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Evaluation of autoantibody positive in multiple sclerosis patients

Multiple skleroz hastalarında otoantikor pozitifliğinin değerlendirilmesi

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SUMMARY

Objective: Multiple sclerosis (MS) is the most common autoimmune disease of the central nervous system in which impaired immune activation is involved. It is known that other autoimmune diseases are seen more frequently in MS patients. Many rheumatologic diseases could cause neurologic disorders that mimic MS. Our aim in this study is to determine the rates of autoantibody positivity and the clinical significance of these positivity rates in patients with MS.
Method: 110 patients who were followed up with MS diagnosis in our clinic between 2008 and 2018 were retrospectively evaluated for autoimmune disease biomarkers. The diagnosis of MS was confirmed using both 2005 and 2010 Revised Mc Donald Criteria.
Results: The ANA (antinuclear antibody) positivity rate in our patients was 10.9%, the ANA profile positivity was 9.1%. Anti-ds DNA (double stranded deoxyribonucleic acid) positivity rate was 1.8%, anti-cardiolipin Ig (immunglobulin) G and Ig M were 0.9% positive. Anti-microsomal antibody positivity was 11.8% while anti-thyroglobulin antibody was positively 13.6%. The value of complement 3 (C3) was found to be 92.7% normal and 4.5% higher and 2.7% lower, respectively. The C4 values were 98.2% normal, while they were 11.8% higher than normal .
Six patients had six different diseases in which ethiopathogenesis the role of autoimmunity was also revealed (ankylosing spondylitis, psoriasis, systemic lupus erythematosus, morfea, ptriyazis, Sjögren's syndrome).
Conclusions: Although some autoantibody positivities in MS patients are more frequent than healthy controls, these positivities are not usually associated with systemic rheumatologic disease and haven't clinical significance. Therefore, the evaluation of autoantibodies in each MS patient does not seem cost effective. So, the MS patients whose autoantibody levels are to be measured should be well selected before the evaluation the patients' medical history and complaints should be taken into consideration.
Keywords: Multiple sclerosis, autoimmune disease, rheumatologic disease, autoantibody

ÖZET

Amaç: Multipl sklerozis (MS) bozulmuş immun aktivasyonun rol aldığı santral sinir sisteminin en sık görülen otoimmun hastalığıdır. MS hastalarında diğer otoimmun hastalıkların daha sık görüldüğü bilinmektedir. Ayrıca birçok romatolojik hastalığın da santral sinir sisteminde MS'i taklit edecek nörolojik bulgulara neden olabildiği saptanmıştır. Bizim bu çalışmadaki amacımız ise hastanemizde MS tanısı ile takipli hastalardaki otoantikor pozitiflik oranlarını ve bu pozitiflik oranlarının klinik önemini ortaya koymaktır.
Yöntem: 2008- 2018 yılları arasında kliniğimizde MS tanısı ile takip edilen 110 hasta, otoimmun hastalık biyomarkıları yönünden retrospektif olarak değerlendirildi. Hastaların tanısının konulmasında hem 2005 hem de 2010 revize edilmiş Mc Donald Kriterleri kullanıldı.
Bulgular: Hastalarımızdaki ANA (antinükleer antikor) pozitifliği oranı %10.9 iken, ANA profili pozitifliği %9.1'di. Anti-ds DNA (double stranded deoksiribonükleik asit) pozitiflik oranı %1.8 iken, anti-kardiyolipin Ig (immunglobulin) G ve Ig M %0.9 oranında pozitifti. Anti mikrozomal antikor pozitifliği %11.8 iken, anti-tiroglobulin antikor %13.6 oranında pozitifti. Kompleman3 (C3) değeri %92.7 oranında normal sınırlarda iken %4.5 oranında yüksek, %2.7 oranında düşük saptandı. C4 değerleri ise %98.2 oranında normal sınırlarda iken %11.8 oranında yüksek olarak tespit edildi.
Altı hastamız etyopatogenezinde otoimmunitenin rolünün saptandığı altı farklı hastalığa sahipti (ankilozan spondilit,

