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Can biotinidase activity be used as a new inflammatory marker in multiple sclerosis?

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Abstract

In this study, the relationship between known inflammatory markers and serum biotidinase activity in multiple sclerosis (MS) patients was evaluated. This study was conducted between June 2022 and December 2022 in a tertiary referral hospital. MS patients with active infection, end-stage disease, malignancy, and trauma or infection in the last month were excluded. Complete blood count was performed by automated hematology analyzer, C-reactive protein (CRP) was determined by turbidimetric method with serum sample, and serum biotidinase activity was studied by enzymatic spectrophotometric method. The relationship between neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), CRP, immature granulocyte (IG) percentage, and serum biotidinase activity were evaluated with Spearman correlation analysis. A total of 126 patients (mean age was 36.5±9.2 years) were included in our study, and 86 of them (68%) were female. Eighty-four patients (66%) had low biotidinase activity. The patients with low and normal biotidinase activity were compared and there was no significant difference between age, NLR, PLR, CRP levels, and incidence of optic neuritis and myelitis (p=0.509, p=0.548, p=0.883, p=0.911, p=0.403, p=0.892 respectively). By Spearman's correlation analysis, there was no significant correlation between biotidinase activity and CRP, IG percentage, NLR and PLR. A significant correlation was found between NLR with PLR and IG [(p<0.001, r=0.756); (p=0.007, r=0.245), respectively]. This study suggests that biotidinase activity is not an inflammatory enzyme. More comprehensive prospective studies are needed on this subject.

Keywords: Multiple sclerosis, neutrophil/lymphocyte ratio, biotidinase activity, platelet/lymphocyte ratio

Introduction

Multiple sclerosis (MS) is the mostly seen progressive neurologic disease of young adults worldwide. MS is two times more common in women than men. MS has an economic burden on society due to treatment costs and workforce losses. Although the etiology of MS has not been totally understood yet, researches have revealed that genetic, environmental, immunological, and inflammatory factors play important roles in the manifestation of the disease [1]. Inflammation is critical in all clinical forms of MS. MS occurs as a result of the disruption of the balance between pro-inflammatory and regulatory inflammatory mechanisms. These mechanisms in MS need to be better understood, and many studies for this purpose are ongoing. Disease modifying treatments (DMT) used in treatment have been developed in line with these inflammatory mechanisms. DMTs are effective in restoring the disturbed balance between pro-inflammation and regulatory inflammation. By maintaining the balance, inflammation will reduce and disease progression will be controlled in this way.

The human body is exposed to many external factors and inflammation is a defensive response of the immune system against a foreign substance or microorganism. In acute injuries, inflammation can begin within minutes and last for days; In cases of chronic injuries or autoimmune diseases, it may last for years [2]. Systemic inflammation is a multi-organ syndrome developing from systemic damage caused by activeted components of the immune system. Amog them, neutrophils, immature granulocytes (IG), lymphocytes and platelets, are important in systemic inflammation. These immune system members undergo some alterations in both morphology and proportion in inflammatory diseases [3]. Neutrophils are the predominant group of leukocytes. The number and percentage of neutrophils increases in inflammation and they are thought to trigger the development of autoantibodies and aggravating inflammation in autoimmune

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diseases [4]. There are many studies finding that neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and IG percentage are increased in several systemic inflammatory diseases. It is thought that mild inflammation is a possible mechanism responsible for the pathogenesis of sarcopenia, and NRL has been found to be high in sarcopenia patients as an indicator of this inflammation. The precursor value of NLR in neurological diseases and their complications has also been shown in many studies. Activation of inflammatory markers has been found in studies on MS, revealing a chronic inflammation in disease progression [5,6]. NLR has been thought to be an indicator of the development of severe pneumonia in patients with hemorrhagic cerebrovascular disease [7,8]. IG, which are the precursors of netrophils, demonstrate enhanced bone marrow activity and are shown to increased in inflammation [9]. NRL, PLR, and ,in many laboratories, IG can be easily calculated from routinely evaluated complete blood counts. Therefore, they are inexpensive and easily accessible.

