Research Article

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Cerebrospinal fluid oligoclonal banding patterns and intrathecal immunoglobulin synthesis: Data comparison from a wide patient group

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Abstract

Objective: This study aimed to evaluate laboratory oligoclonal band (OCB) patterns together with related IgG results and compare these results with data obtained through final clinical diagnosis. Also, to evaluate electrophoretic patterns based on reibergrams and the diagnostic value of OCBs in patients with multiple sclerosis (MS).

Methods: Patients were grouped based on their diagnosis. Six classic patterns were determined. Oligoclonal band patterns and related IgG results were evaluated and these results were later compared with final clinical diagnoses.

Results: A total of 1022 patients with known diagnoses were studied. Electrophoretic patterns and band counting based on Reibergram depictions were significantly different among patients with MS and other neurologic diseases. For all patients with MS, the OCB band positivity rate was 82.4%. Additionally, in the MS group, a significantly higher percentage (36.60%) of OCB positivity with more than 10 bands was detected. When reibergram results in the intrathecal IgG synthesis area and OCB counts (>10) were evaluated together, the diagnostic sensitivity (37%) and specificity (95%) were increased.

Conclusion: OCB positivity, band counts, and Reibergram depictions contribute further to the diagnosis of ms when performed together for the neurologic diseases spectrum. OCB count, IgG index values, and Reibergram depictions should all be included in cerebrospinal fluid electrophoresis reports. The combined use of several laboratory test results are expected to provide valuable input for differential diagnosis of neurologic diseases.

Keywords: Multiple sclerosis, cerebrospinal fluid, Oligoclonal IgG, IgG index, isoelectric focusing electrophoresis

INTRODUCTION

Cerebrospinal fluid (CSF), as a metabolically active environment, is a key specimen for the diagnosis of neurologic diseases. Changes in the composition of CSF accurately reflect pathologic events providing a unique perspective for the evaluation of central nervous system (CNS) disorders. Thus, CSF analysis is a valuable diagnostic tool for the evaluation of inflammatory, infectious or non-infectious conditions of the brain, spinal cord, and meninges. On the other hand, different diseases may result in similar alterations in CSF leading to interpretation-related challenges. For the purpose of increasing diagnostic specificity, using a set of CSF parameters (i.e., albumin, total protein, immunoglobulin, glucose, lactate, cell count, and electrophoretic analysis) is recommended (1). A broad spectrum of neurologic diseases necessitates an analysis of this set of CSF parameters for differential diagnosis purposes.

Abnormal immunoglobulin (Ig)-G in the CSF can be detected quantitatively and qualitatively in demyelinating diseases, especially in multiple sclerosis (MS), as well as different neurologic, infectious or inflammatory diseases of the CNS. Quantitative CSF IgG is generally expressed by the IgG index, whereas qualitative CSF IgG is determined using isoelectric focusing (IEF) electrophoresis, followed by immunoblotting or immunofixation for IgG. The detection of oligoclonal bands (OCBs) in the CSF of patients suspected of having multiple sclerosis supports the intrathecal synthesis, which is compatible with MS. Oligoclonal IgG bands are present in serum in many disorders, as well as being present in the CSF due to disruption of the blood-brain barrier, thus parallel analysis of CSF and serum samples is imperative (2-4).

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Six classic patterns were observed in electrophoretic analysis: type 1, no bands in CSF and serum; type 2, oligoclonal IgG bands in CSF, type 3, oligoclonal bands in CSF and serum with additional bands in CSF; type 4, identical oligoclonal bands in CSF and serum, type 5, monoclonal bands in CSF and serum, and type 6, presence of a single band limited to the CSF. Type 2 and 3 indicate intrathecal synthesis, and type 1, 4, 5, and 6 are considered as negative results (4, 5).

MS is an autoimmune, inflammatory demyelinating disease of the CNS. Finding oligoclonal IgG bands in the CSF but not in the sera of a high percentage of patients with MS indicates intrathecal IgG synthesis (6). However, OCBs may also be found in other diseases of the CNS and even in systematic conditions (7, 8). With the Reibergram being the unique part of CSF analysis, albumin and immunoglobulin quotients were calculated with serum and CSF albumin and immunoglobulin results. The calculated albumin (Q_{Alb}) and immunoglobulin (Q_{IgG}) quotients could be spotted in Reibergram. It provides additional information related to the function of blood-brain barriers (BBB) and intrathecal synthesis of immunoglobulin in neurologic diseases (Figure 1).