psöriyazis, sistemik lupus eritematozus, morfea, pitriyazis, Sjögren sendromu).
Sonuç: MS hastalarında otoantikor pozitifliklerinin bazıları topluma göre daha sık olsa da çoğunlukla bu otoantikor pozitiflikleri sistemik romatolojik hastalık varlığı ile ilişkili değildir ve klinik açıdan anlam içermemektedir. Bu nedenle her MS hastasında otoantikorların araştırılması maliyet açısından etkin görünmemektedir. Bu yüzden otoantikor düzeyi ölçülecek MS hastaları iyi seçilmeli ve ölçüm öncesinde hastaların öykü ve yakınmaları dikkate alınmalıdır.
Anahtar sözcükler: Multipl skleroz, otoimmun hastalık, romatolojik hastalık, otoantikor

INTRODUCTION

Autoimmunity plays a significant role in the emergence of many diseases such as systemic lupus erythematosus (SLE), Behçet's disease and Sjögren's syndrome. In recent years, a large number of extensive studies have been conducted to determine the pathophysiological mechanisms of autoimmune diseases [1,2]. Multiple Sclerosis (MS) is the most common autoimmune disease of the central nervous system in which impaired immune activation plays a role [3]. Numerous studies have demonstrated that genetic, epigenetic, environmental and infectious agents play a role in the emergence of many autoimmune diseases, such as MS, Behçet's disease, and Sjögren's syndrome, by interacting with each other. Unfortunately, the underlying etiology and pathological mechanisms are not fully understood yet.

There are many rheumatic diseases with central nervous system involvement, and their symptoms may mimic MS [4]. As a result of this, numerous serum autoantibodies such as ANA (antinuclear antibody), SS-A, SS-B, rheumatoid factor (RF), anticardiolipin antibody are evaluated for differential diagnosis in patients whose diagnosis of MS is suspicious. The information obtained from the studies on the prevalence and clinical significance of these antibodies detected in patients who have a definite diagnosis of MS but no finding of an additional rheumatic syndrome is both confusing and limited [5-8]. In addition, individuals with an autoimmune disease such as MS due to autoimmune predisposition are known to have increased risk of contracting other autoimmune diseases [9]. Therefore, the thought that the current findings in MS patients diagnosed with rheumatic disease may be related to this rheumatic disease is quite confusing.

This study aims to reveal the rates of autoantibody positivity and the clinical significance of these positivity rates in patients diagnosed with MS according to the Mc Donald criteria and followed up in our clinic.

MATERIAL AND METHODS

The study included 110 patients whose MS diagnosis was confirmed by Cumhuriyet University Neurology Department between 2008 and 2018. The 2005 or 2010 revised Mc Donald criteria were used to diagnose patients. No restriction was put regarding age and gender between patients. Patients with lymphoma or HIV infection were not included in the study. ANA, ANA profile, Anti-ds DNA, Anti-cardiolipin Ig G, Anti-cardiolipin Ig M, Anti-microsomal antibody, Anti-thyroglobulin antibody, P-ANCA, C-ANCA, C3, C4, RF levels were evaluated retrospectively with patients' current clinical pictures and histories. In case of need, consultations of Rheumatology, Endocrinology, and Dermatology departments were requested.

Statistical Method: The obtained data were downloaded into SPSS 22.0 program, and after determining the mean, standard deviation, median values, and frequency distributions, number and percentage were indicated.

RESULTS

The minimum age of the patients was 20, the maximum age was 59, the mean age was 39.01 ± 9.1 years, and the median age was 37 years. When the duration of the disease was evaluated, it was observed that the minimum disease duration was two years, the maximum disease duration was 23 years, the mean disease duration was 7.83 ± 4.47 years, and the median duration was 6.5 years. 70.9% of the patients included in the study were female (n = 78) and 29.1% were male (n = 32). Upon examining the subtypes of MS, 80.3% of the patients were RRMS (relapsing-remitting MS), 15.9% were SPMS (secondary progressive MS), 2.8% were PPMS (primary progressive MS), and 0.9% were RPMS (relapsing progressive MS) (Table 1). While 35.5% of the patients were under IF b-1a, 18.8% were under IF b-1b, 13.5% were under glatiramer acetate, 10.4% were under fingolimod, 7.3% were under mitoxantrone, 3.1% were under dimethyl fumarate, 2.1% were under ocrelizumab, rituximab and teriflunomide, and 0.9% were under natalizumab treatment, 4.2% patients were not receiving treatment (Table 2).