Biotin is a not only necessary vitamin but also a coenzyme for carboxylation enzymes. It is supplied in the diet and rich in egg, legumes, nuts, and seeds. Biotin is recycled for further use by the biotinidase enzyme (EC 3.5.1.12) [10]. There are reviews that biotin is a key-point vitamin improving immunological and inflammatory functions [11]. On the contrary, biotin or biotinidase deficiency can also increase inflammation by impairing immunity. Biotinidase deficiency is inherited in an autosomal recessive manner and causes a number of neurocutaneous diseases associated with significant morbidity and mortality [12]. However, patients with partial biotinidase deficiency may have few or no symptoms [13].

Considering the contribution of biotin to immunological functions, low biotinidase activity can be thought to be associated with inflammation. We have not seen a study in the literature about the relation between biotidinase activity and inflammatory markers (NLR, PLR, IG percentage) in patients with MS. Based on this, we investigated the association of proven inflammatory markers and biotidinase activity levels in patients with MS.

Material and Methods

This study was conducted between June 2022 and December 2022 in the MS outpatient clinic of a tertiary hospital. Patients with relapsing-remitting MS diagnosis according to McDonald criteria 2017 were recruited for the study consecutively [14]. Patients who did not want to participate in the study, patients with infection, end-stage disease, malignancy, and a history of trauma and infection in the last month were excluded. Informed consent were taken from all the participants, and the study protocol was approved by local ethics committee (decision number: 2022/514/228/10), conforming to the ethical guidelines of the 1975 Declaration of Helsinki.

All the patients were evaluated by a detailed history and neurological examination. Demographic data, history of optic neuritis, history of myelitis, and current treatment were noted. Magnetic resonance imaging (MRI) findings of the patients were evaluated by the researchers. All cranial and spinal MRI studies were performed on a 1.5 Tesla MRI system. A standardized protocol including T1 and T2 weighted images acquired from coronal, axial, and sagittal plane using a slime thickness of 4-7 mm were used. An area of increased signal intensity on MRI scans larger than 3 mm was accepted as a lesion.

For the analysis of inflammatory markers and serum biotinidase activity, blood samples were taken from the patients between 08:00 and 9:00 in the morning after 12 hours of fasting. Hemogram (neutrophil, lymphocyte, thrombocyte, IG percentage) parameters were determined as complete blood by automated method and C-reactive protein (CRP) was studied by turbidimetric method in serum sample. For the evaluation of serum biotinidase activity, blood samples were collected in serum gel separator tubes and the cells were separated from serum by centrifugation within 1 hour of blood collection. The samples were immediately frozen at -80 oC, kept frozen until the spectrophotometrical enzymatic analysis of biotinidase activity. According to the guideline of the American College of Medical Genetics and Genomics, the average biotinidase activity is 9.61 nmol/mL/min, and lower and upper limit for biotinidase activity are 4.2 and 12.8 nmol/mL/min, respectively, for our laboratory [15].

A sample size of 40 patients per group was counted to ensure 80% power to determine the expected difference between the two groups. Statistical analysis was done with SPSS-22 package program. Categorical variables were presented as frequencies. Numerical variables with normal distribution were shown as mean±standard deviation and non-normally distributed variables were represented as median and interquartile intervals (IQRs). Categorical variables were analyzed by using Chi-square test. Unpaired student's t test was used for normally distributed continuous variables. Non normally distributed continuous variables were analysed with Mann–Whitney U test. Spearman correlation coefficient was applied between NLR, PLR, CRP, IG percentage, and biotidinase activity. A p value less than 0.05 was accepted as significant.

Results

The mean age of 126 patients included in our study was 36.5±9.2, and 86 of them (68%) were female. Eighty-four (66%) patients had lower biotidinase activity than the laboratory average. When the two groups with low and normal biotidinase activity were compared, there was no significant difference in age (p=0.509). The proportion of women in the group with low biotodinase activity was significantly higher than those with normal biotinidase activity (p=0.007). There was no significant difference between the two groups in terms of NLR, PLR, and CRP levels (p=0.548, p=0.883, p=0.911, respectively) (Table 1).