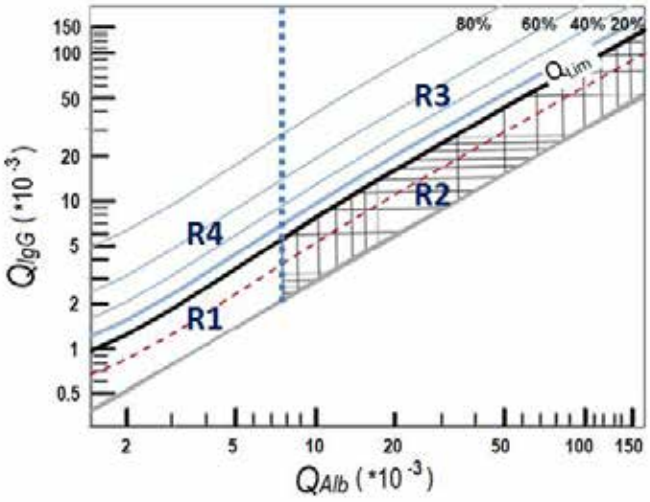
This study aimed to evaluate laboratory OCB patterns together with related IgG results and compare these results with data obtained through the final clinical diagnosis. It also attempted to elaborate on additional evaluations of electrophoretic patterns based on Reibergrams and the diagnostic value of OCBs in MS.

METHODS

Study Population

From July 2009 to June 2014, data regarding the results of oligoclonal band analyses and IgG indexes with related parameters (albumin and IgG in both serum and CSF) of Hacettepe University Hospitals Clinical Pathology Laboratory were compiled from the Laboratory Information Database (LID) and were processed. Patients aged older than 18 years with co-existing results of IgG indexes and oligoclonal band analyses were included in the study. A total of 1022 patients fulfilled the inclusion criteria. For patients with multiple LPs, only the first result was used in the study. After a detailed analysis of 1022 patient results, it was seen that a total of 975 patients had one, 40 patients had two, 6 patients had three, and 1 patient had four LPs and corresponding oligoclonal band analyses performed. The diagnosis of MS was based on Mcdonald's 2010 criteria (9). The final diagnoses of these patients were confirmed through a careful investigation of medical records and discharge reports by expert neurologists, and then these 1022 patients were divided into 6 groups based on their diagnoses: group I included patients with MS; group II included non-MS demyelinating diseases (CNS demyelinating diseases (CNS DMD), neuromyelitis optica (NMO), optic neuritis (ON), acute disseminated encephalomyelitis (ADEM), MS and chronic inflammatory demyelinating polyneuropathy

Figure 1. CSF/serum quotient diagram for IgG according to Reiber (19). The four areas: R1, normal; R2, abnormal BBB function without local synthesis of IgG (reduced CSF turnover); R3, local IgG synthesis with abnormal BBB function; R4, local synthesis of IgG with normal BBB function (10, 20).



(MS+CIDP)); group III included CNS infectious and inflammatory diseases (CNS infections, CNS inflammatory diseases, neuro Behcet, autoimmune encephalitis, granulomatous, type 1 vasculitis, type 2 vasculitis, myelitis and optic neuropathy); group IV included other diagnosis (neurodegenerative, prion, pseudotumor cerebri, amyloidosis, cerebrovascular occlusion, movement disorders, mitochondrial diseases neoplasms, leukodystrophy, toxic-metabolic encephalopathies, paraneoplastic syndromes, and other diagnoses); group V peripheral neuropathy (PNP), and lastly, group VI comprised unknown diagnoses.

The study protocol was approved by the Hacettepe University / Non-interventional Clinical Research Ethics Board (Protocol approval date 09/10/2013, number GO 13/451).

Determination of Albumin and IgG

For IgG indexes and oligoclonal band analyses, our laboratory accepts CSF samples together with blood obtained in tandem. Analysis of each paired CSF and blood sample was performed in the same analytical run.

