.0) package program. While the mean ± standard deviation was used for HDL that fits the normal distribution pattern in our data, median 25th-75th percentile was used for our other data that did not fit the normal distribution pattern and categorical variables as numbers (percent). In the independent group comparisons, when parametric test assumptions are provided, Student's T-Test was used; when parametric test assumptions were not provided, Mann-Whitney U test was used. In the analysis of clinical and biochemical data with CCI, the Pearson correlation test for HDL cholesterol and Spearman's correlation test was used in other data since it did not meet the normality assumptions. In the triple group comparisons, the Kruskal-Wallis test was used because the data set displayed a nonparametric distribution. Bonferroni correction for post-hoc evaluation and group comparison analyzes were performed. Categorical data were analyzed using the chi-square test. Statistical significance level was considered as $p \leq 0.05$.

RESULTS

The median age of MS patients was 39.5 (31–45); female/male ratio was 33/25; the median body mass index (BMI) value was 24.75 (22.43–27.77) and there was no difference between the groups in terms of age, gender and BMI. The median duration of disease in MS patients was 8 years (4.75–12); the median EDSS score was 1.75 (1–2.62); the median treatment duration was 3 years (1–5). The median fatigue severity scale score was 5.26 (3.64–6.30) in the patient group. The demographic characteristics and laboratory data of the patient and the control groups are summarized in Table 1. When both groups were compared in terms of hematological and biochemical values, the folate level in the MS group was lower ($p=0.029$) and the triglyceride level was higher ($p=0.010$). There was no difference in terms of any other biochemical parameters ($p>0.05$). The corpus callosum index (CCI) value was 4.95±1.02 in the patient group and 7.87±0.83 in the control group, this difference was statistically significant ($p<0.001$).

Seventeen (29.3%) of patients were receiving interferon, 10 (17.2%) were on glatiramer acetate, 11 (19%) were on fingolimod, 7 (12.1%) were on teriflunamide, 4 (6.9%) were on dimethyl fumarate, 3 (5.2%) were on ocrelizumab therapy and 2 (3.4%) were receiving natalizumab treatment. Four of the patients (6.9%) were not receiving any treatment.

When the correlation between fatigue and demographic characteristics, corpus callosum index value and laboratory data (hemoglobin, sedimentation, glucose, sodium, potassium, calcium, magnesium, TSH and vitamin B12) in MS patients were evaluated; a negative correlation was

Table 1. The demographic characteristics and biochemical data of patients with MS and controls

	Multiple sclerosis patients (n=58)	Control group (n=42)	p
Age (years)	39.5 (31–45)	35 (30.75–40.25)	0.071
Sex (female/male)	33/25	31/11	0.084
BMI (kg/m²)	24.75 (22.43–27.77)	23.82 (22.05–24.27)	0.088
Disease duration (years)	8 (4.75–12)	–	–
EDSS	1.75 (1–2.62)	–	–
Treatment duration (years)	3 (1–5)	–	–
Fatigue Severity Scale	5.26 (3.64–6.30)	–	–
Biochemical data			
Glucose (mg/dL)	90.65 (83.80–95.81)	85.82 (78.72–92.62)	0.055
Creatinine (mg/dL)	0.73 (0.65–0.79)	0.71 (0.66–0.76)	0.588
AST (U/L)	17.17 (13.67–19.82)	16 (13.15–17.42)	0.080
HDL (mg/dL)	50.1±11.27	52.2±12.07	0.374
LDL (mg/dL)	97.50 (76.37–122.81)	96.94 (78.62–107.80)	0.683
Cholesterol (mg/dL)	172.95 (145.65–202.45)	167.82 (149.67–181.85)	0.379
Triglycerides (mg/dL)	122.10 (73.75–166.02)	85.5 (61.42–101.07)	0.010
Sodium (mEg/L)	140 (139–141)	140 (139–141)	0.372
Potassium (mEg/L)	4.40 (4.2–4.61)	4.35 (4.09–4.55)	0.377
Calcium (mg/dL)	9.30 (9.1–9.54)	9.46 (9.30–9.60)	0.074
Magnesium (mg/dL)	1.98 (1.91–2.06)	1.98 (1.90–1.98)	0.325
Vitamin D (ng/ml)	17.98 (10.57–22.54)	17 (12.77–17)	0.444
Vitamin B12 (pq/mL)	332 (250.5–386)	323 (250–341.2)	0.333
Folate (ng/ml)	6.55 (5.39–7.94)	8.03 (6.3–9.22)	0.029
TSH (µIU/mL)	1.46 (0.96–1.99)	1.68 (0.96–2.23)	0.820
Radiological finding			
CCI	5.10 (4.05–5.80)	8 (7.20–8.45)	<0.001