Of the patients included in the study, 36 (29%) had a history of optic neuritis and 86 (68%) had a history of myelitis. No significant difference was found in the frequency of optic neuritis and myelitis between the groups with low and normal biotinidase activity (p=0.403, p=0.892, respectively). When we classified the patients according to the treatment, the first three group of patients were receiving teriflunamide (n=28, 22%), dimethyl fumarate (n=26, 21%) and patients with no treatment

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(n=26, 21%). When we classified the low and normal biotinidase activity groups according to treatment, there was no significant difference between them. According to MRI findings; there was no significant difference between cranial T1 black hole lesions, cranial T2 hyperintense lesions, spinal T2 hyperintense lesions, and cranial or spinal T1 contrasting lesions between biotidinase groups with normal and low levels (p=0.899, p=0.257, p=0.962, p=0.700, respectively). Detailed analysis is given in table 1.

According to Spearman's correlation analysis, no significant correlation was found between serum biotinidase level and CRP, IG percentage, NLR and PLR. A significant correlation was found between IG percentage and NLR (p=0.007, r=0.245). A significant correlation was also found between NLR and PLR (p<0.001, r=0.756) (Table 2).

Table 1. Clinical characteristics of multiple sclerosis patients with low and normal biotinidase activity (n=126)

	Total (n=126)	Biotinidase activity Low (n=84)	Biotinidase activity Normal (n=42)	p value
Age*	36.5±9.2	36.1±9.2	37.3±9.3	0.509
Sex				
Female	86 (68%)	64 (76%)	22 (52%)	**0.007**
Male	40 (32%)	20 (24%)	20 (48%)	
Mean of biotinidase activity (nmol/mL/min)*	8.6±1.7	7.6±1.0	10.6±0.8	**<0.001**
NLR**	2.2 (1.6-3.7)	2.1 (1.6-3.8)	2.3 (1.7-3.4)	0.548
PLR**	146.8 (113.1-223.7)	144.6 (111.3-230.7)	153.3 (113.8-209.6)	0.883
CRP**	3 (0.5-5.2)	2 (0.5-6.1)	3 (0.4-4.6)	0.911
IG percentage (%)**	0.3 (0.2-0.4)	0.3 (0.2-0.4)	0.3 (0.2-0.5)	**0.037**
Treatment of participants				
Teriflunamide	28 (22%)	18 (21%)	10 (24%)	0.762
Dimethyl Fumarate	26 (21%)	20 (24%)	6 (14%)	0.213
Fingolimod	16 (13%)	10 (12%)	6 (14%)	0.705
Glatiramer acetate	14 (11%)	9 (11%)	5 (12%)	0.841
Interferon	9 (7%)	8 (10%)	1 (1%)	0.270
Ocrelizumab	4 (3%)	2 (2%)	2 (2%)	0.600
Natalizumab	3 (2%)	2(2%)	1 (1%)	1.000
No treatment	26 (21%)	15 (18%)	11 (26%)	0.276
History of optic neuritis	36 (29%)	22 (26%)	14 (33%)	0.403
History of myelitis	86 (68%)	57 (67%)	29 (69%)	0.892
MRI findings **				
T1 black hole lesions	2 (0-5)	2 (0-5)	2 (0-5)	0.899
T2 hyperintense lesions cranial	15 (10-23)	15 (10-24)	14 (10-21)	0.257
T2 hyperintense lesions-spinal	1 (0-3)	1 (0-3)	1 (0-3)	0.962
T1 contrast enhancing lesions	0	0	0	0.700

*arithmetic mean±standard deviation, **median and interquartile range, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, CRP: C-reactive protein, IG: immature granulocyte, MRI: magnetic resonance imaging

