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Clinical significance and prognostic value of serum autoantibody tests in multiple sclerosis

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ABSTRACT

Introduction. It is known that multiple sclerosis (MS) often coexists with other autoimmune diseases. Hence, autoantibody (auto-Ab) tests may prove useful in the differential diagnosis of MS. The objectives of this study were to: (a) investigate the prevalence of auto-Ab positivity at the beginning of the MS diagnostic process; (b) assess whether Auto-Ab+ and Auto-Ab- patients differ in baseline clinical, laboratory, and radiological parameters; and (c) investigate the prognostic value during a two-year follow-up period.

Material and methods. This retrospective study consisted of 450 patients aged between 18 and 55 years. All patients underwent a wide range of auto-Ab tests, anti-nuclear antibody (ANA) tests in particular. The expanded disability status scale (EDSS) scores of the patients were recorded at the time of diagnosis and at the end of a two-year follow-up period.

Results. The mean age of the 212 patients, 148 (69.8%) female and 64 (30.2%) male, included in the study sample was 37 ± 10.83 years. The rate of relapsing cases was 84% (178). Oligoclonal band (OCB) was positive in 142 (86.6%) of the 164 tested cases. At least one of the auto-Ab tests was positive in 51 (24.1%) of the cases. ANA test was positive in 21 (9.9%) cases. There was no significant difference between patients with at least one positive auto-Ab test and without any positive auto-Ab test and between ANA-positive and ANA-negative patients in terms of age, gender, clinical features of MS, presence of brain stem lesion, presence of spinal lesion, OCB positivity, level of clinical improvement after the first pulse steroid treatment, family history, presence of comorbidity, presence of autoimmune disease, or EDSS scores recorded at the end of the two-year follow-up period ($p > 0.05$).

Conclusions. Our study findings revealed that Auto-Ab positivity was more common in MS patients than in the general population. However, given their limited contribution to the diagnosis and differential diagnosis of MS with no effect on the prognostic process, auto-Ab tests should be requested only in the event of accompanying autoimmune disease symptoms, and in cases where the diagnosis of MS may be suspected.

Key words: multiple sclerosis, antinuclear autoantibodies, antineutrophil autoantibodies, autoimmunity

Introduction

The diagnosis of multiple sclerosis (MS) requires not only the demonstration of central nervous system (CNS) demyelinating lesions that spread in space and time, but also the active exclusion of alternative diagnoses [1]. As a rule, an MS diagnosis can be made only if there is "no better explanation" for the clinical condition of the patient. However, the absence of a diagnostic test that can easily distinguish MS from other diseases renders the diagnosis of MS a significant challenge [2]. A number of uncommon inflammatory and non-inflammatory diseases should be considered in the differential diagnosis of MS [2–4].

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Some conditions, e.g. compressive myelopathy, stroke etc, can be easily excluded in the differential diagnosis of MS, whereas others, e.g. neuromyelitis optica spectrum disorder (NMOSD), neurosarcoidosis, Susac syndrome, etc. featuring abnormalities in magnetic resonance imaging (MRI) may strongly indicate an alternative diagnosis, and hence require autoantibody (auto-Ab) tests [3, 5]. It is known that MS predisposes to other autoimmune diseases, possibly due to the increased humoral autoimmune response associated with MS. In this context, biomarkers used in the diagnoses of autoimmune diseases known to accompany MS may be used in the differential diagnosis of MS [6–8].

The use of comprehensive laboratory tests, e.g. anti-nuclear, antiphospholipid, antithyroid and aquaporin antibody tests, has only contributed a little to the differential diagnosis of MS [9, 10]. Anti-nuclear antibody (ANA) is one of the most frequently used autoimmune markers in the differential diagnosis of MS. The rate of MS patients with ANA positivity reported in the literature ranges between 3.6% and 63.5% [7]. Although the clinical significance of the prevalence of ANA positivity in MS patients situation is not yet clear, some studies have stated that ANA positivity is associated with disease activity, while others have reported that ANA positivity will not have a clinical significance unless there are systemic symptoms indicating an underlying connective tissue disorder [11, 12]. Different studies have reported the prevalence of anticardiolipin antibody (aCL) in MS patients of between 4.8% and 44%, and did not find any significant difference between MS patients and healthy controls in this regard. Thus, it has been concluded that aCL was not associated with any clinical features of MS patients or symptoms suggestive of primary antiphospholipid syndrome [13]. The prevalence of anti-Sjögren's syndrome type A (anti-SSA) and type B (anti-SSB) antibodies in MS patients reported in the literature varies between 0–13.3% and 0–1.7%, respectively [14, 15]. The relationship between Auto-Ab positivity and MS disease remains unclear and the positivity for most auto-antibodies is not necessarily specific to a particular autoimmune disease, yet may indicate an increased risk for disease development [16].