Table 1: Evaluation of patients according to MS subtypes

Disease Subtype	Percentage (n)
RRMS(relapsing remmiting MS)	80.3%(88)
SPMS (secondary progressive MS)	15.9%(18)
PPMS(primary progressive MS)	2.8%(3)
RPMS (relapsing progressive MS)	0.9%(1)

Table 2: Evaluation of MS patients according to the treatment agent

Treatment Agent	Percentage (n)
IF b-1a	35.5%(40)
IF b-1b	18.8%(22)
Glatiramer acetate	13.5%(15)
Fingolimod	10.4%(11)
Teriflunomide	2.1%(2)
Dimetilfumarat	2.1%(2)
Mitoxantrone	7.3%(8)
Ocrelizumab	2.1%(2)
Rituximab	2.1%(2)
Natalizumab	0.9%(1)
No	4.2%(5)

Table 3: Antibody positivity rates in MS patients

Antibody	Positivity	+/-	Negativity
ANA	10.9%	4.5%	84.6%
ANA profile	9.1%	4.5%	86.4%
Anti-ds DNA	1.8%	-	98.2%
Anti-cardiolipin Ig G	0.9%	-	99.1%
Anti-cardiolipin Ig M	0.9%	-	99.1%
Anti-microsomal antibody	11.8%	-	88.2%
Anti-thyroglobulin antibody	13.6%	-	86.4%
P-ANCA	-	-	100%
C-ANCA	-	-	100%
C3	4.5%(High)	2.7%(Low)	92.7%(Normal)
C4	11.8%(High)	-	88.2%(Normal)
RF	1.8%(High)		98.2%(Normal)

While the rate of ANA (antinuclear antibody) positivity in the patients was 10.9%, the rate of +/- was 4.5%. Upon evaluating the ANA profile of the patients, it was observed that while negativity was 86.4%, positivity was 9.1%, and the +/- ratio was 4.5%. Among the 12 patients with the positive ANA value, 11 were female, and one patient was male. While ANA was stained at a ratio of 1/100 and homogeneously in two of these patients (2%), it was stained at a ratio of 1/80 and granularly in two of them (2%), and at a ratio of 1/160 and centromerically in one of them (0.9%). In 5 of these 12 patients, positivity was present in the ANA profile. Histones and Ds DNA were detected in one patient, SS-A was detected in one patient, and SCL 70 (1/80) was detected as positive in one patient. While in one of the other two patients positivity was present in SS-A and AMA M2, the patient was diagnosed with psoriasis. While the other patient had CENPB positivity, his/her C3 value was found to be low, and the patient was diagnosed with SLE. In one of the 12 patients with ANA positivity, the ANA profile was found to be +/-, in this patient Histones were +/-, and the patient was diagnosed with Morphea (localized scleroderma). In a patient with ANA positivity, the RF value was also positive. This patient had Sjögren's syndrome diagnosis. In a patient with the ANA value of +/-, the ANA profile was also +/-, and the patient had Jo -1 positivity (Table 3).

Table 4: Other positivities and diagnoses accompanying patients with ANA positivity

Gender	**ANA**	**ANA Profile**	**Antibody**	**Diagnosis**
Female	Positive	Positive	Histones and Ds DNA +	
Female	Positive	Positive	SS-A+	
Female	Positive	Positive	SCL 70+	
Female	Positive	Positive	SS-A and AMA M2+	Psöriyazis
Female	Positive	Positive	CENPB +,C3 low	SLE
Female	Positive	+/-	Histones +/-	Morphea(localized scleroderma)
Female	Positive	Negative	RF+,SS-A+	Sjögren's Syndrome
Female	+/-	+/-	Jo-1+	

Of the ten patients whose ANA profile was positive, 8 were female, and 2 were male. The ANA value of 5 of these ten patients was positive (Table 3). In one of the other five patients, the PCNA value was +2 positive, the other patient had anti-ribosomal antibody, and the other one had SCL 70 +2 positivity. In one of the patients whose ANA profile was positive, the anti ss DNA value was +/-, and the patient had a diagnosis of Behçet's disease. While the PCNA value of 1 of the five patients, whose ANA profile was found to be +/-, was +/-, he/she had a diagnosis of Behçet's disease. Of the other patients, the Histones value in one of them was +/-, and the Ds DNA value in the other one was found to be positive.

