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Inflammation and Oxidative Stress are Related with Fatigue and Depression among Multiple Sclerosis Patients during Clinical Remission?

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Abstract

Background and aim: Multiple sclerosis (MS) is a chronic inflammatory disease accompanied with lower quality of life due to disabling symptoms such as depression and fatigue. The pathologic basis of such symptoms is still unknown. This study was performed to assess pro-inflammatory and anti-inflammatory cytokine levels as well as oxidative stress (OS) biomarkers in MS patients with and without fatigue and depression in the remission course of disease.

Material and methods: Forty eight patients with a definite diagnosis of relapsing –remitting MS were studied. All the patients have not experienced relapses at least for 6 months. We scored Expanded Disability Status Scale (EDSS) as well as the Beck depression inventory (BDI) questionnaire and Fatigue severity scale (FSS) to assess depression-related symptoms and fatigue severity in the participants, respectively. Furthermore, we analyzed fasting blood samples to determine serum TNF- α , IL-4, IL-6, TGF- β , INF- γ and MMP-9 levels as well as OS parameters including serum superoxide dismutase (SOD) and glutathione peroxidase (GPx) activity, total antioxidant capacity (TAC) and malondialdehyde (MDA).

Results: No significant differences were observed in the levels of inflammatory and OS biomarkers in depressed and non-depressed MS patients. The same was noted for fatigued and non-fatigued patients. However, the EDSS score for fatigued and depressed patients was higher than the control group.

Conclusion: Our study results indicated that the activation of inflammatory pass ways or OS stress cannot be regarded as the primary cause of depression and fatigue in MS patients with mild disability. This is the first report to assess the primary pathogenesis of fatigue and depression in MS patients.

Keywords: Multiple sclerosis; Fatigue; Depression; Cytokines; Oxidative stress biomarkers

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease which is associated with disabling symptoms and lower quality of life in the affected patients. The most apparent source of disability in MS patients is physical impact of the disease. However, the mental consequences of the disease which have frequently been neglected are also important [1]. Depression, as a main determinant of quality of life, is a common symptom in MS patients. Depression can affect the relationships and patients' adaption with disease modifying treatments [2].

MS related depression feeds back to changes in neuroimmunology, neurophsycology, neurocytology aspects of disease and possibly to other variables as well, including fatigue, cognitive dysfunction, pain, social support, psychosocial factors, negative life events and stress [3].

The mechanisms responsible for the increased prevalence of depression in MS patients are subject to debate and controversy [4]. Smith et al. has suggested the macrophage theory of depression [5] which explains the excessive level of inflammatory mediators as a probable mechanism for depression in these patients. It's also proposed that inflammatory cytokines play a role in the development of depression through different pass ways such as monoamine metabolism, neuroendocrine function, synaptic plasticity, and neurocircuits relevant to mood regulation [6,7].

Based on this hypothesis, in patients with systemic inflammatory diseases, peripherally released cytokines can affect the brain and induce mental disorders such as sleep disturbances, fatigue, anxiety, and social withdrawal maybe appeared [7-9]. Similarly, elevated levels of inflammatory cytokines as well as soluble receptors of these agents have been detected in peripheral blood and cerebrospinal fluid (CFS) of major depressive patients [7]. Therefore, the probable role of cytokines such as interleukin (IL)-6, tumor necrosis factor (TNF)- α , and interferon (IFN)- γ in demyelination and axonal damage may explain the increased prevalence of depression in MS patients [10,11].

In MS patients, fatigue can either be primary and may result from disease specific processes such as demyelination and axonal loss in the central nervous system or immune actions. The secondary fatigue may also be the consequence of peripheral mechanisms at muscle level. Other factors that may lead to fatigue include sleep problems, lower activity, depression, psychological disorders, pain, and medication use [12].

