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Research Article

Autoantibodies and Vitamin Levels: Is A Player Or Not in Pathophysiology of Multiple Sclerosis Patients?

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Abstract

Introduction and Aim: Multiple sclerosis is a demyelinating autoimmune disease of the central nervous system. ANA, anti-dsDNA, and ENA profiles have been used in the diagnosis and treatment of autoimmune diseases. Low vitamin D and B12, and folate levels, and high homocysteine levels are often detected in autoimmune diseases. In the present study, we aimed to investigate these parameters in patients with Multiple sclerosis and Multiple sclerosis like disease, as diagnosed in accordance with the revised McDonald criteria.

Methods: The laboratory results of 161 (53Multiple sclerosis, 108 Multiple sclerosis like) patients who were examined for the differential diagnosis of vasculitis/Multiple sclerosis in the last 14 months were evaluated in this present retrospective, cross-sectional study. ANA, anti-dsDNA, ENA profile, vitamin D and B12, folic acid, and homocysteine levels were recorded.

Results: ANA levels in 12 patients with Multiple sclerosis and in 34 patients with Multiple sclerosis like disease were positive; however, ANA levels were negative in 37 patients Multiple sclerosis, and 72 patients with Multiple sclerosis like disease. Anti-dsDNA levels in 4 patients Multiple sclerosis and in 23 with Multiple sclerosis like disease were positive; however, they were negative in 44 patients with Multiple sclerosis and 81 with Multiple sclerosis like disease. The mean vitamin B12 and D, and folate levels of 111 patients were found below the lower normal limit, whereas PTH and homocysteine levels were found over the upper normal limit.

Conclusion: The present study was the first to report the autoimmune parameters and vitamin D levels in patients with Multiple sclerosis and Multiple sclerosis like disease in Bolu province in the Western Black Sea region. Although ANA positivity comes to the forefront in the diagnosis of autoimmune diseases, high anti-dsDNA positivity in patients with MS-like disease suggests different underlying mechanisms. In the present study, vitamin D and B12, and folic acid levels were detected at the lower limit of normal, and homocysteine levels were found at the upper limit of normal. Prospective studies including a control group, in addition to retrospective studies are required to elucidate the roles of autoantibodies and vitamins in the pathogenesis Multiple sclerosis.

Keywords: ANA; Anti ds-DNA; Vitamin B12; Multiple sclerosis; Folate

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) that is associated with relapse and remissions. The CNS is associated with an autoimmune response against the protein myelin. Although the cause of MS is unknown, researchers have suggested that various environmental and genetic factors have a role in the etiology [1]. Researchers have blamed various infectious and non-infectious environmental factors such as the Epstein-Barr Virus (EBV), vitamin D, smoking, and toxins for the etiopathogenesis MS in recent studies [2, 3].

The differential diagnosis of MS includes rheumatologic causes such as systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APS), Behcet's disease, Sjögren syndrome, isolated CNS vasculitis, and infectious causes such as neurosarcoidosis, neuroborreliosis, and syphilis, which have similar clinical and magnetic resonance imaging (MRI) findings [4-9]. In addition, studies reported that vitamin D deficiency was associated with cancer and autoimmune diseases, and researchers emphasized in a study investigating the association of vitamin D deficiency and anti-nuclear antibody (ANA) among young and midlife groups that vitamin D was a significant modulator in autoimmune diseases [10]. The monitoring and replacement of deficient levels of ANA, vitamin D, and folate are important for the course of autoimmune diseases such as multiple sclerosis. The screening test of ANA must first be evaluated in patients under suspicion of having an autoimmune disease [11, 12]. The confirmatory tests are the extractable nuclear antigen (ENA) and anti-dsDNA tests, which are studied as an enzyme-linked immunosorbent assay (ELISA) in routine laboratories after the detection of ANA positivity. The monitoring of vitamin levels together with these tests are important.