Table 2. Correlation analysis

			Biotidinase activity	CRP	IG percentage (%)	PLR
Spearman's rho	**NLR**	r	-.042	.210	.245*	.756*
		p	.643	.304	.007	.000
	Biotidinase activity	r		-.154	.122	-.041
		p		.454	.181	.647
	CRP	r			.051	.184
		p			.803	.367
	IG percentage (%)	r				.151
		p				.097

*p<0.05. PLR: platelet/lymphocyte ratio. NLR: neutrophil/lymphocyte ratio. CRP: C-reactive protein. IG: immature granulocyte

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Discussion

The importance of early diagnosis and new treatment choices in MS is increasing day by day due to the positive contribution of treatment to the prognosis. Although clinical and imaging findings are at the forefront in the diagnosis of MS, biochemical parameters have gained importance in recent years for both diagnosis and treatment follow-up. Therefore, in this study, we investigated whether we can use serum biotidinase activity as an inflammatory marker by comparing it with proven inflammatory markers. In this way, we think that biotin replacement might contribute positively to prognosis, with the hypothesis that inflammation may increase in patients with low biotinidase activity.

In addition to its immunological effects, biotin is also thought to have neuroprotective effects [16]. In a study conducted by Couloume et al. with 178 primary progressive or secondary progressive MS patients, patients were given high-dose biotin (300 mg per day) replacement. At the end of 12 months, approximately one quarter of the patients reported feeling improved, however no objective improvement on disease progression was noted [17]. Furthermore, a systematic review and meta-analyses revealed that high-dose biotin does not cause serious side effects compared to placebo. Moreover, they suggested that high dose biotin can be relatively a safe and beneficial treatment option in MS patients [18].

Zhou et al. published a review on the importance of NLR in MS in 2022. In this review, it was thought that there is a low-grade neuroinflammation in MS and NLR may be a cheap and easily available complementary marker in MS [19]. If this neuroinflammation, which is thought to occur in MS, can be reduced, it will contribute positively to the prognosis, and many treatments target this issue. Olsson et al. conducted a systematic review on the relationship of CRP and NLR with MS. There was inconsistency in studies with CRP in this review, but NLR values were increased in all case-control studies in which MS patients were compared with healthy controls [20]. In our study, while NLR was significantly correlated with PLR and IG percentage, it was not significantly correlated with CRP. In this respect, it is compatible with our study. We found a significant correlation between NLR with IG percentage and PLR. In the study of Hasselbach et al. conducted with 740 MS and 1420 control patients, NLR was significantly higher in MS patients [21]. As seen in these studies and reviews, NRL is a significant marker of neuroinflammation and there is a close relationship between MS and NLR. In our study, NLR was significantly correlated with both PLR and IG percentages. In this way, PLR and IG percentage have been shown to be important neuroinflammation markers in MS. The correlation of inflammatory markers with each other increases the reliability of our study. There are hypotheses that there may be low biotidinase activity in MS patients . Furthermore, low biotinidase activity is associated with increased inflammation and late-onset biotidinase deficiency may mimic MS and neuromyelitis optica spectrum disorders [8-12]. In our study, no correlation was found between serum biotidinase activity and inflammatory markers, NLR, PLR, IG percentage, and CRP.

Conclusion

In conclusion, the correlation between NLR with PLR and IG percentage support that there is chronic low-grade inflammation in MS, and PR and IG percentage are also serum markers indicating inflammation in MS. In this study, no significant correlation was found between serum biotidinase activity and NLR, PLR, and IG percentage, suggesting that biotidinase is not an inflammatory enzyme. It is important that, to the best of our knowledge, this is the first study in the literature studying whether biotinidase activity is a marker of inflammation in MS and the correlation of biotidinase activity and inflammatory markers. Easily approachable disease activity markers are necessary for MS patients and more prospective studies with larger number of patients are needed on this subject. If it can be proven that low serum biotinidase activity is a marker of inflammation in MS patients, we think that patients will benefit from biotin replacement.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study protocol was approved by local ethics committee (decision number: 2022/514/228/10).

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