MS: Multiple sclerosis; BMI: Body mass index; EDSS: Expanded disability status scale; AST: Aspartate aminotransferase; HDL: High density lipoprotein; LDL: Low density lipoprotein; TSH: Thyroid stimulating hormone; CCI: Corpus callosum index. Data are expressed as mean±standard deviation or median (25th, 75th percentile). Bold indicates statistically significant values (p<0.05).

found with CCI; there was a positive correlation with EDSS (p=0.033, r=-0.280 and p=0.001, r=0.421, respectively). When the relationship between fatigue and other data was evaluated, no significant correlation was found (p>0.05). Details are given in Table 2.

When MS patients with and without fatigue symptoms and the control group were evaluated as 3 groups, there was a difference between the three groups in terms of folate (p=0.011), when we look at the statistical analysis in terms of folate in the subgroups, p=0.028 in the groups of MS with and without fatigue, p=0.708 between the MS group without fatigue and the control group, and p=0.006 between the groups with fatigue and the control group. No difference was found in terms of other data (Table 3). The corpus callosum index measurements of the three groups are shown in Figure 1.

As shown in Table 4, when the fatigue level of MS patients and the distribution of drug treatments were evaluated, no relation was found between medications and fatigue (p (Fisher's exact test)=0.145). In the group with significant fatigue (FSS>4), it was observed that the patients received mostly interferon therapy (25.6%), and the second most frequently used treatment was fingolimod (17.9%).

DISCUSSION

The results of this study suggested that fatigue in MS patients was associated with a higher level of disability, corpus callosum atrophy, and a lower folate level. In addition,

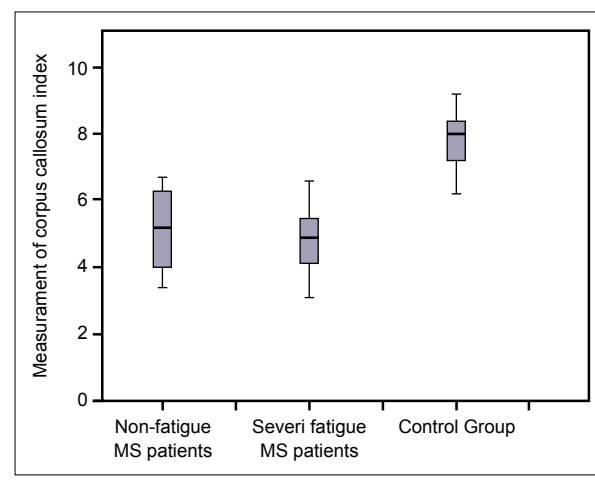

Figure 1. Box plot presentation of corpus callosum measurement in MS patients with and without fatigue symptoms and control group.

