Original Article

Is there an association between the Expanded Disability Status Scale and inflammatory markers in multiple sclerosis?

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Abstract

Background: Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease characterized by inflammation of white matter in the central nervous system. It has been indicated that this inflammation causes increased levels of proinflammatory cytokines. Therefore, we aimed to evaluate if there is a possible association between inflammatory markers and the Expanded Disability Status Scale (EDSS) score in patients with MS.

Methods: We reviewed the data of 127 patients (91 women and 36 men) who were retrospectively diagnosed as MS according to the revised Mc Donald's criteria who were seen at our facility between January 2007 and December 2012. Patients were divided into two groups according to EDSS score: Group 1, EDSS < 5; and Group 2, EDSS ≥ 5. The risk factors that were evaluated included age and sex of the patients, duration of MS, drugs, thyroid function tests, vitamin B12 levels, homocysteine levels, immunoglobulins (Ig) A, G, and M, rheumatoid factor, complement 3 and 4, antistreptolysin O, C reactive protein (CRP), white blood cell count, and neutrophile-lymphocyte ratio (NLR).

Results: There was a statistically significant difference between the groups in terms of age, duration of the disease, drug received, Ig M, free T3, serum homocysteine levels, CRP, and NLR ($p < 0.05$). Pearson's correlation analysis showed a significant correlation between age, duration of MS, IgM, serum homocysteine levels, CRP, and NLR. According to the receiver operating characteristic curve analysis, IgM and NLR were discriminative factors in patients in Group 2.

Conclusion: According to this study, inflammation may have a role in the pathogenesis of MS and in patients with EDSS > 5. Additionally, NLR and CRP levels may be discriminative factors of adverse clinical outcomes.

1. Introduction

Multiple sclerosis (MS) is a chronic degenerative disease of the central nervous system with multiple focal demyelinated lesions of the white matter.[1] The initial and precise etiology of MS remains unknown and is probably multifactorial.[2] It is debatable whether inflammation initiates neurodegeneration or neurodegeneration occurs independently of inflammation.[3] This inflammatory process is thought to be due to an interaction between T cells, B cells, macrophages, dendritic cells, and endothelial cells.[4] Previous studies reported increased levels of proinflammatory cytokines in MS lesions such as interferon-gamma, interleukin (IL)-17, IL21, IL23, and tumor necrosis factor-alpha.[5−7] The inflammation biomarker neutrophile-lymphocyte ratio (NLR) has been reported to be cost-effective, readily available, and easy to calculate.[8] Cytokines including growth factors or ILs may also contribute to the accumulation of neutrophils.[9] Increased neutrophil levels inhibit the lymphocyte activity and stimulate lymphopenia by

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increasing lymphocytes apoptosis.[10] This is the physiological immune response of circulating leukocytes to various stressful events such as inflammation or malignancy which is characterized by an increased neutrophil count and decreased lymphocyte count.[11] Expanded disability status scale (EDSS) is a scale that is used to evaluate the levels of MS. EDSS is a 20-step scale of disease severity ranging from 0 (normal) to 10 (death due to MS).[12] Although EDSS is the most frequently used scale to assess MS severity, the Multiple Sclerosis Severity Score combines the EDSS and disease duration, and is also used to determine the different EDSS scores in patients with similar disease duration.[13]

The aim of the study was to clarify the relationship between patient NLR and its association between EDSS and MS.

2. Methods

2.1. Ethics statement

The study was approved by the Ethics Committee of Ankara Numune Research and Education Hospital. Owing to the retrospective study design, informed consent was not necessary.

2.2. Study population and design

The present study was a retrospective review of MS cases between January 1, 2007 and December 31, 2012 in the Ankara Numune Research and Education Hospital. This is a tertiary referral hospital in the capital city of Turkey. A total of 127 patients (91 women and 36 men) with MS were included in the study. A diagnosis of MS was made according to the revised Mc Donald's criteria.[14] Patients with autoimmune diseases, acute disseminated encephalomyelitis, and chronic inflammatory diseases such as brucellosis and stroke were excluded from the study.