Table 5: Other positivities and diagnoses accompanying patients with positivity in the ANA profile

Gender	ANA Profile	Antibody	Diagnosis
Female	Positive	PCNA ++	
Male	Positive	Anti-ribosomal P protein +	
Female	Positive	SCL 70 ++	
Male	Positive	Anti-ssDNA +/-	Behçet's disease
Male	+/-	PCNA +/-	Behçet's disease
Male	+/-	Histones +/-	
Female	+/-	Ds DNA+	

While the anti-ds DNA positivity rate was 1.8%, anti-cardiolipin Ig (immunoglobulin) G and Ig M positivity rates were 0.9%. While anti-microsomal antibody positivity was 11.8%, anti-thyroglobulin antibody was positive at a rate of 13.6%. P-ANCA (perinuclear anti-neutrophil cytoplasmic antibody) and C-ANCA (cytoplasmic anti-neutrophil cytoplasmic antibody) positivities were not observed. Complement3 (C3) value was found to be within the normal range in 92.7% of the patients, high in 4.5%, and low in 2.7% of the patients. While C4 values were found to be within the normal ranges in 98.2% of the patients, they were high in 1.8%. There was no patient with the low C4 value. One of the patients with the high C4 value had a diagnosis of ankylosing spondylitis (other parameters were negative). Upon examining the RF (rheumatoid factor) values, the values were within the normal ranges in 98.2% of the patients, and high in 1.8% (n=2).

While one of the two patients, who did not have any positivity in the parameters examined, was under azathioprine treatment due to bilateral uveitis, the other one was followed up by the Dermatology department due to pityriasis rubra pilaris.

DISCUSSION

Based on the data of this study, it could be stated that the positivity of some autoantibodies is more frequent in MS patients, and some of them are equally frequent in society. However, the data demonstrated that these positivities do not have any clinical meaning. Furthermore, according to the results, the association of MS with other rheumatic diseases is common.

The positivity rate of the ANA value in healthy people was found to be 32% in 1/40 dilution, 13% in 1/80 dilution, 5% in 1/160 dilution, and approximately 3% in dilutions above 1/160 (10). The rate of ANA positivity in MS patients was relatively more frequent, and it was found to be approximately 23- 33% (5,6,11-13). In a study performed on patients with MS, the positivity rate of the ANA value was found out to be 18% in 1/40 dilution, 3% in 1/80 dilution, 9% in 1/160 dilution, and approximately 1% in dilutions above 1/160 (14). While the ANA positivity rate was 10.9% in the present study, this value was lower than that of MS patients. In this study, the rate of ANA positivity was found to be 2% in 1/100 dilution, 2% in 1/80 dilution, and 0.9% in 1/160 dilution, and these rates are similar to the study conducted on MS patients.

Furthermore, in the present study, while the SS-A positivity rate was around 2%, there was not SS-B positivity. These values are lower compared to the previous studies which indicated that SS-A positivity was 3-13% and SS-B positivity was 1-2% in MS patients (5,15). Besides, while the prevalence of Sjögren's syndrome in society is between 1% and 5%, this rate was found to be 0.9% in the present study (15). These results contradict the previous studies, which have demonstrated that Sjögren's syndrome is more frequent in MS patients, but they are similar to the ratios found out in the study carried out by Solomon et al. on MS patients (14).

Similarly to the previous studies, RF positivity is also rare in the present study (1.8%) (12). Moreover, the frequency of anti-cardiolipin antibodies and anti-ds DNA positivity in our study is close to that in healthy adults.