Table 2. The correlation of fatigue with disease characteristics, laboratory data and cospus callosum index value in patients with MS

	p	r/rho
Age (years)	0.818	0.031
Sex (female/male)	0.223	-0.162
BMI (kg/m^2)	0.271	0.147
Disease duration (years)	0.661	0.059
EDSS	0.003	0.389
Treatment duration (years)	0.948	-0.009
Glucose (mg/dL)	0.439	-0.104
HDL (mg/dL)*	0.508	-0.089
LDL (mg/dL)	0.085	0.228
Cholesterol (mg/dL)	0.089	0.225
Triglycerides (mg/dL)	0.424	0.107
Sodium (mEg/L)	0.991	0.001
Potassium (mEg/L)	0.562	0.078
Calcium (mg/dL)	0.721	-0.048
Magnesium (mg/dL)	0.519	0.086
Vitamin D (ng/ml)	0.622	0.066
Vitamin B12 (pq/mL)	0.337	0.160
Folate (ng/ml)	0.010	-0.334
TSH (µIU/mL)	0.712	0.049
Corpus callosum index	0.041	-0.269

*Data are presented as r value. Bold indicates statistically significant values (p<0.05). MS: Multiple sclerosis; BMI: Body mass index; EDSS: Expanded disability status scale; HDL: High density lipoprotein; LDL: Low density lipoprotein; TSH: Thyroid stimulating hormone.

triglyceride level was found higher in MS patients.

The relationship between fatigue, a subjective symptom in MS patients affecting the quality of life and the disability level of MS patients has been evaluated in many studies, and the results differ. While some studies have stated that fatigue is associated with disability,[18–20] this has not been confirmed in other studies.[21,22] In our study, we found a strong relationship between fatigue and disability. On the other hand, in a study with a large patient series, it was emphasized that the initial severe fatigue may be predictive for worsening of disability.[23]

In a recent study using multimodal MRI, it has been reported that fatigue in MS patients is associated with apparently normal diffuse white matter damage, not lesion load or gray matter atrophy. It has been suggested that functional disconnection caused by diffuse microstructural damage in white matter may be the main neural basis of fatigue in MS.[24] In our study, we detected corpus callosum atrophy evaluated by CCI measurement in MS patients. CCI measurement is a practical method that gives an idea about the whole brain volume of MS patients and shows a strong correlation with the total lesion load.[25] Similar to our finding, Yaldizli et al.[10] found that fatigue and corpus callosum atrophy are correlated. Furthermore, apart from fatigue, corpus callosum atrophy was also associated with cognitive dysfunction.[26]

One of the most important findings of our study is that the folate level is lower in MS patients, the fatigue increases as the folate level decreases, and the folate level is the lowest in MS patients with fatigue. Similar to our results,

Table 3. Demographic and laboratory values of MS patients with and without fatigue and controls

	MS patients without fatigue (n=19)	MS patients with fatigue (n=39)	Control group (n=42)	p
Age (years)	40 (30–44)	39 (31–46)	35 (30–40)	0.881
BMI (kg/m^2)	24.8 (21.8–27.6)	24.6 (22.4–28.1)	23.8 (22–24.2)	0.934
Glucose (mg/dL)	92.9 (84.2–99)	90.3 (83.2–95.7)	85.8 (78.7–92.6)	0.380
HDL (mg/dL)	50.39±10.77	49.96±11.65	52.20±12.07	0.892
LDL (mg/dL)	88.7 (69.2–124.0)	98.5 (83.1–119)	96.9 (78.6–107.8)	0.332
Cholesterol (mg/dL)	155.1 (137.8–199.6)	175.1 (155.3–203.8)	167.8 (149.6–181.8)	0.123
Triglycerides(mg/dL)	130 (59–134.3)	117.2 (74.4–171)	85.5 (61.4–101)	0.584
Sodium (mEg/L)	140(139–141)	140 (139–142)	140 (139–141)	0.519
Potassium (mEg/L)	4.30 (4–4.4)	4.40 (4.2–4.7)	4.35 (4–4.5)	0.208
Calcium (mEg/L)	9.2 (9.1–9.5)	9.3 (9.1–9.5)	9.4 (9.3–9.6)	0.590
Magnesium (mEg/L)	1.98 (1.89–2.19)	1.97 (1.92–2.06)	1.98 (1.9–1.98)	0.849
Vitamin D (ng/ml)	14 (9.6–22.2)	18.2 (13.2–23.1)	17 (12.7–17)	0.312
Vitamin B12(pq/mL)	334.4 (252–346)	331.2 (243–417)	323.1 (250–341.2)	0.545
Folate (ng/ml)	6.7 (6.3–8.6)	5.9 (5.2–6.7)	7.6 (6.3–8.9)	0.011[a]
TSH (µIU/mL)	1.78 (0.79–2.28)	1.40 (1.02–1.97)	1.68 (0.96–2.23)	0.842
CCI	5.2 (3.9–6.3)	4.9 (4.1–5.5)	8 (7.2–8.45)	0.158