In the present study, we aimed to compare the etiopathogenesis and epidemiology of patients with MS with those of patients with MS-like disease, as diagnosed in accordance with the revised McDonald criteria, by comparing the prevalence of antibodies and vitamin levels (13) of patients who presented to our clinic over a 14 month period.

2. Materials and methods

This study was performed in accordance with the Declaration of Helsinki, having obtained approval (No: 2017/134) from the local ethics committee. In the present retrospective, cross-sectional study, we evaluated the laboratory

results of patients who presented to our clinic for the differentiation of vasculitis and MS over the last 14 months. The patients were classified as those with MS and those with an MS-like condition in accordance with the revised McDonald criteria. The sociodemographic characteristics, ANA, anti-dsDNA, ENA profile, and vitamin D and B12, folate, and homocysteine levels were recorded. The correlation of patients with MS with the expanded disability status scale (EDSS) scores was examined, and the correlation with folate and homocysteine levels was investigated.

2.1 Statistical analysis

The results are given as median ± SD. All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows 17.0. Student's t-test was used in the comparison of age distribution between the MS and MS-like groups. Pearson's Chi-square test was used for the comparison of sex. $P < 0.05$ was regarded as statistical significance.

3. Results

One hundred sixty-one patients were included in the study, and the average age was 40 years (range, 18-68 years). The mean age showed no normal distribution (p=0.03). The median age of the 53 patients with MS was 34 years (range, 18-68 years), 38 were women, and the median age of 108 patients with MS-like disease was 45 years (range, 19-61 years), 78 of whom were women (Table 1). A significant difference was detected considering the age between the two groups; the mean age in the MS group was significantly lower than in the MS-like group (Mann-Whitney U, p<0.001). No significant difference was detected regarding sex between the two groups (Chi-square, p=0.9).

Group		**MS**		**MS-like**		**P**
		n=53	**%**	**n=108**	**%**	
Sex	Women (n)	38	72	78	72	0.9
	Men (n)	15	28	30	28	
Age (years)		34 (18-68)		45 (19-61)		**<0.001**

Table 1: General characteristics and laboratory data of the MS and MS-like groups

MS: Multiple sclerosis, MS-like: Patients not diagnosed as having MS

The median EDSS scores of the patients with MS was 1, and 0.5 as min-maximum. Seven patients with MS had radiologically isolated syndrome (RIS) and only had cranial lesions, 8 had clinically isolated syndrome (CIS); 4 of whom had cranial lesions, 2 had spinal, and 2 had both cranial and spinal lesions. Thirty-eight patients were found to relapsing-remitting MS (RRMS), 4 of these patients had cranial lesions in were detected, and 34 had both cranial and spinal lesions. Cranial lesions were detected in 107 of 108 patients with MS-like disease; both cranial and spinal lesions were detected in 1 patient (Table 2).

	MS n=53				MS-like n=108
	RIS	CIS	RRMS	Total	
No MRI finding	0	3	0	3	
Cranial	7	1	4	12	107
Spinal	0	2	0	2	
Cranial + spinal	0	2	34	36	1
Total	7	8	38	53	108

Table 2: The localization of MRI findings and MS clinical subtypes of the two groups

MS: Multiple sclerosis, MS-like: Patients not diagnosed as having MS, RIS: radiologically isolated syndrome, CIS: clinically isolated syndrome, RRMS: relapsing remitting multiple sclerosis, MRI: magnetic resonance imaging

The ANA levels in 12 patients with MS and 34 with MS-like disease were positive; however, they were negative in 37 with MS and 72 with MS-like disease. The results of 4 patients with MS and 2 with MS-like disease could not be obtained. No statistical difference was detected between the groups (Chi-square p=0.3) (Table 3).