In addition, most of the MS patients complain of fatigue, as another disabling symptom. The altered levels of pro-inflammatory and antiinflammatory cytokines are reported as complications of chronic fatigue syndrome, sleep apnea, glucocorticoid withdrawal syndrome, and depression, while the pathological basis for fatigue in MS patients is still unclear.

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In addition to the inflammatory basis of these symptoms, there is emerging evidence representing the oxidative stress (OS) as the main mechanism for the development of fatigue and depression in this disease [13]. OS via activation of microglial in neurodegenerative disease such as Alzheimer, Parkinson disease, stroke and MS can explain the cooccurrence of fatigue with depression in the patients [14].

Fatigue and depression can both be potentially due to treatment or reactivation of immune system, so the primary cause of these symptoms is difficult to examine. One of the solutions to overcome this problem is to investigate the patients in remission course of disease.

So this study aimed to assess pro-inflammatory and antiinflammatory cytokine levels as well as OS biomarkers in MS patients with and without fatigue and depression during the remission. We hypothesized that biomarkers related to inflammation and OS would be significantly higher in the serum blood flow of MS patients with depression and fatigue.

Methods and Materials

Subjects and study design

Forty-eight patients with definite diagnosis of MS, according to McDonalds et al.'s criteria and relapsing-remitting course, were recruited from MS clinic at Sina Hospital in Tehran.

For all the participants, Expanded Disability Status Scale (EDSS) scores [15] were rated by an expert neurologist in our outpatient clinic. Patients with ongoing clinical relapse, pregnancy and lactation were excluded. Other criteria for exclusion were the use of corticosteroid agents, occurrence of relapses during the study within the past 4 weeks, MS diagnosed for less than 1 year and current smoking. Additionally, those with regular intake of antioxidants, vitamin supplements, antidepressants, or fatigue modulating drugs didn't include from the study. All patients signed an informed consent form before the commencement of the study. Furthermore, the protocol of the study was approved by the medical ethics committee of Tehran University of medical sciences.

Anthropometric assessment

We asked the patients to barefoot and wear light clothing. They stood straight on the electronic weighing scale, and the weight on the screen was recorded. Weight was assessed by Seca Electronic Weighting Scale (Seca, Hamburg, Germany) to the nearest 100 g. Height was recorded using a non-stretchable tape to the nearest 0.1 cm. Body mass index (BMI) was determined by dividing the weight (kg) by the square of height (m²).

Fatigue assessment

Patients with lack of physical or mental energy or a feeling of tiredness were considered as fatigue. Fatigue severity scale (FSS) which is known as a valid scale in MS was used to assess fatigue severity in the patients. FSS consists of nine items with scores on a seven-point scale from one (strongly disagree) to seven (strongly agree). Higher scores indicate more severe fatigue. The overall score is the mean of the scores of the nine items. Patients with FSS mean scores \geq 5 were allocated to the "Fatigue" group, while those with FSS scores <5 were allocated to the "No fatigue" group.

Depression assessment

The Beck depression inventory (BDI) which consists of 21 questions with 4 statements describing depression-related symptoms (self-rated

from 0 (absent) to 3 (severe)) was used to evaluate depressive symptoms. Patients choose the one statement of each question that describes how they have felt during the "past week up to today" in the best way. The score ranges is 0–63 with higher scores indicating higher intensity. A BDI score ≥ 10 was used to confirm the presence of elevated depression symptoms, indicating likely mild or greater depression [16].

Blood sample collection and biochemical analyses

Fasting blood samples (8 mL) were collected from all the patients in seated position, according to the standard protocol. Serum TNF- α , IL-4, IL-6, TGF- β , INF- γ and MMP-9 were determined using the enzymelinked immune-sorbent (ELISA) assay kit (R&D Systems, USA). OS parameters including serum superoxide dismutase (SOD) and glutathione peroxidase (GPx) activity and total antioxidant capacity (TAC) as well as malondialdehyde (MDA) were measured. Serum SOD and GPx activity were assessed by a kit (Caymon chemical Co., MI, and USA) with a good absorbance at 340 nm wavelength. MDA and TAC levels were analyzed using high-performance liquid chromatography based on Steghens method [17] at 254 nm and modified Wang method [18] at 290 nm absorption wavelength, respectively.