Clinical information included age and sex of the patients, duration of MS, drugs, thyroid function tests, vitamin B12 levels, homocysteine levels, immunoglobulin (Ig) A, G, and M, rheumatoid factor, complement 3 and 4, antistreptolysin O, C reactive protein (CRP), white blood cell count, and NLR. The blood samples were obtained during patient MS flare-up events. Thereafter, patients were divided into two groups according to their EDSS score: Group 1 patients had an EDSS score < 5, and Group 2 patients had an EDSS score ≥ 5.

2.3. Statistical analysis

Mean and standard deviation were calculated for continuous variables, and the normality of the variables was analyzed by use of the Kolmogorov−Smirnov test. We also used the independent samples t-test and Chi-square test to evaluate the associations between the categorical and continuous variables. All variables were included in the backward stepwise regression procedure. Additionally, Pearson's correlation coefficient was used for the association between clinical parameters. The

receiver operator characteristic (ROC) curve analysis was used to establish the cut-off values for CRP and NLR. Two-sided p values were considered statistically significant at $p < 0.05$. Statistical analyses were carried out using the statistical packages for SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

The patients were divided into two groups according to their EDSS score. Group 1 had 80 patients, with a mean age of 40.18 ± 9.25 years. In Group 2, there were 27 patients with a mean age of 42.43 ± 9.78 years ($p < 0.05$). Table 1 shows the demographic and clinical characteristics of the patients. The mean duration of MS was 4.78 years in Group 1 and 8.5 years in Group 2; this difference was statistically significant between the groups ($p < 0.001$). There was no statistically significant difference between the groups in terms of sex, thyroid stimulating hormone levels, vitamin B12 levels, complement 3 and complement 4, antistreptolysin O, and rheumatoid factor ($p > 0.05$). The mean IgM, homocysteine, CRP, and NLR levels were significantly higher in Group 2 ($p < 0.005$). In Group 1, 27 (72.9 %) patients and in Group 2, 83 (95.4 %) patients took medication. There was a statistically significant difference between the groups in terms of medications (Table 1, $p < 0.05$). Correlation analysis showed that there was a correlation between EDSS and age, IgM, homocysteine, CRP, and NLR (Table 2). It also appeared that ROC curve analysis (Fig. 1) demonstrated that CRP and NLR levels may be

Table 1
The demographic and clinical differences between the groups.

	Patients with EDSS ≤ 5 ($n = 90$)	Patients with EDSS > 5 ($n = 37$)	p*
Age mean ± SD	40.18 ± 9.25	42.43 ± 9.78	0.054
Sex			0.137
Male	33	17	
Female	57	20	
Duration of MS (y)	4.78 ± 2.66	8.50 ± 5.02	<0.01
Drugs			0.026*
No drugs	22	4	
Interferon-β 1a	33	7	
Glatiramer acetate	14	4	
Interferon-β 1b	11	5	
Mitoxantrone	0	7	
Prednisolone	3	0	
IgA (mg/dL)	228.77 ± 109.74	203.42 ± 48.01	0.987
IgM (mg/dL)	177.38 ± 80.90	120.00 ± 52.93	0.041
IgG (mg/dL)	1149.08 ± 258.96	1081.75 ± 341.02	0.427
TSH (μIU/mL)	1.90 ± 1.31	1.83 ± 1.19	0.799
FT3 (pg/mL)	3.00 ± 0.67	2.62 ± 0.83	0.038
C3 (mg/dL)	130.52 ± 20.96	126.25 ± 27.60	0.901
C4 (mg/dL)	27.20 ± 9.86	26.87 ± 9.43	0.453
Homocysteine (μmol/mL)	9.26 ± 5.65	15.64 ± 6.06	0.003
CRP (mg/dL)	3.42 ± 1.56	10.62 ± 18.76	<0.001
NLR	2.12 ± 0.87	4.88 ± 3.71	<0.001

C = complement; CRP = C-reactive protein; EDSS = Expanded Disability Status Scale; FT3 = free T3; Ig = immunoglobulin; MS = multiple sclerosis; NLR = neutrophil-lymphocyte ratio; SD = standard deviation; TSH = thyroid stimulating hormone.
* p was calculated using Chi-square test.