In light of the foregoing, the primary objective of this study was to evaluate the benefit of including auto-Ab tests in the initial evaluation of patients with suspected MS who do not have the primary clinical signs indicating other autoimmune diseases. In this context, the secondary objectives of this study were to (a) investigate the prevalence of auto-Ab positivity in the beginning of the MS diagnostic process, (b) assess whether Auto-Ab+ and Auto-Ab- patients differ in baseline clinical, laboratory, and radiological parameters of demyelinating disease, and (c) investigate the relationship between Auto-Ab positivity and disease prognosis during a two-year follow-up period.

Material and methods

The population of this retrospective study consisted of 480 Turkish patients aged between 18 and 55 years who were diagnosed with MS according to the McDonald 2017 criteria [1] and followed up in Sakarya University Education and Research Hospital's MS outpatient clinic. Patient data was obtained from their medical records dated between 2018 and 2022. The patients who underwent immunological tests [ANA, extractable nuclear antigen (ENA) profile (SSA, SSB), antineutrophil cytoplasmic antibodies (ANCA), aCL antibodies, anti-thyroid peroxidase antibodies (anti-TPO), anti-thyroglobulin antibodies (Anti-TG), angiotensin-converting enzyme (ACE), lupus anticoagulant (LA), anti-dense fine speckled-70 antibodies (DFS-70), anti-mitochondrial antibodies (AMA), and rheumatoid factor (RF)] within the scope of the initial diagnostic process prior to the immunomodulator and/or steroid therapy were included in the study. On the other hand, patients who had received corticosteroid or immunomodulatory treatment in the previous three months and patients with missing laboratory tests were excluded from the study. Eventually, the study sample consisted of 212 patients.

The study protocol was approved by the Sakarya University Ethics Committee. Patients' demographic characteristics, family histories, and MS subtype, disease severity, disease duration, oligoclonal band positivity, the presence of brainstem and spinal lesions, response to pulse steroid therapy, and concomitant rheumatological disease data, as well as information on other accompanying diseases, were recorded. All patients were interviewed by a neurologist at three- to six-month intervals in terms of accompanying rheumatological symptoms (including specific questions about arthritis, oral or genital ulcers, alopecia, sicca syndrome, Raynaud's disease, photosensitivity, recurrent abortion and other symptoms that would suggest the presence of other autoimmune diseases) and family history. Laboratory tests were not repeated as there were no associated rheumatological symptoms. The Expanded Disability Status Scale (EDSS) was used to determine the severity of the disease [17]. The EDSS scores of the patients were recorded at the time of diagnosis and at the end of the two-year follow-up period.

All laboratory tests were performed under the same laboratory conditions, using standard methods recommended by the manufacturer. Blood samples were taken in the seated position after 12–14 hours of fasting. Routine biochemical tests were performed by using a Beckman Automatic Analyser at the University of Sakarya Faculty of Medicine's Laboratory of Biochemistry. All samples were evaluated by the STA Analyser (Diagnostica Stago) for aPTT (with STA-CK Prest Kit) and PT (with STA Neoplastin CI Plus Kit). The measurement methods and kit information used in autoantibody tests are given in Table 1. Given its high sensitivity in rheumatic diseases, an ANA titre above 1:100 dilution was accepted as the positive cut-off point.

In MRI examinations, T1 weighted-imaging (WI), T2 weighted-imaging T2-WI and fluid attenuated inversion recovery (FLAIR) sequences were analysed with a 1.5 Tesla MRI device (GE Healthcare, Chicago, IL, US). The MRI

Table 1. Auto-antibody assay methods

Auto-Ab tests	Methods	Kit name, company name, country
ANA	IIF	HEp 20-10, Euroimmun, Germany
Serum ACE	Automated kinetic assay	Commercial kits (SENTINEL, Italy) Autoanalyzer (Beckman Coulter, AU5800, CA, USA)
aCL antibodies	ELISA	Orgentec Diagnostika GmbH, Mainz, Germany
Anti-thyroglobulin	IIF	Euroimmun, Lubeck, Germany
Anti-TPO	IIF	Euroimmun, Lubeck, Germany
ANCA	IIF	Euroimmun, Lubeck, Germany
LA	DRVVT	Staclot Lupus Anticoagulant Kit (Diagnostica Stago)
DFS-70	IIF	Euroimmun, Lubeck, Germany
Anti-SSB	IIF	Euroimmun, Lubeck, Germany
Anti-ENA	IIF	Anti-ENA Profile Plus IgG, Euroimmun, Lubeck, Germany
AMA	IIF	Euroimmun, Lubeck, Germany

