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Comparison of neurophysiological and MRI findings of patients with multiple sclerosis using oligoclonal band technique

Hamit Y Ellidag[1], Esin Eren[2], Nezahat Erdogan[3], Sabiha Ture[4], Necat Yilmaz[1]

[1]Central laboratories of Antalya Education and Research Hospital of Ministry of Health, Antalya; [2]Antalya Public Health Center of Ministry of Health, Antalya; [3]Radiology clinic; [4]Neurology clinic of Izmir Ataturk Education and Research Hospital of Ministry of Health, Izmir, TURKEY

KEY WORDS

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Corresponding Author:

Hamit Y Ellidag, MD
Tel : 00902422494400
E-mail : hayael1980@hotmail.com

ABSTRACT

Background: The correlation of oligoclonal bands (OCBs) and intrathecal IgG synthesis are not yet clear in multiple sclerosis (MS). **Purpose:** In this study, we investigated the OCB situation and IgG index, cranial and cervical magnetic resonance imaging (MRI) findings and also compared visual evoked potentials (VEP) and somatosensorial evoked potentials (SEP) in order to better understand the OCB pattern and pathogenesis. **Methods:** Retrospective study included 40 patients (19 male, 21 female, mean age 29 $\pm$ 4,24) with precise MS diagnosis according to McDonald criteria. **Result:** Sixteen of the patients were OCB negative, and 24 patients were positive. The different between the OCB situation and number of plaques in cranial and cervical MRI, atrophy, oedema and contrast material retention were insignificant. The different between the OCB situation and VEP and SEP were insignificant. **Conclusion:** These laboratory findings are all specific, all developing via independent mechanisms and are not related to each other during the silence periods of patients.

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Introduction

Multiple sclerosis (MS) is an inflammatory autoimmune disease of the central nervous system (CNS). It is characterized pathologically by acute multifocal demyelination as well as axonal loss and death of oligodendrocyte. The aetiology of MS is not completely understood and is widely believed to have genetic susceptibility, which may or may not be triggered by environmental factors.[1,2]

There is no accurate diagnostic test or clinical finding for the diagnosis of MS.[3–6] The diagnosis of MS is based on neurologic history, and exclusion of other disorders. Different paraclinical tests, such as detection of intrathecal IgG synthesis (present in most patients with MS), evoked potentials, and imaging techniques, are used to support the diagnosis when necessary. The single most consistent laboratory abnormality in patients with MS exclusive of magnetic resonance imaging (MRI) is increased oligoclonal immunoglobulins in cerebrospinal fluid (CSF).[4–7] Many methods and modifications of different sensitivity and specificity have been described to define oligoclonal bands (OCBs) in CSF.[7–8] Isoelectrical focusing (IF) is considered reliable modality in defining OCBs.[7–10]

The pathogenesis of OCBs and intrathecal IgG synthesis are not yet clear. In this study, we investigated the OCB situation and IgG index, cranial and cervical MRI findings and also compared visual and somatosensorial evoked potentials in order to better understand the OCB pattern and pathogenesis of MS.

Methods

Patient selection

Retrospective study included 40 patients (19 male, 21 female, mean age 29 $\pm$ 4,24) with precise MS diagnosis according to McDonald criteria,[11] who consulted Education and Investigation Hospital Neurology Clinics. Sixteen of the MS patients were OCB negative, and 24 were positive. Patients with dubious MS or clinic isole syndrome, or who had a previously diagnosed MS history were excluded from the study.

This study was performed in accordance with the ethical standards set by the Declaration of Helsinki and approved by the local ethics committee.

Biochemical analyses

Serum and CSF samples of all patients included in the study were taken concomitantly. These samples were frozen and kept until the day of analysis, and then CSF albumin, CSF IgG, serum albumin, serum IgG and oligoclonal band examinations were carried out collectively. CSF IgG, CSF albumin, serum IgG and serum albumin were detected by immunoturbidimetric and spectrophotometric methods using commercially available assay kits (Olympus) with an Olympus AU640 instrument.

