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The Effect of Oligoclonal Bands in Patients with Multiple Sclerosis

Multipl Skleroz Hastalarında Oligoklonal Bantların Etkisi

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Abstract

Objective: The data for oligoclonal bands (OCB) in cerebrospinal fluid (CSF) and their association with clinical profiles of patients with multiple sclerosis (MS) are limited. In this study, we aimed to investigate the relationship between OCB and clinical and magnetic resonance imaging (MRI) features in patients with MS.

Materials and Methods: Patients between the ages of 18-65 who were diagnosed as having MS in the first 3 months of the onset of the disease were included. The difference between the clinical (gender, age of onset of disease, clinical presentation and subtypes of disease) and MRI characteristics as well as the choice of the treatment regimen of OCB-positive and negative patients were evaluated. The data of the patients were obtained retrospectively from our hospital records.

Results: Sixty-four patients who met the criteria were included in the study. Two groups were formed. Group 1 involved 50 OCB positive patients with MS and group 2 involved 14 OCB negative patients with MS. In CSF parameters, cell number (p=0.001), and IgG index were statistically significantly higher in OCB (+) patients compared to OCB (-) patients (p<0.001). In MRI, higher lesion number in the lower cervical spinal segment was found in OCB (+) patients compared to OCB (-) patients. There were no significant differences between OCB (+) and (-) patients with MS in relation to the course of the disease, symptoms of the first attack and severity, relapse rate, or disease modifying therapy.

Conclusion: Our results showed that the presence of OCB had a negative effect on MRI in patients with MS. Larger studies are warranted in patients with MS.

Keywords: Multiple sclerosis, biomarkers, oligoclonal bands, imaging

Öz

Amaç: Multipl sklerozlu (MS) hastalarda beyin omurilik sıvısındaki (BOS) oligoklonal bantlar (OKB) ile klinik profil arasındaki ilişki henüz net değildir. Bu çalışmada, MS'li hastalarda OKB ile klinik ve manyetik rezonans görüntüleme (MRG) özellikleri arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem: Hastalığın başlangıcından itibaren ilk 3 ayda MS tanısı alan 18-65 yaş arası hastalar dahil edildi. OKB pozitif ve negatif hastaların klinik (cinsiyet, hastalığın başlangıç yaşı, klinik prezentasyon ve hastalık alt tipi) ve MRG özellikleri ile tedavi rejimi seçimi arasındaki fark değerlendirildi. Hastaların verileri retrospektif olarak hastane kayıtlarımızdan elde edildi.

Bulgular: Çalışmaya kriterleri karşılayan 64 hasta dahil edildi. Elli OKB pozitif (grup 1) MS'li hasta ve 14 OKB negatif (grup 2) MS'li hastadan iki grup oluşturuldu. BOS parametrelerinden hücre sayısı (p=0,001) ve IgG indeksi OKB (+) hastalarda OKB (-) hastalara göre istatistiksel olarak anlamlı derecede yüksekti (p<0,001). MRG'de, OKB (-) hastalara göre OKB (+) hastalarda alt servikal spinal segmentte daha fazla sayıda lezyon saptandı. Hastalığın seyri, ilk atak semptomları ve ciddiyeti, nüks oranı veya hastalık modifikasyon terapisi ile ilişkili olarak OKB pozitif ya da negatif MS'li hastalar arasında önemli bir fark yoktu.

Sonuç: Çalışmamızda MS'li hastalarda OKB varlığının servikal MRG'yi olumsuz etkilediği gösterilmiştir. Bu sonuçlar doğrultsunda MS'li hastalarda bu ilişkiyi inceleyen daha büyük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Multipl skleroz, biyobelirteçler, oligoklonal bantlar, görüntüleme

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that affects young adults. In contrast to the earlier traditional T-cell model, the current concept of pathogenesis includes that T and B-lymphocytes are involved in coexisting processes (1). Successful responses to B-cell-mediated therapies have prompted curiosity about the effects of B-lymphocytes on MS disease (2). The presence of immunoglobulins produced by B-cells in the cerebrospinal fluid (CSF) is one of the most consistent findings in MS.