Analyses of albumin and IgG in serum and CSF were performed using nephelometry (Immage 800; Beckman Coulter, Inc. Fullerton, CA, USA). During the study period, quality control monitoring was conducted both through a domestic internal quality control program of our laboratory for each run, and an external quality control program from "UK NEQAS for CSF proteins and biochemistry." IgG indexes were calculated using the following formula (9):

$$\text{IgG index} = \frac{\text{CSF IgG (mg/dL)} / \text{serum IgG (mg/dL)}}{\text{CSF Albumin (mg/dL)} / \text{Serum Albumin (mg/dL)}}$$

Table 1. Demographics, IgG, and OCB positivity index parameters of the study population

Diagnostic Group	n	Female, N (%)	Male, N (%)	Age	QAlb*	IgG Index**	OCB Positivity (%)
I. MS	262	165 (63.0%)	97 (37.0%)	34.5 (±11)	4.54 [0.39 - 58.16]	0.70 [0.16 - 3.93]	82.4
II. NonMS-DMD	48	30 (62.5%)	18 (37.5%)	39.3 (±15)	5.09 [1.43 - 55.09]	0.51 [0.04 - 3.08]	35.4
III. Inflammatory	184	98 (53.3%)	86 (46.7%)	42.8 (±16)	5.66 [0.77 - 72.31]	0.55 [0.05 - 6.95]	29.9
IV. Noninflammatory	332	158 (47.6%)	174 (52.4%)	45.9 (±17)	5.71 [1.14 - 76.15]	0.47 [0.05 - 3.33]	9.6
V. PNP	90	29 (32.2%)	61 (67.8%)	53.9 (±17)	9.62 [1.01 - 46.24]	0.49 [0.19 - 2.05]	3.3
VI. Unknown	106	74 (69.8%)	32 (30.2%)	36.0 (±12)	4.24 [1.95 - 20.00]	0.51 [0.10 - 2.83]	41.5

OCB: oligoclonal band; MS: multiple sclerosis; NonMS-DMD: non multiple sclerosis-demyelinating diseases; PNP: peripheral neuropathy
Mean (±SD) for age; Median [Min–Max] for QAlb and IgG index; *QAlb results: Group I and group VI were significantly different from groups III, IV and V ($p<0.001$); **IgG index results: Group I was significantly different from the other groups ($p<0.001$)

Oligoclonal Band Analysis

Each paired sample of serum and CSF was analyzed on Hydragel CSF Isofocusing (Sebia) gel, performed using Sebia® Hydrasys system (Sebia; Norcross, GA). The procedure involves isoelectric focusing on agarose gel followed by immunofixation with peroxidase labeled anti-IgG antiserum. IgG concentrations in both CSFs and sera were adjusted to the same level. The assay then was performed in accordance with the manufacturer's guidelines. Although OCB analyses were first performed according to 5 classic banding patterns, reevaluation of IEF gels were performed by two blinded expert biochemists based on six newly recommended pattern types (6). Type 2 and 3 were interpreted as OCB positive results. The presence of two or more discrete bands of IgG was interpreted as oligoclonal bands. OCB counts were grouped as: OCB, OCB+ <10 (2 to 10 bands), OCB+ >10 (10 bands or more). OCB positive and negative controls were used in each run on Hydragel 9 CSF IEF. Our laboratory is also a member of the external quality control program of "UK NEQAS for CSF Oligoclonal bands," and internal quality control was also monitored during the study period.

Reibergram Evaluation

Reibergram analyses were also performed in order to evaluate IgG index results (10). Albumin and immunoglobulin quotients were calculated by assessing albumin and IgG levels in the CSF and serum of our patients based on the following formula:

Q_{Alb} = CSF albumin (mg/dL) / serum albumin (mg/dL) and

Q_{IgG} = CSF IgG (mg/dL) / serum IgG (mg/dL).

The calculated Q_{Alb} and Q_{IgG} quotients were first spotted on Reibergram (Figure 1). Patients were then grouped as R1-R4 in terms of their spotted areas. Q_{Alb} cut-off values for age groups were assigned using the formula: $Q_{Alb} = (4+age(y)/15) \times 10^{-3}$ (10).