After these examinations, IgG index was calculated as follows:

$$\text{IgG Index} = \frac{\text{CSF IgG / Serum IgG}}{\text{CSF albumin / Serum albumin}}$$

IgG specific oligoclonal bands in serum and CSF were detected using agarose gel isoelectric focusing and immunblotting techniques (using standard peroxidase method) via Helena Biosciences Europe Electrophoresis instrument. The pH gradients of agarose gels used in this method are between 3 and 10. Two or more bands in CSF is defined as OCB positive.

MRI analysis

MRI examinations are conducted by 1,5 tesla Philips Intera instrument. The MRI findings were evaluated with regard to the number of plaques in cranial and cervical MRI, atrophy, oedema and contrast material retention. Number of the plaques were evaluated as 5–10, 10–20 or more than 20. The localization of the plaques in cranial MRI was not taken into consideration. Also, contrast material retention, atrophy and oedema findings were evaluated as positive or negative.

The applied MS protocol is stated as follow:

Cranial, T2 Axial, T1 Axial, FLAIR Sagittal, T1 Sagittal (Negative contrast).

Cranial, T2 Axial, T1 Axial, FLAIR Sagittal, (Positive contrast, IV Gadolinium) T1 Axial, T1 coronal, T1 Sagittal.

Cervical, T2 Sagittal, T1 Sagittal, T2 Axial, (Positive contrast, IV Gadolinium) T1 Sagittal, T1 Axial.

Evoked potential analysis

VEP (Visual Evoked Potentials) and SEP (Somatosensory Evoked Potentials) analyses of all patients were done via Medelec Sapphire 4ME and Nihon Kohden instruments.

Statistical analysis

Statistical analysis was carried out using the statistical software version 11.5.1.0 (MedCalc, Mariakerke, Belgium). The direction and significance of association between variables were evaluated by using Chi-square and Fisher's exact test. P values less than 0.05 was accepted as the significance level.

Results

There were no significant differences in age or male/female ratio between OCB (+) and OCB (−) MS patients. IgG index, CSF protein, CSF LDH, EDSS and CSF WBC levels did not differ significantly between OCB (+) and OCB (−) MS patients (Table 1).

Cranial MRI and OCB

When the plaque numbers in the MRIs were evaluated, 16 patients had >20 plaques, 18 had 11–20 plaques, and 6 had 5–10 plaques. The relationship between the OCB status and number of plaques in cranial MRI was not significant ($p = 0.99$). According to the cranial MRI, atrophy was positive in 5 and negative in 35 patients, oedema was negative in all, contrast material retention was positive in 18 and negative in 22 patients. The relationship between these parameters and OCB status are shown in Table 2.

Cervical MRI and OCB

When the plaque numbers in cervical MRIs were evaluated, 9 patients had >20 plaques, 14 had 11–20 plaques, and 17 had 5–10 plaques. The relationships between the OCB status and number of plaques in cervical MRI were insignificant ($p = 0.74$). According to the cervical MRI, atrophy was positive in 13 patients and negative in 27, oedema was negative in

Table 1: Demographic and laboratory findings obtained from MS patients

Parameter	*OCB (+)*	*OCB (−)*	*P*
Patients (n = 40)	24 (60%)	16 (40%)	
Mean age	29,64	31,75	0,61
Gender; Male (19; 47,5%)	11	8	0,89
Female (21; 52,5%)	13	8	0,89
IgG index	1.15 (0.8–1.4)	0.8 (0.5–1.3)	0.10
CSF protein, g/L	40.5 (27.6–58.2)	39.9 (27.5–47.2)	0.99
CSF LDH, U/L	18 (11.9–25.9)	17.9 (14.8–23.5)	0.96
CSF WBC (cell/HPF)	0 (0–10)	0 (0–0,46)	0.35

Table 2: The relationship between cranial MRI findings and OCB pattern

Cranial MRI	*OCB (+)*	*OCB (−)*	*p*
Number of plaques			
5–10	4 (16.6%)	2 (12.5%)	0.99
11–20	10 (41.6%)	8 (50%)	
>20	10 (41.6%)	6 (37.5%)	
Atrophy			
Positive	4 (16.6%)	1 (6.25%)	0.63
Negative	20 (83.3%)	15 (93.75%)	
Oedem	Negative in all patients		
Contrast material retention			
Positive	12 (50%)	6 (37.5%)	0.52
Negative	12 (50%)	10 (62.5%)	

19 and positive in 21, contrast material retention was positive in 17 and negative in 23 patients. The relationship between these parameters and the OCB situation gave insignificant results (Table 3).