ACE — angiotensin-converting enzyme; aCL — anticardiolipin; AMA — anti-mitochondrial antibodies; ANA — anti-nuclear antibody; ANCA — antineutrophil cytoplasmic antibodies; Anti SSB — anti–Sjögren's-syndrome-related antigen B; Anti-TPO — anti-thyroid peroxidase antibodies; Auto-Ab — autoantibody; DFS-70 — anti-dense fine speckled-70 antibodies; DRVVT — dilute Russell viper venom time; ELISA — enzyme-linked immunosorbent assay; ENA — extractable nuclear antigen; IIF — indirect immune fluorescent; LA — lupus anticoagulant; MS — multiple sclerosis

examinations of all patients were evaluated for the presence and distribution of demyelinating lesions in the beginning, and at the end of the six, 12 and 24-month follow-up periods. Radiological findings were interpreted by the same neuroradiologist.

Statistical analysis

Statistical analyses of the collected data were carried out using the SPSS 23.0 (Statistical Product and Service Solutions for Windows, Version 23.0, IBM Corp., Armonk, NY, US) software package. Descriptive statistical methods, i.e. mean and standard deviation, frequency (n), percentage (%) values, were used to express the data. Pearson's chi-squared test was used to compare the categorical data. Kolmogorov-Smirnov test was used to analyse the normal distribution characteristics of the quantitative data. Levene's test was used to evaluate the homogeneity of the data determined to conform to the normal distribution. Student's t-test was used to compare two independent groups featuring homogeneous data. The probability (p) statistics of < 0.05 were deemed to indicate statistical significance.

Results

The study sample consisted of 212 MS patients, 64 (30.2%) male and 148 (69.8%) female. The mean age of the sample was 37 ± 10.83 years. There was no significant difference between the gender-based groups in terms of age ($p > 0.05$). Of the 212 MS patients, 178 (84%) had relapsing-remitting MS (RMS), 27 (12.7%) had secondary progressive MS (SPMS), and seven (3.3%) had primary progressive MS (PPMS). Oligoclonal band (OCB) was not studied in 48 (22.6%) cases. Of the 164 tested cases, 142 (86.6%) were OCB positive and 22 (13.4%) were OCB negative.

The analysis of the MRI data revealed that 114 (53.8%) patients had brainstem lesions and 172 (81.1%) had spinal lesions. Twenty (9.4%) patients had a family history of MS. Of the 200 patients who received pulse steroid therapy, 96 (48%) and 98 (49%) patients had partial and complete clinical improvement, respectively. Six patients did not respond to steroid treatment, and so plasmapheresis was applied in these patients. The most common comorbidity was neuropathic pain which was observed in 17 (8%) patients, followed by restless leg syndrome in 16 (7.5%) patients, depression in 15 (7.1%) patients, thyroid dysfunction and anxiety disorder in nine (4.2%) patients each, epilepsy in five (2.4%) patients, psoriasis in three (1.4%) patients, Behçet's disease in two (0.9%) patients, and diabetes and malignancy in one (0.5%) patient each. There was no significant difference between those with and without at least one comorbidity in mean EDSS scores recorded at the end of the two-year follow-up period (1.23 ± 1.14 vs. 1.17 ± 1.04, respectively; $p = 0.825$).

The number of patients with at least one positive auto-Ab test was 51 (24.1%). Of these patients, 21 (9.9%) had a positive ANA test result. The results of other auto-Ab tests are given in Table 2. There was no significant difference between the patients with at least one positive auto-Ab test and without any positive auto-Ab test in terms of age, gender, clinical features of MS, presence of brainstem lesion, presence of spinal lesion, OCB positivity, level of clinical improvement after the first pulse steroid treatment, family history, presence of comorbidity, presence of autoimmune disease, or EDSS scores recorded at the end of the two-year follow-up period ($p > 0.05$) (Tab. 3). There was also no significant difference between the patients with and without ANA positivity in age, gender, clinical features of MS, presence of brainstem or spinal lesion, OCB positivity, level of clinical improvement after the first pulse