	ANA (+)	**ANA (-)**	**%**	**?**	Anti-**dsDNA (+)**	Anti- **dsDNA (-)**	**%**	**?**	**ENA profile**		
MS	12	37	25	4	4	44	8	5	**Normal**	**SS-A**	**Anti-Scl-70**
									45	2	1
MS-like	34	72	32	2	23	81	22	4	**Normal**	**SS-A**	**Anti-Scl-70**
									92	5	4
	Chi-square p=0.3				**Chi square p=0.04**				**Anti-RNP**	**SS-B**	**Anti-SmD1**
									1	2	1

Table 3: ANA, anti-dsDNA, and ENA profile results of the two groups

?: patients whose data could not be reached, MS: Multiple sclerosis, MS-like: Patients not diagnosed as having MS, ANA: Anti-nuclear antibody, ENA: Extractable nuclear antigen

The anti-dsDNA levels in 4 patients with MS and 23 with MS-like disease were positive; however, they were negative in 44 with MS and 81 with MS-like disease. The results of 5 patients with MS and 4 with MS-like disease

could not be obtained. A statistical difference was detected between the two groups (Chi-square p=0.04). Positive anti ds-DNA was higher in the MS-like group compared with the MS group (Table 3).

Although no specific feature was detected in 45 of 48 patients' ENA profiles whose results were obtainable, SS-A in 2 patients and anti-Scl-70 in 1 were detected positive. The results of 5 patients could not be reached. Although the ENA profile results of 2 patients with MS-like disease could not be reached, no specific feature was detected in the ENA profiles of 92 patients; SS-A in 5 patients, SS-B in 2 patients, anti-Scl-70 in 4 patients, anti-SmD1 in 1 patient, anti-RN in 1 patient, and anti-Jo1 in 1 patient were found positive (Table 3).

Homocysteine, vitamin B12, vitamin D, PTH level, and folate levels were investigated in 111 patients; the tests were not investigated in 50 patients. Of the 111 patients were diagnosed as having MS, and 81 had MS-like diseases.

The median homocysteine level in 39 patients with MS was 12.5 mmol/L (range, 7-18 mmol/L), and the level was 12 mmol/L (4-27 mmol/L) in 93 patients with MS-like disease. The homocysteine level was found at the upper limit of normal (5-15 mmol/L) and no statistical difference was detected between two groups (p=0.6) (Table 4).

	Vitamin B12 (pg/mL)	**Folate** (ng/mL)	**Homocysteine** (mmol/L)	**Vitamin D** (ng/mL)	**PTH** (pg/mL)
MS	235 (105-666) n=50	6 (3-14) n=43	12.5 (7-18) n=39	14 (3-27) n=47	47.5 (25-128) n=43
MS-like	272 (31-1300) n=103	12 (3-15) n=104	12 (4-27) n=93	14 (1-34) n=102	66 (17-231) n=98
p	0.6	0.1	0.6	0.7	**0.01**

Table 4: Vitamin B12, folate, homocysteine, vitamin D, and PTH levels of the two groups
MS: Multiple sclerosis, MS-like: Patients not diagnosed as having MS, PTH: Parathyroid hormone

The median vitamin D level in 47 patients with MS was 14 ng/mL (range, 3-27 ng/mL), and the level was 14 ng/mL (range, 1-34 ng/mL) in 102 patients with MS-like disease. The vitamin D level was found below the normal value (<40 ng/mL) and no statistical difference was detected between two groups (p=0.7).

The median PTH level in 43 patients with MS was 47.5 pg/mL (rage, 25-128 pg/mL), and the level was 66 pg/mL (range, 17-231 pg/mL) in 98 patients with MS-like disease. The PTH was found at the upper limit of normal (15-65 pg/mL) and was statistically significant between two groups (p=0.01). The PTH level in MS-like group was found higher.

The median folate level in 51 patients with MS was 6 ng/mL (range, 3-14 ng/mL); however, the value in 104 patients with MS-like disease 12 ng/mL (range, 3-15 ng/mL). The folate level was found at the lower limit of normal value (3.1-20.5 ng/mL) and no statistical difference was detected between the two groups (p=0.1).

The median vitamin B12 level in 50 patients with MS was 235 pg/mL (range, 105-666 pg/mL), and was 272 pg/mL (range, 31-1300 pg/mL) in 103 patients with MS-like disease. Although the Vitamin D was within the normal range in both groups (187-883 pg/mL), it was found near the lower limit, and no statistical difference was detected between the two groups (p=0.6)

A statistical difference was detected between the PTH levels of the two groups. The PTH levels in the MS-like group were found higher.