Statistical Analysis

Statistical analyses were generated using the IBM SPSS for Windows Version 21.0 (IBM Corp.; Armonk, NY, USA) statistical package. Continuous variables are presented as mean±standard deviation and median [minimum – maximum]. Categorical variables are summarized as frequencies and percentages. Normality of the continuous variables was examined using the Shapiro-Wilks test. Independent group comparisons were performed using the Kruskal-Wallis test. A p value of less than 0.05 was flagged by SPSS as significant.

RESULTS

Patient Subgroups with Different Diagnoses and IgG Indexes

Patient demographics and quantitative CSF and serum results were reported in Table 1. The female/male ratios of group I and group II were significantly higher than in the other groups ($p<0.001$). The Q_{Alb} results of group I and group II were significantly different than in group III, group IV, and group V ($p<0.001$). The IgG index and OCB positivity (type 2 and type 3 patterns) in group I was observed to be significantly higher than the other groups ($p<0.001$).

The electrophoretic pattern distributions of all groups are given in Table 2 and Figure 2. Among all the groups (1022 patients), 367 (35.9%) OCB-positive results (type 2 and 3) were detected.

For all patients with MS, the OCB band positivity rate was 82.4%.

Patients with multiple lumbar punctures

A total of 1022 results were evaluated in our study. The first results of the patients with multiple lumbar punctures (LPs) were evaluated for OCB and Reibergram analysis. With a detailed analysis of 1022 results, 974 patients had one, 41 patients had two, 6 patients had three, and 1 patient had four LPs and oligoclonal band analyses were performed for each of

Table 2. OCB patterns in patient groups

		OCB patterns (%)					
Diagnostic Group	**n**	**Type 1 n (%)**	**Type 2 n (%)**	**Type 3 n (%)**	**Type 4 n (%)**	**Type 5 n (%)**	**Type 6 n (%)**
I. MS	262	42 (16.2)	201 (76.2)	15 (5.7)	0	0	4 (1.9)
II. NonMS-DMD	48	27 (52.9)	15 (27.5)	2 (7.8)	2 (5.9)	0	2 (5.9)
CNS DMD	23	8	12	2	1	-	-
NMO	13	9	3	-	1	-	-
ON	8	8	-	-	-	-	-
ADEM	2	2	-	-	-	-	-
MS+CIDP	2	-	-	-	-	-	2
III. Inflammatory	184	117 (62.5)	40 (23.3)	15 (7.1)	11 (5.2)	0	1 (1.4)
CNS infections	42	18	11	7	6	-	-
CNS inflammatory diseases	18	12	4	1	-	-	1
Neuro Behcet	13	10	3	-	-	-	-
Autoimmune encephalitis	16	13	2	1	-	-	-
Granulomatous	15	9	4	-	2	-	-
Type 1 vasculitis	36	26	6	3	1	-	-
Type 2 vasculitis	30	18	8	3	1	-	-
Myelitis	9	6	2	-	1	-	-
Optic neuropathy	5	5	-	-	-	-	-
IV. Noninflammatory	332	274 (82.5)	23 (6.9)	9 (2.7)	23 (6.9)	1 (0.3)	2 (0.6)
Neurodegenerative	75	68	3	1	3	-	-
Prion	12	11	-	-	1	-	-
CVO	47	45	-	-	2	-	-
Neoplastic	32	22	1	2	6	1	-
Toxic-metabolic	15	14	-	1	-	-	-
Paraneoplastic	8	5	2	-	1	-	-
Pseudotumor cerebri	13	11	-	-	2	-	-
Mitochondrial	18	14	3	-	-	-	1
Movement disorders	26	25	1	-	-	-	-
Amyloidosis	6	4	1	-	1	-	-
Leukodystrophy	3	3	-	-	-	-	-
Others	77	52	12	5	7	-	1
V. PNP	90	77 (85.6)	1 (1.1)	2 (2.2)	7 (7.8)	1 (1.1)	2 (2.2)
VI. Unknown	106	58 (54.7)	40 (37.7)	4 (3.8)	2 (1.9)	-	2 (1.9)

OCB: oligoclonal band; MS: multiple sclerosis; NonMS-DMD: non multiple sclerosis-demyelinating diseases; PNP: peripheral neuropathy

them (Table 3). The aim of multiple LPs was to reach the correct final diagnosis. Bearing that in mind, this diagnosis was used in the study.