The subtypes of MS are relapsing-remitting (RR), secondary progressive (SP), progressive-relapsing (PR), and primary progressive (PP). There is no clear indication in which subtype the

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disease will progress (3). However, a clinician has some clues to predict prognosis in MS. The initial progressive course, higher basal Expanded Disability Status Scale (EDSS) scores, greater number of functional systems affected at disease onset, higher residual deficits in the pyramidal, visual, sphincteric, and cerebellar systems, and the shortest first inter-attack interval are consistent factors associated with a worse prognosis in MS (4). However, studies are still being conducted to understand whether biomarkers or imaging techniques can contribute to prediction. As a result of these studies, it has been suggested that cerebral atrophy and CSF markers may be associated with disease progression (5,6,7).

The diagnosis of MS is complex due to the heterogeneity of the disease. The diagnostic criteria are mainly based on the evaluation of clinical, imaging and laboratory findings described in the "McDonald criteria", which have been gradually updated over the years (2005, 2010 and 2017). The McDonald criteria emphasize that CSF examination is "a valuable diagnostic test", particularly when clinical evaluation and imaging techniques do not provide sufficient evidence for a diagnosis of MS or in the presence of PP-MS. In addition, in the most recent revision of the McDonald criteria, the detection of oligoclonal bands (OCB) in CSF examination contributes to the diagnosis of MS by fulfilling the criterion of dissemination in time (8). Besides its diagnostic significance, there is still no consensus on whether they affect the clinical character of the disease.

There are limited number of studies conducted in Turkey on OCB in MS in the literature. In this study, we investigated the effect of OCB on the clinical character of the disease, magnetic resonance imaging (MRI), and preference for disease-modifying therapy (DMT).

Materials and Methods

Clinical Data

We included patients who were diagnosed as having MS (according to the revised 2017 McDonald criteria) after enrollment in our clinic and whose medical records were completed between 2017-2019. Patients' demographic and clinical data (gender, age at onset, clinical presentation, subtypes of disease including RR, SP, PR, and PP MS, EDSS, MRI, and CSF findings) were retrospectively obtained from our hospital records. We also investigated the relationship between OCB status and DMT preference. Patients with suspicious MS, clinically isolated syndrome, history of previously diagnosed MS, or whose serum and CSF samples were collected after intravenous methylprednisolone treatment during relapse were excluded from the study. The study was approved by the Ethics Committee of University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital (decision no: 2020.12.2.01.201, date: 25.12.2020). All subjects gave written informed consent for the study.

OCB detection in CSF

The OCB detection was performed by isoelectric focusing, with each step performed according to the manufacturer's instructions. OCB positivity was defined as two or more bands present in CSF and not in serum.

MRI Evaluation

The MRI images of patients within 3 months of disease onset were analyzed. Images were obtained in 1.5 Tesla MRI with a contiguous section thickness of 3 mm. The number of lesions on the T2-weighted images and the number of Gd-enhancing lesions on brain MRI were assessed. The number of lesions (0, 1, ≥2) and the presence of Gd enhancement on MRI of the spinal cord (upper cervical spine, lower cervical spine, and thoracic spine) were recorded.

Treatment Regimens

After diagnosis, the selected treatment regimens in patients were classified as follows: First line; interferon, glatiramer acetate, teriflunamide, dimethyl fumarate, second line; fingolimod, natalizumab, ocrelizumab, and the 3rd line.

Statistical Analysis

Statistical analyses were performed using IBM SPSS (Statistics Package Program for Social Sciences) version 24.0 (IBM Corporation, Armonk, NY, USA). The direction and significance of association between variables were assessed using chi-square test (Fisher's exact test and Linear-by- Linear Association, where appropriate). Mann-Whitney's U test as a non-parametric test was used to compare variables between two groups. Continuous variables were expressed as mean ± standard deviation, categorical data as numbers and percentages. When continuous variables were analyzed across groups, normality analyses were performed using Kolmogorov-Smirnov Goodness from fit test. A p value less than 0.05 was accepted as statistical significance.

Results

Sixty-four patients (age 16-58 years, disease duration 3-144 months) met the required criteria. Fifty (78.12%) were OCB positive (group 1) and 14 (21.88%) were OCB negative (group 2). All patients in group 1 had type 2 positivity. Routine CSF analysis revealed that the mean white blood cell count (6.81±7.31 and 1.25±1.35, respectively) and IgG index (1.79±1.76 and 0.51±0.07, respectively) were statistically significantly higher in group 1 compared to group 2 ($p<0.001$) (Table 1). There was no statistically significant difference between groups in terms of age at onset, gender, symptoms at onset, EDSS at OCB sampling, number of relapses, and presence of MS subtypes (RRMS, SPMS, PPMS, PRMS) ($p>0.05$) (Table 1, Figure 1).