4. Discussion

MS is a neuro inflammatory autoimmune disease that mainly affects the white matter of the CNS [13]. Women are more affected by MS as in many autoimmune diseases [14]. Although the cause is unknown, hormonal, genetic, and environmental factors have been reported to have a role in the greater prevalence for the diseases in women [13, 15]. Approximately 60-78% of individuals affected by autoimmune diseases were reported to be women in the literature [16-18]. Similarly, we found the ratio of women as 72% in both the MS and MS-like groups in our study.

Researchers reported the age range in the detection of MS as between 25-45 years [19, 20], with a mean age of 37 years. Other autoimmune diseases such as SLE may be detected in advanced ages with mean age of 40 years (range, 30-50 years) [21], systemic sclerosis at 50 years (range 35-65 years) [22], and Sjögren syndrome at 59 years (range, 43-75 years) [23]. In our study, compatible with the literature, the mean age in the MS group was 34 years (range, 18-68 years), and the mean age in the MS-like group was 45 years (range, 19-61 years); a statistically significant difference was observed between the groups. The average age of the MS group was found lower than the MS-like group.

Both cranial and spinal lesions in MRI were present in 36 out of 53 patients with MS, cranial involvement only was detected in 12 patients. Both cranial and spinal lesions were found in 34 of 38 patients with RRMS. The most frequent clinical type of MS was RRMS, which was most frequently found with the co-existence of cranial and spinal lesions, compatible with the literature [24, 25].

Investigations such as cranial MRI findings demonstrating the expansion in time and place, and cerebrospinal fluid analysis demonstrating increased immunoglobulin levels, and electrophysiologic investigations conducted using stimulated potential tests are required in addition to comprehensive patient history in the diagnosis of MS. The diagnosis is based on the revised McDonald criteria [26]. Researchers in recent studies concentrated on specific components of the immune system for diagnosis at the possible earliest stage because of the autoimmune characteristics of MS. Correlative associations with autoantibodies that target myelin surface proteins such as myelin

oligodendrocyte glycoprotein, myelin basic protein, myelin proteolipid protein, and myelin-associated glycoprotein, and MS were demonstrated. Although not routinely used as accurate diagnostic biologic indicators, MS-specific autoantibody tests have been developed [27-29]. The significance of these tests, which have been preferred for investigation purposes, will be confirmed with advanced and qualified studies. The ANA test is studied when someone is suspected of having a systemic autoimmune disease [30, 31]. The detection of some patterns/motifs even in healthy patients led physicians to conduct confirmatory tests such as the ENA profile test and anti-dsDNA ELISA test following ANA positivity.

Although no statistically significant difference was detected in ANA positivity in either the MS or MS-like groups, positivity was detected as 25% and 32%, respectively. Similar to our results, Barned et al. [32] found the prevalence of ANA as 26.7% in their study, which they conducted in the years when autoimmunity was not so intensely discussed (1995). In addition, researchers found compatible results with our study in 2014 in the first study conducted in Bolu and even in the Western Black Sea Region, and reported that ANA positivity was clinically compatible [33]. However, the detection of higher ANA positivity in MS-like groups suggests the requirement for more comprehensive and mechanism-involving studies in patients with MS-like disease. ANA positivity is known to be detected as the first parameter in autoimmune diseases; however, the evaluation of ANA positivity alone may be misleading because the amount of staining patterns detected in fluorescence microscopy using indirect immunofluorescence (IIF) is also important in the detection of ANA positivity. Is the positivity similar to the spotted/granular pattern/motif that may be detected in healthy individuals or does positivity include disease-specific patterns such as homogenous, nucleolar, centromere, and peripheral? This issue was more clearly explained in the study investigating the association/coherence between clinical and ANA positivity in the Bolu province [33]. ANA positivity becomes more significant when combined with the clinic and confirmed by further tests.