It is known that the frequency of autoimmune thyroiditis is higher in MS patients than in the healthy population. In the present study, while the anti-microsomal antibody positivity rate in MS

patients was found to be 11.6%, the antithyroglobulin antibody frequency was detected to be 13.6%, and none of the patients had hypothyroidism. In a study performed by Posselt et al., it was found out that the rate of antithyroglobulin antibody positivity was 4.9% without hypothyroidism in healthy controls, that this rate was much higher in patients with rheumatic disease, and that the highest rate was observed in SLE patients (16). Based on the data of our study, it can be said that the positivity of thyroid autoantibodies is higher compared to the normal population in MS disease like in the other autoimmune diseases.

Furthermore, in the present study, besides the diagnosis of MS, two patients had a diagnosis of Behçet's disease, one patient had a diagnosis of Sjögren's syndrome, and one patient had a diagnosis of SLE. In the etiology of two patients, they had a diagnosis of Morphea and Psoriasis, including autoimmunity.

Although some of the autoantibody positivities in MS patients are more frequent compared to the society and some of them are close to the society, these autoantibody positivities are mostly not related to the presence of systemic rheumatic disease and do not have any clinical meaning. Therefore, the investigation of autoantibodies in every MS patient does not seem effective in terms of cost. As a result, MS patients whose autoantibody level will be measured should be selected well, and the patients' history and complaints should be taken into consideration before measurement.

REFERENCES

1. Barcellos LF, Kamdar BB, Ramsay PP et al. Clustering of autoimmune diseases in families with a high-risk for multiple sclerosis: a descriptive study. Lancet Neurol 2006; 5: 924–31.
2. Marrie RA, Reider N, Cohen J et al. A systematic review of the incidence and prevalence of autoimmune disease in multiple sclerosis. Mult Scler 2015; 21: 282–93.
3. Kamm CP, Uitdehaag BM, Polman CH. Multiple sclerosis: current knowledge and future outlook. Eur Neurol 2014; 72: 132–41.
4. Miller DH, Weinshenker BG, Filippi M et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult Scler 2008; 14: 1157–74.
5. de Andre´s C, Guillem A, Rodrı´guez-Mahou M, Lo´pez Longo FJ. Frequency and significance of anti-Ro (SS-A) antibodies in multiple sclerosis patients. Acta Neurol Scand 2001; 104: 83–7.
6. Collard RC, Koehler RP, Mattson DH. Frequency and significance of anti nuclear antibodies in multiple sclerosis. Neurology 1997; 49: 857–61.
7. Garg N, Zivadinov R, Ramanathan M et al. Clinical and MRI correlates of autoreactive antibodies in multiple sclerosis patients. J Neuroimmunol 2007; 187: 159–65.
8. Heinzlef O, Weill B, Johanet C et al. Anti cardiolipin antibodies in patients with multiple sclerosis do not represent a subgroup of patients according to clinical, familial, and biological characteristics. J Neurol Neurosurg Psychiatry 2002; 72: 647–9.
9. Richard-Miceli C, Criswell LA. Emerging patterns of genetic overlap across autoimmune disorders. GenomeMed 2012; 4: 6.
10. Tan EM, Feltkamp TE, Smolen JS et al. Range of antinuclear antibodies in "healthy" individuals. Arthritis Rheum 1997; 40: 1601–11.
11. Tourbah A, Clapin A, Gout O et al. Systemic autoimmune features and multiple sclerosis: a 5-year follow-up study. Arch Neurol 1998; 55: 517–21.
12. Spadaro M, Amendolea MA, Mazzuconi MG et al. Autoimmunity in multiple sclerosis: study of a wide spectrum of autoantibodies. Mult Scler 1999; 5: 121–5.
13. Barned S, Goodman AD, Mattson DH. Frequency of anti-nuclear antibodies in multiple sclerosis. Neurology 1995; 45: 384–5.
14. Solomon AJ, Hills W, Chen Z et al. Autoantibodies and Sjogren's Syndrome in multiple sclerosis, a reappraisal. PLoS One, 2013; 8: e65385.
15. de Seze J, Devos D, Castelnovo G et al. The prevalence of Sjogren syndrome in patients with primary progressive multiple sclerosis. Neurology 2001; 57: 1359–63.
16. Posselt RT, Coelho VN, Pigozzo DC et al. Prevalence of thyroid autoantibodies in patients with systematic autoimmune rheumatic diseases. Cross-sectional study. Sao Paulo Medical Journal 2017; 135: 535-540.