One patient from each group refused to receive DMT. Treatment decisions for the remaining patients are shown in Table 2. In group 1, 91.8% received first-line therapy and 8.2% received second-line therapy. In group 2, 92.3% of patients received first-line therapy, while 7.7% of patients received second-line therapy. Third-line therapy was not required in either group. There was no statistically significant difference between the groups in terms of treatment choice ($p>0.05$) (Table 2).

The groups were compared in terms of the number of plaques in the cranial MRI. Of group 1 50% had >10 lesions, while this rate was 21.4% in group 2 (Table 3). The rate of cranial contrast enhancement was higher in group 1 (44.0% vs. 28.6%) than in group 2. The total number of lesions and the number of enhancing lesions in the cranial MRI were not different between groups ($p>0.05$) (Table 2).

In the upper cervical spinal MRI, 42.0% of group 1 had at least one lesion, whereas this rate was 28.6% in group 2. At least

1 contrast enhancing lesion was present in 10% of group 1 and in 7.1% of group 2. The total number of lesions and the number of contrast enhancing lesions in the upper cervical spinal cord were not different between groups (p>0.05) (Table 4).

In the lower cervical spinal MRI, 28% of group 1 had at least one lesion, this rate was only 14% in group 2. The difference was statistically significant (p=0.006). At least 1 contrast enhancing lesion was present in 8% of group 1 and 0% of group 2. The number of contrast enhancing lesions in the lower cervical spinal cord was not different between groups (p>0.05) (Table 4).

In thoracic MRI, 38% of group 1 had at least 1 lesion, while this rate was 35.7% in group 2. At least 1 contrast enhancing lesion was present in 8% of group 1 and 14.3% of group 2. The total number of lesions and the number of contrast enhancing lesions in the thoracic spinal cord were not different between groups (p>0.05) (Table 5).

Table 1. Comparison of demographic and clinical parameters of patients with MS according to OCB status

	OCB negative (n=14)	OCB positive (n=50)	p
Onset age (year) (mean ± SD)	34.42±12.45	33.37±10.20	0.853*
Sex (female/male)	11/3	35/15	0.739**
EDSS	2.07±1.20	2.01±1.03	0.875*
Number of attacks	1.78±0.69	1.48±0.61	0.118*
Cell count	1.79±1.76	6.81±7.31	**0.001***
IgG index	0.51±0.07	1.25±1.35	**<0.001***
RRMS (negative/positive)	1/13	1/49	0.392**
SPMS (negative/positive)	13/1	49/1	0.392**
PPMS (negative/positive)	Negative in all patients		
PRMS	Negative in all patients		

*Mann-Whitney U test, **hi square test (Fisher's exact test). EDSS: Expanded Disability Status Scale, RRMS: Relapsing remitting multiple sclerosis, SPMS: Secondary progressive multiple sclerosis, PPMS: Primer progressive multiple sclerosis, PRMS: Progressive relapsing multiple sclerosis, OCB: Oligoclonal bands, SD: Standard deviation

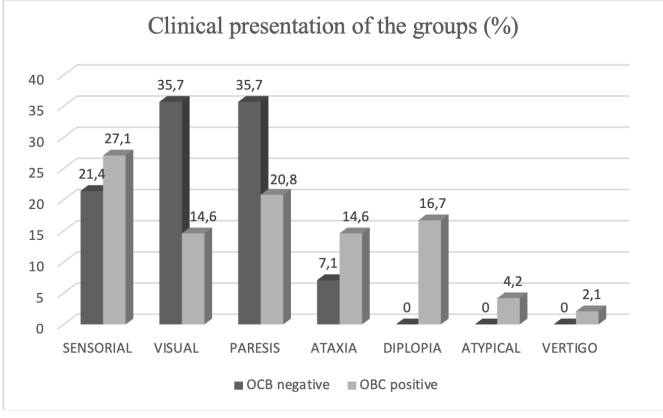

Figure 1. Clinical presentation of the groups

Discussion

The result of this study was that the OCB-positive rate in our MS cohort was 78.12%. Different results have been reported in studies on the frequency of OCB positivity in patients with MS. The frequency of OCB positivity reaches up to 95% in Northern Europe (9,10,11). In contrast, a higher rate of OCB negativity has been reported from Eastern and Far Eastern countries, suggesting that there may be an association between genetic and environmental factors and OCB (12). More recently, Lu et al. (13) reported that OCB was positive in 60% of patients with MS diagnosed according to the McDonald 2017 criteria in two independent cohorts from Southern China. The number of studies on OCB in patients with MS in Turkey is quite limited. In a study by Ellidag et al. (14) from Turkey which included 40 patients with MS, the negativity rate of OCB was 40%. In another study from Turkey, Idiman et al. (15) found a negativity rate of 14.3% in their cohort of 210 patients with MS.