Anti-dsDNA positivity in both MS and MS-like patient groups was found statistically significantly different with detection of positivity as 8% and 22%, respectively ($p=0.04$). The preferred anti ds-DNA antibodies together with the ANA test in systemic autoimmune rheumatism diseases such as Sjögren syndrome, SLE, and rheumatoid arthritis (RA) are mostly detected in SLE. The specificity and sensitivity of this test in SLE is 97% and 57%, respectively [34, 35]. Studies have been conducted investigating the prevalence of anti-dsDNA, and systemic autoimmune diseases in the literature; however, the prevalence of anti- dsDNA has not been emphasized directly in patients with MS and MS-like disease. The present study is the first study in this regard. Anti-dsDNA antibodies may also be detected in mixed connective tissue diseases (MCTD), myositis, Graves' disease, and antiphospholipid syndrome in addition to the detection in RA, SLE, and Sjögren syndrome. Therefore, the underlying factors and the association with the diseases described above must be investigated owing to the detection of high levels in the MS-like patient group.

The ENA profile test is one of the described advanced tests, and we detected low positivity in our study results. Therefore, ANA results of must be awaited if the test has been requested. In the event of ANA positivity, the ENA

profile must be studied with the referral of the laboratory. Thus, unnecessary requests and the high costs of these tests may be avoided.

Considering vitamin levels in MS and MS-like groups, Brzostek and Ukleja investigated the association of nutrition with the occurrence and course of disease in their study. The researchers demonstrated that the intake of high levels of saturated fatty acids and salts had negative effects on the development and course of MS. In addition, the researchers found a correlation between the adequate intake of omega-3, vitamin D and B12, and folic acid with MS exacerbation and symptoms risk. They concluded that the effect of nutritional factors in the development and course of MS was not clear, therefore such type of studies must be continued [36]. Researchers in a recent study emphasized the significance of vitamin D3 levels in the preservation of immune hemostasis in MS [37]. Researchers investigating the levels of vitamin B12, folate, and homocysteine levels in patients with MS and a control group found higher levels of homocysteine in patients with MS compared with the control group. The authors stated that high levels of homocysteine might have a role in the pathogenesis of MS [38]. Researchers evaluated the vitamin B complex (B1, B2, B3, B4, B5, B6, B7, B9, B12) in a study investigating whether the deficiency/role of vitamin B was associated with MS. They concluded that more studies must be conducted to identify the role of the vitamin B supplements alone or with other therapeutic agents in the prevention or slowing of MS progression, and there was a prompt need for such studies to assist the improvement of the quality of life of patients with MS [39]. Researchers in a more recent meta-analysis suggested that the higher levels of homocysteine might have a role in MS pathogenesis; however, the levels of vitamin B12 and folate might have a more limited effect [40]. Although we found no statistically significant difference in the MS and MS-like groups, the levels of vitamin B12 and folic acid were found at the lower limit of normal in both groups. Similarly, no statistical difference was detected regarding homocysteine levels; however, it was found at the upper limit of normal in both groups. More prospective studies with the inclusion of control groups are required in addition to retrospective studies.

The present study is the first study to report on autoimmunity parameters and vitamin levels in patients with MS and MS-like disease in Bolu province, in the Western Black Sea region. It should be born in mind that autoimmune diseases may develop with increased age together with genetic factors and underlying causes. Although ANA positivity is important in the diagnosis of autoimmune diseases, the detection of higher anti-dsDNA positivity in patients with MS-like disease suggests the presence of different underlying mechanisms in addition to the detection of higher PTH with advanced age, and the detection of lower vitamin D levels in younger patients. We concluded that new studies must be conducted to enable the use of more specific antibody tests in laboratories in diseases such as MS because although ANA is used particularly in the diagnosis of neurologic diseases, it may be detected in various diseases. More advanced studies (antibodies against antigens in the CNS such as anti-neuronal antibodies and/or the peripheral nervous system) are required to clarify the role of autoantibodies in the pathogenesis of MS.

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