Positive oligoclonal band results

The number of patients who were OCB positive (82.4%) in group I was significantly higher than in all the other groups ($p<0.001$) (Table 1, Figure 2). The electrophoretic pattern groups of all patients spotted on Reibergrams are shown in Figure 3.

Oligoclonal band results in patients with the known diagnosis

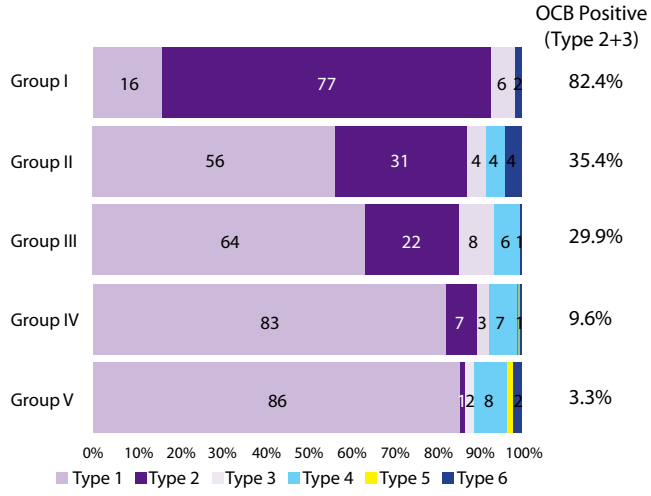
Patients with known diagnoses were studied. The Q_{Alb} and Q_{IgG} values were determined and the results were processed on Reibergrams with their corresponding diagnostic groups. Reibergram locations for each patient were spotted, and grouped as R1, R2, R3, and R4. Reevaluation of patients who were OCB positive was also performed using IEF, accordingly (Figure 4). In group I, a significantly high percentage (36.60%)

Table 3. OCB patterns of multiple LPs

Diagnostic Group	Patient, n	OCB Unchanged	OCB Changed
I. MS	2	1 patient type 6	1 patient type 3→2
II. Non-MS DMD	4	1 patient type 1	1 patient type 4→3 1 patient type 2→3 1 patient type 2→1
III. Inflammatory	23	12 patient type 1 4 patient type 2 1 patient type 4	3 patient 1→2 1 patient 3→2 1 patient 2→6 1 patient 1→4
IV. Non-inflammatory	15	9 patient type 1 2 patient type 2 1 patient type 4	1 patient 2→3 1 patient 4→1 1 patient 3→2
V. PNP	4	3 patient type 1	1 patient 1→3
VI. Unknown	0	0	0

OCB: oligoclonal band; MS: multiple sclerosis; NonMS-DMD: non multiple sclerosis-demyelinating diseases; PNP: peripheral neuropathy

Figure 2. OCB type distributions according to patient groups. There was a significant difference between group I and the other groups according to OCB positivity (p<0.001). Although no difference was observed between groups II and III, a significant difference was seen between group IV and group V compared with the other groups (p<0.001).



of OCB positivity with more than 10 bands was detected (p<0.001). In the same group, a small percentage of OCB-negative patients mostly fell into R1 and R2 areas.

A total of 262 patients with MS were reevaluated for the clinical course of the disease. Only 222 patients with MS were classified in to MS subgroups because of an unknown course in 40 patients: 165 relapsing-remitting MS (RRMS); 53 primary-progressive MS (PPMS); and 4 secondary-progressive MS (SPMS). There was no statistically significant difference between the RRMS and PPMS groups for IgG index and Q_{Alb} results. In terms of the number of oligoclonal bands (<10 vs. >10), there were no differences between the patients with RRMS and PPMS.