In the present study, no difference was found between the demographic characteristics of OCB (-) and OCB (+) patients with MS in terms of age at onset, clinical features at onset, number of attacks at 2-year follow-up, and subtypes of the disease. OCB status was also found to have no effect on treatment regimens. Lu et al. (13) reported that OCB-negative patients had a later age of onset

Table 2. Comparison of OCB status and treatment regimens

	OCB positive (n=49)	OCB negative (n=13)	Total (n=62)	p
Treatment regimens (n, %)				
First line	45 (91.8)	12 (92.3)	57 (91.23)	1.000*
Second line	4 (8.2)	1 (7.7)	5 (8.77)	
Third line	-	None	-	

*Chi-square test, first line = interferon beta-1A/beta-1B, glatiramer acetate, teriflunamide, dimethyl fumarate; second line = fingolimod, natalizumab (1 patient in each group = treatment refusal). OCB: Oligoclonal bands

Table 3. Comparison of cranial MRI lesions and contrast enhancement according to OCB positivity

	OCB negative (n=14)	OCB positive (n=50)	Total (n=64)	p
Number of cranial plaques (n, %)				
<5	3 (21.4)	7 (14.0)	10 (15.6)	0.092*
5-10	8 (57.1)	18 (36.0)	26 (40.6)	
11-20	2 (14.3)	15 (30.0)	17 (26.6)	
>20	1 (7.1)	10 (20.0)	11 (17.2)	
Number of cranial lesions with contrast enhancement (n, %)				
0	10 (71.4)	28 (56.0)	38 (59.4)	0.190*
1-5	4 (28.6)	17 (34.0)	21 (32.8)	
>5	0 (0.0)	5 (10.0)	5 (7.8)	

*Chi-square test (Linear-by-Linear Association). OCB: Oligoclonal bands, MRI: Magnetic resonance imaging

Table 4. Comparison of cervical MRI lesions and contrast enhancement according to OCB positivity

	OCB negative (n=14)	OCB positive (n=50)	Total (n=64)	p
Number of upper cervical spine plaques (n, %)				
0	10 (71.4)	29 (58.0)	39 (60.9)	0.425*
1	**2 (14.3)**	**11 (22.0)**	13 (20.3)	
≥2	**2 (14.3)**	**10 (20.0)**	12 (18.8)	
Number of upper cervical spine lesions with contrast enhancement (n, %)				
0	13 (92.3)	45 (90.0)	58 (90.6)	0.657*
1	1 (7.1)	4 (8.0)	5 (7.8)	
≥2	0 (0.0)	1 (2.0)	1 (1.6)	
Number of lower cervical spine plaques (n, %)				
0	12 (85.7)	30 (60.0)	42 (65.6)	**0.006***
1	**2 (14.3)**	**14 (28.0)**	16 (25.0)	
≥2	**0 (0.0)**	**6 (12.0)**	6 (9.4)	
Number of lower cervical spine lesions with contrast enhancement (n, %)				
0	14 (100.0)	46 (92.0)	60 (93.8)	0.307*
1	0 (0.0)	3 (6.0)	3 (4.7)	
≥2	0 (0.0)	1 (2.0)	1 (1.6)	

*Chi-square test (Linear-by-Linear Association). OCB: Oligoclonal bands, MRI: Magnetic resonance imaging

Table 5. Comparison of thoracic MRI lesions and contrast enhancement according to OCB positivity