Statistical Analyses

Data were analyzed using version 16.0 of SPSS on a personal computer (SPSS Inc., Chicago, IL, USA). We used Student's t-test, chi-square, and Fisher's exact test for groups' differences regarding to demographic and disease related variables when appropriate. Logtransformed values of inflammatory and oxidative stress biomarkers were used to arrange normally distributed variables. Pearson correlation was applied for detecting association between Log-transformed levels of inflammatory and OS biomarkers with fatigue and depression severity as continuous variables. Furthermore, age, BMI, duration of disease, disease severity (EDSS) included as controlled covariates in correlation analyses. Finally, Multivariate logistic regression analyses were used to assess the association between depression and fatigue with high versus low levels of inflammation and OS biomarkers. Odds ratios (ORs) and 95% confidence intervals (CIs) tended to show an association.

Results

The mean age, BMI and EDSS of patients were 32.11 ± 7.8 years, 23.8 ± 4.1 kg/m² and 1.96 ± 1.18 respectively. The 75% of MS patients were fatigued and 65% were depressed. As presented in Table 1, fatigue and depression status did not have significant difference by age, gender, BMI and EDSS. We found that fatigued patients had a higher level of fatigue severity (FSS) (P=0.001) either depression severity (BDI) (P=0.01) compared to non- fatigued patients. Similarly, depressed MS patients had higher levels of FSS (0.02) and BDI (0.001) scores comparing with non-depressed patients.

While, the log-transformed of inflammatory and OS markers were compared with fatigue and depression status in Table 2, no significant difference was observed. The association between inflammation and OS biomarkers with FSS and BDI was determined by the Pearson correlation coefficient in Table 3. As shown, before controlling covariates, we observed significant correlation between TGF level and fatigue severity. We found no significant correlation after controlling for covariates.

We used logistic regression analyses to calculate the OR of fatigue and depression for high (above 75th population percentile level) versus low (below 25th population percentile level) plasma levels of inflammatory markers after adjustment for age, BMI, disease Citation: Khalili M, Aliasgharzadeh F, Izadi A, Azimi A, Seifar F (2016) Inflammation and Oxidative Stress are Related with Fatigue and Depression among Multiple Sclerosis Patients during Clinical Remission? J Depress Anxiety S1: 019. doi:10.4172/2167-1044.S1-019

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Variable [*] (n=11)	Non-Fatigue	Fatigue (n=33)	Р	Non-depressed (n=15)	Depressed (n=29)	Р
Age (years)	30.3 ± 7.4	32.6 ± 7.9	0.38	34.9 ± 7.6	30.6 ± 7.6	0.08
Gender: n (%)			0.24		0.32	
Male	36.3	33.2		46.6	41.3	
Female	63.7	62.7		53.4	58.7	
BMI (kg/m ²)	23.9 ± 4.5	23.8 ± 4.1	0.34	24.6 ± 3.9	23.4 ± 4.2	0.38
EDSS	1.5 ± 1.1	2.1 ± 1.2	0.63	1.8 ± 1.3	2 ± 1.1	0.17
FSS	2.9 ± 0.71	5.3 ± 1.02	0.001	3.9 ± 1.2	5.1 ± 1.1	0.02
BDI	10.3 ± 8.4	18.5 ± 0.1	0.01	7.3 ± 2.6	21.2 ± 9.3	0.001

Note: 'Data presented as mean ± standard deviation

BDI: Beck Depression Inventory; EDSS: Expanded Disability Status Scale; FSS: Fatigue severity scale.

P values obtained from Independent t-test.

Table 1: Demographic and clinical characteristics of multiple sclerosis patients.