Data are expressed as mean±standard deviation or median (25th, 75th percentile). Kruskal Wallis analysis is used. Bold indicates statistically significant values (p<0.05). [a]There was a significant difference between the groups without fatigue and the control group in the post–hoc comparison (p=0.006). MS: Multiple sclerosis; BMI: Body mass index; EDSS: Expanded disability status scale; HDL: High density lipoprotein; LDL: Low density lipoprotein; TSH: Thyroid stimulating hormone; CCI: Corpus callosum index.

Table 4. Distribution of drug treatments according to fatigue severity scale cut of value

Drugs	MS Patients (n=58)	Fatigue Severity Scale		Total
		Non-fatigue patients (n=19)	Severe-fatigue patients (n=39)	
None	Count, n (%)	2 (50)	2 (50)	4
	Within groups (%)	10.5	5.1	6.9
Interferons	Count, n (%)	7 (41.2)	10 (58.8)	17
	Within groups (%)	36.8	25.6	29.8
Glatiramer Asetat	Count, n (%)	4 (40)	6 (60)	10
	Within groups (%)	21.1	15.4	17.2
Dimetil Fumarat	Count, n (%)	1 (25)	3 (75)	4
	Within groups (%)	5.3	7.7	6.9
Teriflunomid	Count, n (%)	1 (14.3)	6 (85.7)	7
	Within groups (%)	5.3	15.4	12.1
Fingolimod	Count, n (%)	4 (36.4)	7 (63.6)	11
	Within groups (%)	21.1	17.9	19
Ocrelizumab	Count, n (%)	0 (0)	3 (100)	3
	Within groups (%)	0	7.7	5.2
Natalizumab	Count, n (%)	0 (0)	2 (100)	2
	Within groups (%)	0	5.1	3.4

P (Fisher's exact test) = 0.145. MS: Multiple sclerosis.

in a study, it was found that the folate level was lower in MS patients; however in their meta-analysis, Zhu et al.[28] did not find any difference in folate levels between MS patients and control groups.[27] In a recent meta-analysis, it was reported that there was no difference in folate levels in the patient and the control groups.[29] This may be related to our patients' nutritional habits. Further studies with larger patient series evaluating homocysteine levels as well can provide additional information.Another finding of this study is that only triglyceride levels are higher among lipid markers in MS patients. Triglyceride metabolism pathways have been shown to interact with the immune system.[30,31] Triglyceride increases the expression of antigen markers on the surface of leukocytes, thereby triggering inflammation.[32] Andersen ve Vance[33] suggested that high triglyceride levels mean increased leukocyte profiles and that lipid-lowering intervention may exert beneficial anti-inflammatory and immunomodulatory effects. In a study evaluating 492 MS patients, it was suggested that high triglycerides in MS patients had a negative effect on the course of the disease.[34] In their study, Pinhas-Hamiel et al.[35] found that 28.8% of patients have high triglyceride levels, although the BMI value of adult MS patients is lower than the normal population. We did not detect any relationship between fatigue and lipid parameters. Yadav and colleagues have shown that a very low-fat, plant-based diet reduced fatigue in patients with RRMS.[36] The results of a diet-based longitudinal study suggested that lipid biomarkers, especially total cholesterol and HDL, contribute to the development of fatigue.[37]