Table 2. Distribution of MS patients by auto-antibody test positivity

Auto-Ab tests	Auto-Ab positive patients (n, %)	Auto-Ab negative patients (n, %)
ANA	21 (9.9%)	191 (90.1%)
Serum ACE	6 (2.8%)	206 (97.2%)
aCL antibodies	1 (0.5%)	211 (99.5%)
Anti-thyroglobulin	13 (6.1%)	199 (93.9%)
Anti-TPO	14 (6.6%)	198 (93.4%)
ANCA	2 (0.9%)	210 (99.1%)
LA	1 (0.5%)	211 (99.5%)
DFS-70	6 (2.8%)	206 (97.2%)
Anti-SSB	1 (0.5%)	211 (99.5%)
Anti-ENA	4 (1.9%)	208 (98.1%)
AMA	1 (0.5%)	211 (99.5%)

ACE — angiotensin-converting enzyme; aCL — anticardiolipin; AMA — anti-mitochondrial antibodies; ANA — anti-nuclear antibody; ANCA — antineutrophil cytoplasmic antibodies; Anti-SSB — anti–Sjögren's-syndrome-related antigen B; Anti-TPO — anti-thyroid peroxidase antibodies; Auto-Ab — autoantibody; DFS-70 — anti-dense fine speckled-70 antibodies; ENA — extractable nuclear antigen; LA — lupus anticoagulant; MS — multiple sclerosis

steroid treatment, family history, presence of comorbidity, presence of autoimmune disease, or EDSS scores recorded at the end of the two-year follow-up period ($p > 0.05$).

Discussion

Nearly a quarter of the MS cases had positivity in at least one of the auto-Ab tests, the most common being ANA positivity. There was no significant difference between the patients with at least one positive auto-Ab test and without any positive auto-Ab test and between patients with and without ANA positivity in any clinical, radiological and 2-year prognostic parameters.

Evaluation of autoantibodies in MS patients is a comprehensive research area subject to ongoing research featuring the complexity underlying the immunological pathways of autoantibodies against CNS structures and serum autoantibodies of other autoimmune diseases [5, 18].

Definitive diagnosis is very important in the context of MS considering the related therapeutic consequences. MS drugs, e.g. monoclonal antibodies, can induce secondary autoimmune processes. Despite the conflicting data in the literature, many studies have shown that autoantibody positivity is higher in MS patients than in the general population [5–7, 11, 12]. Collard et al. [12] determined that MS patients had higher serum ANA levels than the general population, and that 22% of MS patients had elevated serum ANA levels. They attributed ANA positivity to systemic immune dysregulation related to exacerbations in MS and other diseases. Similarly, Spadaro et al. reported significantly higher serum levels of various autoantibodies in MS patients than in the general population (66.6–13.3%). They also reported higher rates of autoantibodies in the progressive phase and during acute exacerbations, indicating the occurrence of a more widespread immune dysregulation in the progressive phase and acute exacerbation periods of the disease. Autoantibody positivity has been shown to be lower in early-onset MS patients than in late-onset MS patients, suggesting a more benign course in early-onset patients [19].

Another study reported a higher frequency of ANA positivity, which was associated with shorter disease duration and lower disability, in MS patients. The effect of ANA on the course of MS remains unclear. However, lower EDSS scores may imply a protective humoral response that prevents neuronal damage resulting in shorter disease durations [7, 20]. Higher rates of antiphospholipid antibody positivity have been reported in MS patients than in the general population. However, no relationship has been found between antiphospholipid antibody positivity and disease severity [13, 21].

In line with the literature data, a higher prevalence of auto-Ab positivity, ANA positivity in particular, was detected in MS patients included in our study than in the normal population. However, there was no significant difference between the patients with at least one positive auto-Ab test in the clinical features of MS, radiological findings, OCB positivity, family history, presence of comorbidity, concomitant autoimmune diseases or 2-year prognosis parameters. No additional autoimmune disease developed in any patient during the follow-up period.

These findings suggest that routine autoantibody testing is not necessary during the initial diagnostic process in all MS patients. Therefore, it would be a more cost-effective approach to subject only those MS patients with atypical clinical-radiological findings to autoantibody tests.