Neurophysiological findings and OCB

VEP (Visual Evoked Potentials) and SEP (Somatosensory Evoked Potentials) results of all included patients could be obtained. 23 patients had abnormal VEP, and 17 had normal VEP. Likewise, 15 had abnormal, and 25 patients had normal SEP. The relationship between OCB and VEP/SEP was found to be insignificant (Table 4).

Discussion

In this retrospective study, we investigated the correlation between cranial/cervical MRIs, neurophysiological tests and OCB status [OCB (+) or OCB (−)] of clinically definite MS patients. We determined that 40 MS patients who had no significant correlation between age/gender were 24 OCB (+) (60%) and 16 were OCB (−) (40%).

Oligoclonal bands are positive in 85-95% patients with clinically confirmed MS. In a 10-year study period, Rot *et al.*[12] reported 12.8% of the patients had oligoclonal band-negative multiple sclerosis. Zeman *et al.*[5] demonstrated that only 3% of their patients with clinically definite multiple sclerosis were oligoclonal band-negative. However, studies investigating OCB (−) MS were scarce. These studies showed that oligoclonal band-negative MS had a better prognosis than oligoclonal band-positive MS.[5,17]

Table 3: The relationship between cervical MRI findings and OCB pattern.

Cervical MRI	*OCB* (+)	*OCB* (−)	*P*
Number of plaques			
5–10	10 (41.6%)	7 (43.75%)	0.74
11–20	8 (33.3%)	6 (37.5%)	
>20	6 (25%)	3 (18.75%)	
Atrophy			
Positive	9 (37.5%)	4 (25%)	0.50
Negative	15 (62.5%)	12 (75%)	
Oedema			
Positive	13 (54.2%)	8 (50%)	0.99
Negative	11 (45.8%)	8 (50%)	
Contrast material retention			
Positive	12 (54.6%)	5 (28%)	0.11
Negative	10 (45.4%)	13 (72%)	

Table 4: The relationship between neurophysiological findings and OCB pattern

Parameters		*OCB* (+)	*OCB* (−)	*P*
VEP	Normal	10 (41.6%)	7 (43.75%)	0.99
	Abnormal	14 (58.4%)	9 (56.25%)	
SEP	Normal	15 (62.5%)	10 (62.5%)	0.99
	Abnormal	9 (52.5%)	6 (52.5%)	

Some authors have found that the frequency of OCB (−) patients with MS was high, which is similar to our results. Fukawaza *et al.*[13] showed that 43.9% of Japanese patients had oligoclonal band-negative multiple sclerosis and Nakashima *et al*.[14] showed that this ratio was 41%. These data show that the eastern and far-eastern populations had a higher OCB (−) MS ratio or the findings may be the result of the method used and the subjective interpretation of the result.[15] Andlovic *et al.*[16] showed that the novel alkaline phosphatase assay is more sensitive than the standard peroxidase method for detection of OCBs. They compared the two methods and concluded that in patients with clinically isolated syndrome and MS OCB were more often present when analysis was performed by using the novel assay.

To date, there has been no definite association of these oligoclonal bands with any consistent antigens in patients with MS. It is clear that intrathecal antibody synthesis against many different antigens contributes to the IgG oligoclonal bands in CSF, either detected by antigen-driven immunoblots or by quantitative detection with the antibody index. But, to date, there has been no definite association of these specific antigens with the cause of MS. Some particular observations, such as the high frequency (despite low intensity) of intrathecal antibodies against neurotropic viruses in MS need further discussion. It is also clear that many of these antibodies have low affinity.[18,19,21] The same pattern consistently seen in an individual over time suggests that a sustained chronic intrathecal immune response may be seen which is unique to each individual. It is also impossible to eliminate the presence of these bands following intensive immunosuppression treatment when a complete immune ablation is needed, such as autologous bone marrow transplantation in MS.[20,22,23]