In a study, similar to our findings, no relationship was found between vitamin D levels and fatigue in MS patients.[38] Fatigue in the clinical isolated syndrome stage was evaluated as an independent predictive factor for the diagnosis of MS.[39] Interestingly, we did not find any difference in vitamin D between the groups. This may be due to the current awareness of both physicians and patients about vitamin D and the treatment of deficiencies with replacement. On the other hand, it has been shown that increasing the levels of vitamin D in the general population does not have a clinically significant effect on fatigue symptoms.[40] In a recent review, it was reported that Magnesium (Mg) deficiency has an impact on immune system functions.[41] In a post-mortem study of definitive MS patients, Yasui et al.[42] took samples from various parts of the central nervous system and found that patients with MS have a lower Mg level and the tissue with the lowest Mg level is demyelinated plaques in white matter. It has been suggested that there is an increase in axonal calcium levels in neuroinflammatory lesions,[43,44] and accumulation of cytoplasmic calcium predicts axonal degeneration.[45] Although magnesium and calcium have a role in inflammation at the cellular level, no difference was found between the groups in terms of electrolytes measured by routine biochemical tests such as calcium, magnesium, sodium and potassium. The most important limitation of the study is the low sample size. A second limitation is that MS patients with relapsing-remitting and progressive forms were included in the study. Further studies comparing larger patient series with equalized groups of progressive and relapsing-remitting forms or medication groups for which these patients could provide more detailed information. It should also be noted that we did not evaluate sleep disorders, which are common in MS or overlap with fatigue in our patients.

CONCLUSION

Our results suggest that fatigue in MS patients is associated with corpus callosum atrophy, a higher level of disability, and a lower folate levels. Even if the folate level is above the specified lower limit in MS patients, folate replacement may reduce fatigue because it is a water-soluble vitamin. Confirming these findings with larger patient series will contribute to a better understanding of fatigue in MS disease and the relationship between fatigue and folate.

Ethics Committee Approval

This study approved by the Yozgat Bozok University Faculty of Medicine Clinical Research Ethics Committee (Date: 19.05.2020, Decision No: 2020-04-73).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: T.A., H.S., M.E.; Design: T.A., H.S., M.E.; Supervision: T.A., H.S., M.E.; Materials: T.A., H.S., M.E.; Data: T.A., H.S., M.E.; Analysis: T.A., H.S.; Literature search: T.A., H.S.; Writing: T.A., H.S., M.E.; Critical revision: T.A., H.S., M.E.

Conflict of Interest

None declared.