Table 4. Sensitivity and specificity study for 262 patients with MS and 654 non-MS cases

Diagnostic Group	Sensitivity (%)	Specificity (%)
Q_{Alb} (cut-off = 6.24)	79.4	48.2
IgG index (cut-off = 0.59)	69.4	76.7
R4	43.5	92.0
OCB (+)	82.4	83.6
OCB (+ >10)	51.5	92.0
R4 with OCB (+ >10)	37.0	95.0

OCB: oligoclonal band
OCB (+): OCB (+ <10) for 2 and 10 bands positive in CSF and more than 10 bands positive in CSF; OCB (+ >10): more than 10 bands positive in CSF; R4: Reibergram location in R4 (local synthesis of IgG with normal BBB function)

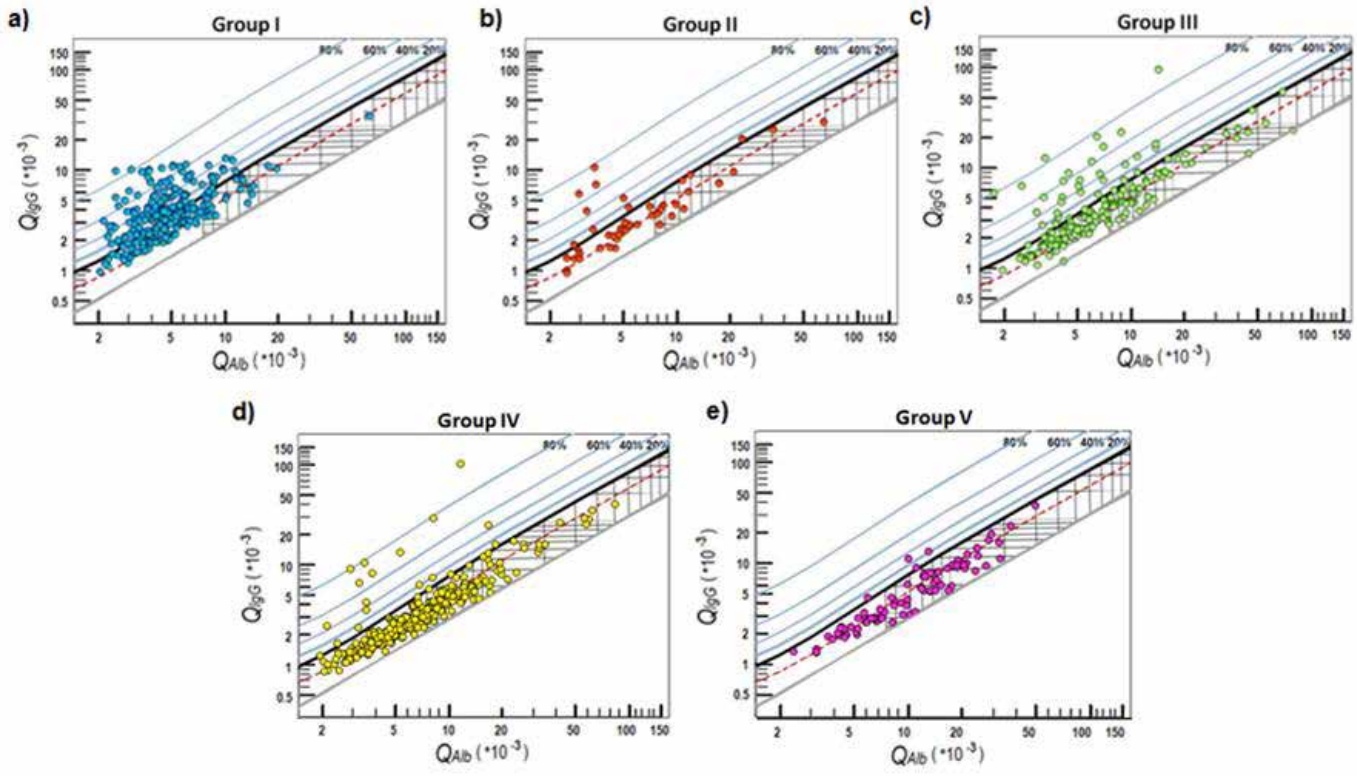
DISCUSSION

MS is the most common demyelinating disorder of the CNS. For a definitive diagnosis, several clinical, laboratory, and magnetic imaging criteria are used. For the detection of intrathecal IgG synthesis, imaging techniques and evoked potentials proved to be useful diagnostic approaches that supported clinical findings.