Many present studies have emphasized the importance of MRI in the diagnosis and follow-up of MS.[24–28] However, studies investigating the relationship between OCB and MRI are limited. In our study we compared the cranial and cervical MRI findings (atrophy, oedema, contrast material retention, number of plaques) of clinically definite MS patients with their OCB conditions and did not get a significant result. Mesaroc *et al*.[29] similarly did not find a significant correlation between OCB (+) and OCB (−) patients in respect to cranial lesion size and atrophy. In the same study, no significant correlation was found between EDSS – a disability scale – and MRI findings of OCB (-) patients, while there was a significant correlation between those of OCB (+) patients. Pou *et al*. showed good correlation between the clinical features and the morphology and location of the plaques determined in spinal cord MRI.[30] On the other hand, Zeman *et al.*[5] found no relationship between OCB (+) and (−) patients with regard to total brain MRI lesions. Fukazawa *et al.*[31] showed no difference between OCB (+) and (−) patients in respect to the size, number, range and width of MRI lesions. The same researchers found no significant correlation between OCB (+) and (−) patients with regard to their MRI findings in another study.[13] Heinonen *et al.*[32] found a correlation between the plaque volume in cranial MRI and intrathecal IgG synthesis rate of MS patients.

In early studies, the evoked potentials abnormalities were mostly correlated with the damage and clinical findings of the

nervous system, while the correlation was poor between the lesions in MRI and the symptoms and findings.[33–36] In our study, a chi-square test was performed between the evoked potentials and OCB situations of patients, but no significant relationship was found. Mesaros *et al.* researched the correlation between CSF findings and evoked potentials and found that SEP abnormalities are more frequent in OCB (+) MS patients compared to OCB (−) patients according to the CSF examinations, while no significant difference was present between two groups in respect to VEP abnormalities.[37] Similar to earlier findings[4–7] another study in ALS patients where the CSF of ALS patients was analysed for OCB stated the presence of IgG in CSF. Out of 259 ALS patients 9 were reported to have presence of IgGs in their CSF.[38] MRI may act as non-invasive tool for analysing such abnormalities whether it may be in form of breaking blood brain barrier or overlapping disease pathophysiologies. In 2012 a group from university of Napels, Italy came out with a case report stating the overlap in disease diagnosis through MRI, CSF analysis and OCB technique. Authors described this overlap as an unusual overlap leading to discussion of common pathway involved in pathophysilogy of both ALS and MS.[39]

Such comparative studies between radiology and molecular investigations could be launched in other degenerative disorders as well such as ALS, AMD, AD, PD. Earlier there have been studies involving biomarkers in body fluids such as blood and CSF for advancing the diagnostic criterias for degenerative diseases like ALS, PD and AMD.[40–48] The purpose for conducting these studies was to ascertain more reliable experiment diagnostic criteria. However *in vitro* studies may facilitate the research in diagnostic field. Studies involving the analysis of cell culture of stem cells in their niche matching the conditions in diseased entity may help more specifically in understanding the pathophysiology of disease. Recently, the putative role of VEGF in nurturing and proliferating the stem cells through different signalling pathways was studied. Human pigmented ciliary epithelium stem cells were cultured and neurospheres were analysed for the proliferation capacity of PCE in presence of VEGF. An increased NOTCH and JAGG, N Cadherin and Beta Cadenin expression was observed in cells at different time points, thus validating the role of VEGF in proliferation of stem cell.[49] This study provides insight about diseased condition body when the production of VEGF may compensate for dying neurons. This is validated by study reporting increased expression of VEGF in ALS (which is also considered as possible biomarker for ALS diagnosis).[40] In current scenario non invasive techniques such as MRI scanning can be more beneficial with respect to patient centric research.

Furthermore, the information in the literature shows that the OCBs in MS show different properties according to the geographic regions. Many studies are carried out in different countries while no approved systematic study is carried out in our country. Thus, the OCB results of MS patients in this geographic region and the relationships of these results with other diagnostic markers should be investigated in more detailed. However, major limitation of the study is the small number of samples. Therefore, larger studies are needed with more cases and extensive MRI scanning.

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