REFERENCES

1. Lerdal A, Celius EG, Krupp L, Dahl AA. A prospective study of patterns of fatigue in multiple sclerosis. Eur J Neurol 2007;14:1338–43.
2. Chaudhuri A, Behan PO. Fatigue in neurological disorders. Lancet 2004;363:978–88. [CrossRef]
3. Heesen C, Nawrath L, Reich C, Bauer N, Schulz KH, Gold SM. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? J Neurol Neurosurg Psychiatry 2006;77:34–9. [CrossRef]
4. Hautecoeur P, Forzy G, Gallois P, Demirbilek V, Feugas O. Variations of IL2, IL6, TNF alpha plasmatic levels in relapsing remitting multiple sclerosis. Acta Neurol Belg 1997;97:240–3.
5. Gottschalk M, Kümpfel T, Flachenecker P, Uhr M, Trenkwalder C, Holsboer F, et al. Fatigue and regulation of the hypothalamo-pituitary-adrenal axis in multiple sclerosis. Arch Neurol 2005;62:277–80. [CrossRef]
6. De Stefano N, Narayanan S, Francis GS, Arnaoutelis R, Tartaglia MC, Antel JP, et al. Evidence of axonal damage in the early stages of multiple sclerosis and its relevance to disability. Arch Neurol 2001;58:65–70. [CrossRef]
7. Garner DJ, Widrick JJ. Cross-bridge mechanisms of muscle weakness in multiple sclerosis. Muscle Nerve 2003;27:456–64. [CrossRef]
8. Evangelou N, Konz D, Esiri MM, Smith S, Palace J, Matthews PM. Regional axonal loss in the corpus callosum correlates with cerebral white matter lesion volume and distribution in multiple sclerosis. Brain 2000;123:1845–9. [CrossRef]
9. Mitchell TN, Free SL, Merschhemke M, Lemieux L, Sisodiya SM, Shorvon SD. Reliable callosal measurement: population normative data confirm sex-related differences. AJNR Am J Neuroradiol 2003;24:410–8.
10. Yaldizli Ö, Glassl S, Sturm D, Papadopoulou A, Gass A, Tettenborn B, et al. Fatigue and progression of corpus callosum atrophy in multiple sclerosis. J Neurol 2011;258:2199–205. [CrossRef]
11. Figueira FF, Santos VS, Figueira GM, Silva AC. Corpus callosum index: a practical method for long-term follow-up in multiple sclerosis. Arq Neuropsiquiatr 2007;65:931–5. [CrossRef]
12. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011;69:292–302. [CrossRef]
13. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444–52.
14. Armutlu K, Korkmaz NC, Keser I, Sumbuloglu V, Akbiyik DI, Guney Z, et al. The validity and reliability of the Fatigue Severity Scale in Turkish multiple sclerosis patients. Int J Rehabil Res 2007;30:81–5.
15. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121–3. [CrossRef]
16. Pilutti LA, Greenlee TA, Motl RW, Nickrent MS, Petruzzello SJ. Effects of exercise training on fatigue in multiple sclerosis: a meta-analysis. Psychosom Med 2013;75:575–80.
17. Yaldizli O, Atefy R, Gass A, Sturm D, Glassl S, Tettenborn B, et al. Corpus callosum index and long-term disability in multiple sclerosis patients. J Neurol 2010;257:1256–64. [CrossRef]
18. Pittion-Vouyovitch S, Debouverie M, Guillemin F, Vandenberghe N, Anxionnat R, Vespignani H. Fatigue in multiple sclerosis is related to disability, depression and quality of life. J Neurol Sci 2006;243:39–45.
19. Kroencke DC, Lynch SG, Denney DR. Fatigue in multiple sclerosis: relationship to depression, disability, and disease pattern. Mult Scler 2000;6:131–6.
20. Schreurs KM, de Ridder DT, Bensing JM. Fatigue in multiple sclerosis: reciprocal relationships with physical disabilities and depression. J Psychosom Res 2002;53:775–81. [CrossRef]
21. Bakshi R, Shaikh ZA, Miletich RS, Czarnecki D, Dmochowski J, Henschel K, et al. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. Mult Scler 2000;6:181–5.
22. Kos D, Kerckhofs E, Nagels G, D'Hooghe BD, Duquet W, Duportail M, et al. Assessing fatigue in multiple sclerosis: Dutch modified fatigue impact scale. Acta Neurol Belg 2003;103:185–91.
23. Vaughn CB, Kavak KS, Dwyer MG, Bushra A, Nadeem M, Cookfair DL, et al; New York State Multiple Sclerosis Consortium. Fatigue at enrollment predicts EDSS worsening in the New York State Multiple Sclerosis Consortium. Mult Scler 2020;26:99–108. [CrossRef]
24. Novo AM, Batista S, Alves C, d'Almeida OC, Marques IB, Macário C, et al. The neural basis of fatigue in multiple sclerosis: A multimodal MRI approach. Neurol Clin Pract 2018;8:492–500. [CrossRef]
25. Gonçalves LI, Dos Passos GR, Conzatti LP, Burger JLP, Tomasi GH, Zandoná MÉ, et al. Correlation between the corpus callosum index and brain atrophy, lesion load, and cognitive dysfunction in multiple sclerosis. Mult Scler Relat Disord 2018;20:154–8. [CrossRef]
26. Yaldizli Ö, Penner IK, Frontzek K, Naegelin Y, Amann M, Papadopoulou A, et al. The relationship between total and regional corpus callosum atrophy, cognitive impairment and fatigue in multiple sclerosis patients. Mult Scler 2014;20:356–64. [CrossRef]
27. Moghaddasi M, Mamarabadi M, Mohebi N, Razjouyan H, Aghaei M. Homocysteine, vitamin B12 and folate levels in Iranian patients with Multiple Sclerosis: a case control study. Clin Neurol Neurosurg 2013;115:1802–5.
28. Zhu Y, He ZY, Liu HN. Meta-analysis of the relationship between homocysteine, vitamin B_{12}, folate, and multiple sclerosis. J Clin Neurosci 2011;18:933–8. [CrossRef]
29. Dardiotis E, Arseniou S, Sokratous M, Tsouris Z, Siokas V, Mentis