In a study by Dal-Bianco et al. featuring comprehensive analyses similar to this study, ANA, perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), cytoplasmic ANCA (c-ANCA), antiphospholipid antibodies, anti-double stranded deoxyribonucleic acid (anti-dsDNA), extractable nuclear antigens (ENA) and rheumatoid factor (RF) were studied in patients with a definite diagnosis of MS. Consequently, it was found that 18.8% of the MS patients had at least one autoantibody positivity. However, only one patient had an autoantibody-related autoimmune disease. In line with the findings of our study, the authors concluded that autoantibody positivity was not associated with disease activity and thus that the results of the autoantibody tests did not have any effect on the diagnosis of any patient with suspected MS, and that routine application of large autoantibody panel was not cost-effective [22].

In a long-term follow-up study conducted with clinically isolated syndrome type MS patients, there was no significant correlation between ANA positivity and clinical, laboratory and radiological parameters, and also no significant difference between MS patients and the general population in the rate of patients with antibody positivity who developed autoimmune diseases. Thus, they concluded that autoantibody studies are not useful in the absence of clinical findings [11]. In another

Table 3. Distribution of demographic, clinical, radiological and 2-year prognosis data by patients with at least one auto-Ab test positivity and without auto-Ab test

		At least one auto-Ab positivity		p-value
		Present (n = 51) (n, %)	Absent (n = 161)	
Clinical type of MS	PMS	1 (2%)	6 (3.7%)	0.379*
	RMS	46 (90.2%)	132 (82%)	
	SPMS	4 (7.8%)	23 (14.3%)	
Brainstem lesion	+	27 (52.9%)	87 (54%)	0.891*
	–	24 (47.1%)	74 (46%)	
Spinal lesion	+	39 (76.5%)	133 (82.6%)	0.329*
	–	12 (23.5%)	28 (17.4%)	
OCB[1]	Positive	36 (83.7%)	106 (87.6%)	0.571*
	Negative	7 (16.3%)	15 (12.4%)	
Level of clinical improvement after first pulse steroid treatment[2]	Partial	24 (47.1%)	72 (48.3%)	0.876*
	Complete	27 (52.9%)	77 (51.7%)	
Familial MS	+	4 (7.8%)	16 (9.9%)	0.656*
	–	47 (92.2%)	145 (90.1%)	
Comorbidity	+	7 (13.7%)	14 (8.7%)	0.295*
	–	44 (86.1%)	147 (91.3%)	
Gender	Male	17 (33.3%)	47 (29.2%)	0.575*
	Female	34 (66.6%)	114 (70.8%)	
Concomitant autoimmune disease[3]	+	6 (11.8%)	10 (6.2%)	0.191*
	–	45 (88.2%)	151 (93.8%)	

*chi-square test
[1]Patients in whom OCB was not studied were excluded from statistical analyses
[2]Patients who did not receive pulse steroid therapy were excluded from statistical analyses
[3]Patients with Behçet's disease, psoriasis, cancers, and thyroid diseases were included in statistical analyses
Auto-Ab — autoantibody; OCB — oligoclonal band; PPMS — primary progressive multiple sclerosis; RMS — relapsing-remitting multiple sclerosis; SPMS — secondary progressive multiple sclerosis

study conducted with clinically isolated syndrome type MS patients, none of the patients with at least one auto-Ab positivity developed an autoimmune disease during the follow-up period [23]. It has been speculated that ANA and antiphospholipid antibody positivity may be associated with ongoing increased B cell-mediated CNS damage [15]. Nevertheless, the prognosis of the MS patients included in this study did not differ under B and T cell mediated treatments during the follow-up period. In conclusion, the relationship between Auto-Ab positivity and MS disease remains unclear.

The primary limitations of our study are its retrospective design and relatively small sample size. The two-year follow-up period featured may be deemed insufficient in terms of arriving at a conclusion regarding autoimmune disease development or disease prognosis, and thus considered a limitation. The absence of grouping in terms of active attack and remission periods was another limitation. Then again, none of the patients received any immunotherapy during the testing period. The absence of recurrent auto-Ab testing may be deemed another limitation of the study as it renders difficult to comment as to whether the result of the respective auto-Ab test was due to a persistent or to a transient response. The strengths of our study include featuring a rigorous analysis, large autoantibody panels, and correlation analyses with respect to the clinical, demographic, radiological and prognostic data.

Conclusion

In conclusion, our study findings have revealed that Auto-Ab positivity is more common in MS patients than in the general population. However, given their limited contribution to the diagnosis and differential diagnosis of MS with no effect on the prognostic process, auto-Ab tests should be requested only in the event of accompanying autoimmune disease symptoms and in cases where the diagnosis of MS may be suspected.

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Ethical approval: *Approval was obtained from the Ethics Committee of Sakarya University. The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants included in the study. The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.*

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