	Fatigue groups			Depression groups		
Log of biomarkers	Non-fatigue	Fatigue	- P -	Non-depressed	Depressed	P
IL-4 (pg/ml)	0.94 ± 0.59	0.96 ± 0.55	0.91	0.78 ± 0.28	0.96 ± 0.55	0.11
IL-6 (pg/ml)	0.37 ± 0.54	0.37 ± 0.81	0.92	0.31 ± 0.76	0.37 ± 0.81	0.73
TNF-α (pg/ml)	0.81 ± 0.06	0.71 ± 0.06	0.21	0.79 ± 0.06	0.71 ± 0.06	0.62
TGF-β (pg/ml)	4.12 ± 0.32	4.21 ± 0.27	0.15	4.21 ± 0.27	4.21 ± 0.27	0.64
MMP-9 (ng/ml)	1.91 ± 0.08	1.91 ± 0.08	0.61	1.91 ± 0.08	1.91 ± 0.08	0.71
SOD (mmol/min/L)	2.21 ± 0.08	2.42 ± 0.11	0.83	2.21 ± 0.08	2.22 ± 0.08	0.82
GPx (mmol/min/L)	2.41 ± 0.11	2.42 ± 0.11	0.62	2.41 ± 0.11	2.42 ± 0.12	0.32
MDA (mmol/L)	0.28 ± 0.12	0.28 ± 0.11	0.22	0.29 ± 0.14	0.27 ± 0.07	0.63
TAC (mmol/L)	3.34 ± 0.06	3.33 ± 0.06	0.13	3.36 ± 0.07	3.34 ± 0.06	0.33

Note: P values obtained from Independent t-test.

Table 2: Inflammatory and antioxidant biomarkers differences between fatigue and depression categorized groups.

I am of his monthana	FSS				BID			
Log of biomarkers	Crude (r)	Р	Controlled (r†)	Р	Crude (r)	Р	Adjusted (r†)	Р
IL-4 (pg/ml)	-0.02	0.91	0.05	0.71	0.18	0.31	0.27	0.08
IL-6 (pg/ml)	0.11	0.53	0.03	0.83	0.12	0.46	0.59	0.08
TNF-α (pg/ml)	-0.23	0.16	-0.15	0.34	-0.18	0.27	-0.18	0.25
TGF-β (pg/ml)	0.29	0.04	0.26	0.06	0.01	0.91	-0.05	0.75
MMP-9 (ng/ml)	0.21	0.20	0.21	0.18	-0.09	0.61	0.02	0.85
SOD (mmol/min/L)	0.01	0.93	-0.10	0.49	0.06	0.75	-0.03	0.86
GPx (mmol/min/L)	-0.11	0.59	-0.24	0.12	-0.07	0.68	-0.17	0.28
MDA (mmol/L)	-0.23	0.19	-0.14	0.35	-0.09	0.61	-0.16	0.31
TAC (mmol/L)	-0.17	0.30	-0.20	0.19	-0.16	0.39	-0.18	0.91

⁺Age, BMI, duration of disease and EDSS considered as controlled covariates.

Table 3: Pearson correlation coefficients (r) of FSS and BID scores with log 10 transformed oxidative stress and inflammatory biomarkers in MS patients.

duration and EDSS (Table 4). Even the level of IL-6 didn't significantly associate with fatigue severity score (95% CI=1.18-10.1, p=0.08). The other markers related to inflammation and OS showed no significant changed risk of depression and fatigue.

Discussion and Conclusion

In this study, we investigated the relation between MS related fatigue and depression with inflammation and oxidative stress.

The comparison of the serum cytokine levels and OS biomarkers of the patients with depression and fatigue with those non- depressed patients with low fatigue scores showed only small, non-significant differences.

It has been proposed that the inflammatory process plays an essential role on the pathological basis of MS related symptoms. Several studies have shown an imbalance in inflammatory factors and increased levels of serum pro-inflammatory cytokines during a relapse in patients with severe fatigue. It can be primary which is due to inflammation, demyelination, and/or axonal loss or secondary which may be occur as a result of sleep disorders, spasm, and/or depression. Moreover, fatigue can be regarded as a side effect of immune-modulatory medications such as beta interferon.