AA, et al. Vitamin B12, folate, and homocysteine levels and multiple sclerosis: A meta-analysis. Mult Scler Relat Disord 2017;17:190–7.
30. Andersen CJ, Murphy KE, Fernandez ML. Impact of obesity and metabolic syndrome on immunity. Adv Nutr 2016;7:66–75.
31. Calder PC. The relationship between the fatty acid composition of immune cells and their function. Prostaglandins Leukot Essent Fatty Acids 2008;79:101–8. [CrossRef]
32. Alipour A, van Oostrom AJ, Izraeljan A, Verseyden C, Collins JM, Frayn KN, et al. Leukocyte activation by triglyceride-rich lipoproteins. Arterioscler Thromb Vasc Biol 2008;28:792–7. [CrossRef]
33. Andersen CJ, Vance TM. Gender dictates the relationship between serum lipids and leukocyte counts in the national health and nutrition examination survey 1999-2004. J Clin Med 2019;8:365. [CrossRef]
34. Weinstock-Guttman B, Zivadinov R, Mahfooz N, Carl E, Drake A, Schneider J, et al. Serum lipid profiles are associated with disability and MRI outcomes in multiple sclerosis. J neuroinflammation 2011;8:127.
35. Pinhas-Hamiel O, Livne M, Harari G, Achiron A. Prevalence of overweight, obesity and metabolic syndrome components in multiple sclerosis patients with significant disability. Eur J Neurol 2015;22:1275–9. [CrossRef]
36. Yadav V, Marracci G, Kim E, Spain R, Cameron M, Overs S, Riddehough A, et al. Low-fat, plant-based diet in multiple sclerosis: A randomized controlled trial. Mult Scler Relat Disord 2016;9:80–90.
37. Fellows Maxwell K, Wahls T, Browne RW, Rubenstein L, Bisht B, Chenard CA, et al. Lipid profile is associated with decreased fatigue in individuals with progressive multiple sclerosis following a diet-based intervention: Results from a pilot study. PLoS One 2019;14:e0218075. [CrossRef]
38. Knippenberg S, Bol Y, Damoiseaux J, Hupperts R, Smolders J. Vitamin D status in patients with MS is negatively correlated with depression, but not with fatigue. Acta Neurol Scand 2011;124:171–5.
39. Runia TF, Jafari N, Siepman DA, Hintzen RQ. Fatigue at time of CIS is an independent predictor of a subsequent diagnosis of multiple sclerosis. J Neurol Neurosurg Psychiatry 2015;86:543–6. [CrossRef]
40. Havdahl A, Mitchell R, Paternoster L, Davey Smith G. Investigating causality in the association between vitamin D status and self-reported tiredness. Sci Rep 2019;9:2880.
41. Shahi A, Aslani S, Ataollahi M, Mahmoudi M. The role of magnesium in different inflammatory diseases. Inflammopharmacology 2019;27:649–61. [CrossRef]
42. Yasui M, Yase Y, Ando K, Adachi K, Mukoyama M, Ohsugi K. Magnesium concentration in brains from multiple sclerosis patients. Acta Neurol Scand 1990;81:197–200. [CrossRef]
43. Siffrin V, Radbruch H, Glumm R, Niesner R, Paterka M, Herz J, et al. In vivo imaging of partially reversible th17 cell-induced neuronal dysfunction in the course of encephalomyelitis. Immunity 2010;33:424–36.
44. Mossakowski AA, Pohlan J, Bremer D, Lindquist R, Millward JM, Bock M, et al. Tracking CNS and systemic sources of oxidative stress during the course of chronic neuroinflammation. Acta Neuropathol 2015;130:799–814.
45. Witte ME, Schumacher AM, Mahler CF, Bewersdorf JP, Lehmitz J, Scheiter A, et al. Calcium influx through plasma-membrane nanoruptures drives axon degeneration in a model of multiple sclerosis. Neuron 2019;101:615–24.e5. [CrossRef]