	OCB negative (n=14)	OCB positive (n=50)	Total (n=65)	p
Number of thoracic spine plaques (n, %)				
0	9 (64.3)	31 (62.0)	40 (62.5)	0.616*
1	**4 (28.6)**	**11 (22.0)**	15 (23.4)	
≥2	**1 (7.1)**	**8 (16.0)**	9 (14.1)	
Number of thoracic spine lesions with contrast enhancement (n, %)				
0	12 (85.7)	46 (92.0)	58 (90.6)	0.695*
1	2 (14.3)	3 (6.0)	5 (7.8)	
≥2	0 (0.0)	1 (2.0)	1 (1.6)	

*Chi-square test (Linear-by-Linear Association). OCB: Oligoclonal bands, MRI: Magnetic resonance imaging

compared with positive patients, but there were no significant clinical differences in their MS cohort. In a study investigating the relationship between disease subtype and OCB, negativity of OCB was observed more frequently in patients with PPMS compared to RRMS (6). In a recent study, positivity of OCB was associated with poor prognosis, both physically and cognitively (16). On the other hand, there were studies that concluded that OCB status was not associated with poor prognosis or even had no prognostic value (17,18,19). Moreover, Rojas et al. (20) observed that OCB-positive patients had a better prognosis and less disability during follow-up than OCB-negative patients. Regarding studies in Turkey, Ellidag et al. (14) reported that there was no difference between OCB-positive and -negative groups in terms of age and gender. Although the clinical characteristics of the patients were not considered in the mentioned study, it was reported that OCB had no effect on neurophysiological evaluations (visual evoked potentials, sensory evoked potentials). Conversly, Idiman et al. (15) found that patients with MS with OCB in the CSF were predominantly female and had a better clinical prognosis and less disability. When the treatment regimens were compared, there was no difference between OCB (+) and OCB (-) patients withMS, as in our study.

Studies investigating the association between OCB and MRI are limited. A study of a cohort of Italian patients with MS showed a lack of correlation between lesion distribution and OCBs (21). Mesaroc et al. (22) showed in their study that there was no significant difference between OCB (+) and OCB (-) patients in terms of cranial lesion size and atrophy. Zeman et al. (11) also found no significant difference in total brain MRI lesions between OCB (+) and (-) patients. In another study, no difference was found between OCB (+) and (-) patients in terms of size, number, range, and width of MRI lesions (23). Karrenbauer et al. (24) also found that OCB positivity did not increase the risk of MRI lesion burden. In contrast to these studies, studies showing that OCB positivity had an effect on MRI were also available in the literature. Heinonen et al. (25) found a correlation between plaque volume

on cranial MRI and intrathecal IgG index in patients with MS. There are studies showing that OCB positivity is associated with periventricular lesions (26,27). Farina et al. (16) showed that there was an association between increased cortical lesion load and OCB positivity in MS (15). Ferreira et al. (28) showed that patients with MS without OCB in the CSF had less global and regional brain atrophy. In our study, we compared the lesion burden on cranial and cervical MRI of patients with clinically definite MS with their OCB status. In terms of cranial lesion burden, although there was no statistical difference in our study, it was remarkable that OCB (+) patients had higher scores than OCB (-) patients. In the cervical spinal cord, OCB status did not differ in terms of the number of lesions and contrast enhancement in the upper segments of the cervical spinal cord. However, in the lower cervical spinal cord segments, a statistically significant difference was found between OCB (+) patients and OCB (-) patients. In terms of the clinical importance of the lower cervical spinal segment, it has been reported that the involvement of this region in patients with MS is associated with disability (29,30). Therefore, if OCB positivity causes more lesions in the lower cervical spine, which is a critical region in patients with MS, OCB positivity can be considered as a poor prognostic factor.

Conclusion

The number of studies investigating negativity of OCB in MS is limited. In this regard, data from Turkey are also insufficient. Since OCB negativity is in the minority of patients with MS, it is difficult to understand the effect of OCB in MS with this insufficient number of patients. The small number of OCB-negative patients was also a limitation in our study. Nevertheless, our study showed that OCB was associated with the number of lesions in the lower cervical segment of the spinal cord, which is a poor prognostic factor. Another limitation of our study could be its retrospective nature. In particular, MRI could have been performed with different protocols. Further randomized studies with a comprehensive follow-up are needed to understand this phenomenon.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, Istanbul Bagcilar Training and Research Hospital (decision no: 2020.12.2.01.201, date: 25.12.2020).

Informed Consent: Written informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.K.T., Design: N.K.İ., Data Collection or Processing: E.S., Analysis or Interpretation: N.K.T., Literature Search: S.Ö., Writing: N.K.T.

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