In our study, we couldn't find higher levels of OS or inflammatory biomarkers in patients suffering from severe fatigue, while a significant correlation observed between log-transformed TGF levels and FSS score. Similar findings have also been reported in the literature [19,20]. Interestingly, Kennedy et al. have shown an increased concentration of active TGF-b levels in MS patients with Chronic fatigue syndrome (CFS) suggesting the probable role of TGF-b in the detectable abnormality of immune cells [20].

In contrast, Giovannoni et al. did not find any correlations between fatigue scores and inflammatory markers including urinary neopterin, CRP, and sICAM-1 levels [21] which were also confirmed by our results.

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Biomarkers	OR of fatigue (95% CI)	P	OR of depression (95% CI)	Р	
IL-4 (pg/ml)		0.43		0.60	
Low < 0.6	1		1		
High > 1.26	0.42 (0.06-3.16)		1.71 (0.21-13.4)		
IL-6 (pg/ml)		0.08		0.46	
Low < -1	1		1		
High > 0.34	1.31 (1.18-10.1)		0.52 (0.12-2.83)		
TNF-α (pg/ml)		0.91		0.85	
Low < 074	1		1		
High > 0.83	1.01 (0.1-9.2)		1.2 (0.16-8.79)		
TGF-β (pg/ml)		0.10		0.88	
Low < 3.94	1		1		
High > 4.36	1.61 (0.7-35.4)		0.85 (0.11-6.61)		
MMP-9 (ng/ml)		0.74		0.67	
Low < 1.88	1		1		
High > 1.99	1.35 (0.16-12.7)		1.5 (0.22-10.07)		
SOD (mmol/min/L)		0.28		0.46	
Low < 2.21	1		1		
High > 2.31	0.81 (0.5-9.9)		1.7 (0.39-7.79)		
GPx (mmol/min/L)		0.88		0.61	
Low < 2.34	1		1		
High > 2.52	0.85 (0.13-5.5)		0.58 (0.07-4.3)		
MDA (mmol/ L)		0.75		0.27	
Low < 0.24	1		1		
High > 0.33	0.75 (0.12-4.6)		0.34 (0.04-2.45)		
TAC (mmol /L)		0.12		0.17	
Low < 3.30	1		1		
High > 3.40	0.25 (0.04-1.45)		0.33 (0.06-1.65)		

Table 4: Risk of fatigue and depression associated with high levels of inflammatory and oxidative stress biomarkers.

Up to now, few reports have demonstrated the effect of inflammatory cytokines and OS in depressive MS patients. Some studies showed that the levels of pro-inflammatory cytokines in the patients with severe depression are significantly higher than the healthy subjects [22]. Two mechanisms are proposed in this regard: 1) Pro-inflammatory cytokines cause serotonin degrading enzymes activation resulting in decrements in tryptophan and serotonin levels which may lead to depression and 2) Reduction of hypothalamic-pituitary-adrenal (HPA) activity which may lead to misbalance of neural hormones [23].

On the other hand, Taraz et al. did not find any significant increase in pro-inflammatory cytokines in depressed patients compared to control subjects. So it's to say that, during the remission course of MS, inflammatory mechanisms and OS cannot be accounted as the major cause of depression and fatigue in these patients.

We have some limitation. First, we did not include MS patients in remission course as well as healthy group for comparing considered variables between groups. The second, our study is a cross sectional study and cannot represent causality relationship.

The strength of this pathophysiological study was that we focused on MS-related fatigue and depression during the remission course of MS. This is the first study that evaluates the role of inflammation and OS in the pathogenesis of depression and fatigue in remitted MS patients. It allowed us to assess primary depression- related and fatigue-associated factors and thus gain insight into the pathophysiological mechanisms affecting primary fatigue and depression.

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