There were higher ratios of female patients in groups I and II, which is expected for MS and non-MS autoimmune demyelinating disorders of the nervous system. Female/male ratios were similar in these two groups; 63%/37% and 62.5%/37%, respectively. Interestingly, there was a higher percentage of males in group V. The mean ages of group I and group II were significantly younger than the other two groups (p<0.001). As a result, significantly different sex and age distributions were observed between MS/non-MS demyelinating disorders compared with other neurologic disorders.

As previously reported, high Q_{Alb} (>20 x 10^{-3}) results were not consistent with MS. Our MS group also did not show high Q_{Alb}

Figure 3. a-e. Diagnostic group distributions for IgG on the Reibergram: a) group I, b) group II, c) group III, d) group IV and e) group V.



readings, which is consistent with previous studies in the field (10). High IgG index and Q_{Alb} results in inflammatory disorders have been previously reported. Our results were also compatible with these findings (11).

In the MS group, all patients with IgG index results higher than 0.7 displayed OCB positivity (type 2). Hacohen et al. also found the median IgG index value as 0.71 in their MS group and claimed that this value was significantly higher than that of the non-inflammatory group (11). Mayringer et al. also found out that there was a positive correlation between the IgG index and the frequency of OCB, as well as the probability of a demyelinating disease (7).

Regional differences in band positivity for patients with MS have previously been reported in the literature (12). Band positivity was approximately 95% in northern Europe, whereas this ratio was lower in southern regions (12, 13). There were higher rates of OCB-negative patients with MS in the Japanese population (14). As a transition zone between Europe and Asia, Turkey has a heterogeneous demographic structure. Hence, band negativity in Turkey has been found to be higher than in Europe. In the present study, 82.4% band positivity was detected in patients with MS. İdiman et al. found 85.7% band positivity, and it was 60% in the study by Ellidag et al. (15, 16). It is worth suggesting that our country also bears regional differences.

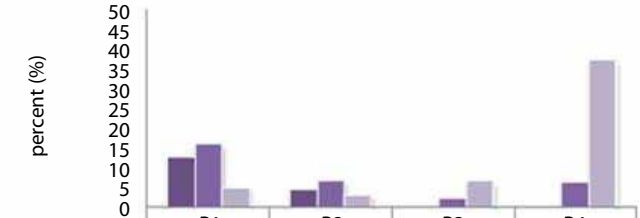
Positive CSF-restricted IgG oligoclonal bands is the main sign of intrathecal IgG synthesis. The presence of OCBs in CSF IEF electrophoresis is the most valuable laboratory test for the diagnosis of MS. Of the 262 patients with MS, 216 (82.4%) showed OCBs in our study. No OCB bands were detected in 46 (17.6%) patients. Type 2 and type 3 patterns were significantly detected in the MS group. As previously suggested, a modern approach to CSF analysis uncovers typical patterns specific for distinct neurologic diseases (19). We also suggest that consideration of band counts and evaluation with Reibergrams has differential values in MS diagnosis (Table 4); when OCBs >10 and Reibergram results in the R4 area (intrathecal IgG synthesis), the sensitivity (37.0%) and specificity (95.0%) were increased. Therefore, combined use of these tests increased the diagnostic specificity.

In the MS group, although few bands were detected in the R1 and R2 areas, significantly more bands (more than 10 bands) were observed in the R4 area. Groups of non-MS and CNS DMD disease followed with the second highest OCB positivity, but showed significantly lower ratios when compared with the MS group. Patients with ON and ADEM showed no OCBs because our group was very small. We found rare OCB band positivity for patients with neuro Behcet in group III. Saruhan-Dreskeneli also previously reported the rare presence of OCB positivity in the CSF of their Behcet's disease group (20).