Multipl Skleroz Hastalarında Yorgunluğun Biyokimyasal Veriler ve Korpus Kallosum Atrofisi İle Değerlendirilmesi

Amaç: Multipl skleroz (MS) hastalarında yorgunluk etyopatogenezi tam aydınlatılamamış sık görülen bir bulgudur. Bu çalışmada yorgunluğun biyokimyasal veriler ve beyin manyetik rezonans (MR) görüntülemede korpus kallosum indeksi (CCI) ile ilişkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Kesitsel özellikte olan bu çalışmaya 58 MS hastası, 42 kontrol olmak üzere 100 kişi dahil edildi. Hastaların özürlülüğü genişletilmiş özürlülük durum ölçeği (EDSS) ile belirlendi ve yorgunlukları Fatigue Severity Scale (FSS) ile değerlendirildi. Biyokimyasal veriler analiz edildi. Beyin MR'da CCI değerleri hesaplandı.

Bulgular: Gruplar arasında yaş, cinsiyet, vücut kitle indeksi açısından farklılık tespit edilmedi ($p>0.05$). MS hastalarında kontrol grubuna göre folat düzeyi ve CCI değeri istatistiksel olarak anlamlı derecede düşük saptandı (sırasıyla $p=0.029$ ve $p<0.001$). MS grubunda trigliserit değerinin anlamlı derecede yüksek olduğu gözlendi, gruplar arasında diğer biyokimyasal veriler açısından anlamlı farklılık yoktu. MS grubunda yorgunluk ile EDSS arasında pozitif korelasyon, korpus kallosum indeks ve folat değeri arasında ise negatif korelasyon olduğu belirlendi. Yorgunluk ile diğer veriler arasında anlamlı korelasyon saptanmadı. Yorgunluğu olan ve olmayan MS hastaları ve kontrol grubu karşılaştırıldığında ise gruplar arasında sadece folat açısından farklılık olduğu tespit edildi ($p=0.011$).

Sonuç: Sonuçlarımız MS hastalarında yorgunluğun; daha belirgin korpus kallosum atrofisi, daha ileri özürlülük seviyesi ve daha düşük folat düzeyi ile ilişkili olduğunu göstermektedir. MS hastalarında belirlenmiş alt sınırın üstünde bile olsa folat replasmanı yorgunluğu azaltabilir. Bu bulguların daha geniş hasta serileri ile doğrulanması MS hastalığındaki yorgunluğun ve yorgunluk ile folat ilişkisinin daha iyi anlaşılmasına katkı sağlayacaktır.

Anahtar Sözcükler: Folat; korpus kallosum atrofi; korpus kallosum indeks; multipl skleroz; trigliserit; yorgunluk.