Oligoclonal band (OCB) positivity and intrathecal IgG synthesis are the most important findings in the diagnosis

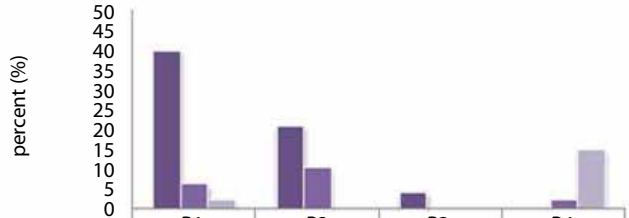
Figure 4. a-e. Patients subgroup comparisons: a) group I, b) group II, c) group III, d) group IV, and e) group V. OCB (-) for OCB negatives, OCB (+<10) for 2 and 10 bands positive in CSF, and OCB (+>10) for more than 10 bands positive in CSF. R1, R2, R3, and R4 groups identified as Reibergram locations. Group I showed a statistically significant difference from other groups according to Reibergram location distributions (p<0.001).

a



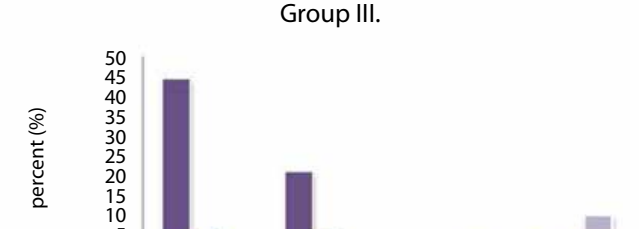
	R1	R2	R3	R4
OCB (-)	12.60	4.58	0.00	0.38
OCB (+<10)	16.03	6.49	2.29	6.11
OCB (+≥10)	4.96	3.05	6.49	37.02

b



	R1	R2	R3	R4
OCB (-)	39.58	20.83	4.17	0.00
OCB (+<10)	6.25	10.42	0.00	2.08
OCB (+≥10)	2.08	0.00	0.00	14.58

c

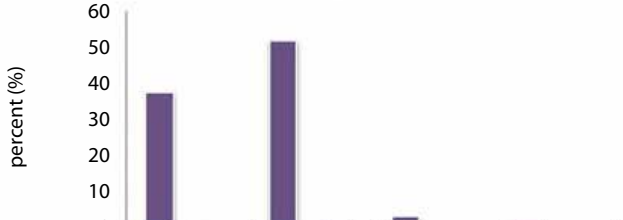


	R1	R2	R3	R4
OCB (-)	44.57	21.74	0.54	3.26
OCB (+<10)	5.43	5.98	1.09	1.09
OCB (+≥10)	1.09	0.54	3.80	10.87

d

	R1	R2	R3	R4
OCB (-)	54.22	31.63	0.90	1.51
OCB (+<10)	2.41	3.92	0.30	0.90
OCB (+≥10)	1.20	0.60	0.60	1.81

e



	R1	R2	R3	R4
OCB (-)	37.78	52.22	3.33	2.22
OCB (+<10)	1.11	1.11	0.00	0.00
OCB (+≥10)	0.00	2.22	0.00	0.00

of MS. OCB evaluation is expected to provide additional insight into the differential diagnosis of non-MS inflammatory and non-inflammatory disorders of the neurologic system. We concentrated on this issue during the evaluation of our results.

To our knowledge, this is the first study in which comparisons of OCB positivity, band counts, and Reibergram evaluations were performed together for the neurologic diseases spectrum. As previously suggested, the combined use of more than one laboratory test might provide more useful results for the differential diagnosis of neurologic diseases (19). OCB count, IgG index values, and Reibergram evaluations should be provided together in CSF electrophoresis reports.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Hacettepe University / Non-interventional Clinical Research Ethics Board (Protocol approval date 09/10/2013, number GO 13/451).

Informed Consent: Written informed consent was waived due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.P.; Design - A.P., A.T.K.; Supervision - A.P., F.A., R.K.; Resources - A.P., İ.L., F.A.; Materials - A.T.K., R.K.; Data Collection and/or Processing - A.P., İ.L., S.K.; Analysis and/or Interpretation - A.P., İ.L., S.K.; Literature Search - A.P., A.T.K., N.P.A., İ.L.; Writing Manuscript - A.P., A.T.K., N.P.A.; Critical Review - A.P., A.T.K., N.P.A.

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Conflict of Interest: No conflict of interest was declared by the authors.

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