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ORIGINAL ARTICLE

The relationship between lesion volume, oligoclonal bands, and cerebrospinal fluid/serum albumin ratio in multiple sclerosis

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ABSTRACT

Objectives: This study aimed to investigate the association between the presence of oligoclonal bands (OCB) in cerebrospinal fluid (CSF), immunoglobulin G (IgG) index, CSF/serum albumin ratio, demyelinating lesions (number and volume), and brain atrophy in patients with multiple sclerosis (MS).

Patients and methods: A total of 47 patients diagnosed with MS, with OCB type 1 (n=21; 14 females, 7 males; median age: 34 years; range, 21 to 58 years) and type 2 (n=26; 20 females, 6 males; median age: 31 years; range, 20 to 53 years) detected, were retrospectively examined between July 2022 and July 2023. Cerebrospinal fluid biomarkers, the number, volume, and distribution (periventricular, subcortical, juxtacortical, or infratentorial) of demyelinating lesions, and lesion burden were compared. The presence of atrophy in the cerebrum, cerebral gray matter, cerebellum, and brainstem at baseline, and Expanded Disability Status Scale (EDSS) scores at baseline, were recorded.

Results: The IgG index was statistically significantly higher in patients with OCB type 2 compared to type 1 ($p<0.05$), irrespective of whether it exceeded 0.70. No significant associations were found between OCB types and CSF/serum albumin ratio, baseline EDSS scores, and baseline total demyelinating lesion volume and distribution ($p>0.05$). A moderate positive correlation was observed between IgG index and periventricular lesion volume ($r=0.507$, $p<0.05$). No significant correlation was found between any two of the other parameters. Among individuals with OCB type 1, atrophy was observed in the total cerebrum (47%), total cerebral gray matter (38%), cerebellum (4.7%), and brainstem (28.5%). Among individuals with OCB type 2, atrophy was observed in the total cerebrum (69%), total cerebral gray matter (26%), cerebellum (4.7%), and brainstem (15.3%). However, atrophy was not directly associated with CSF biomarkers or EDSS score.

Conclusion: The association between the volume of periventricular lesions (PVL) and the IgG index suggests that this may be related to proximity to cerebrospinal fluid; however, the number of PVLs does not seem to provide additional diagnostic information. The detection of brain atrophy in most patients has highlighted the need for more comprehensive disease severity scales to evaluate the location and clinical implications of atrophy in MS.

Keywords: Cerebrospinal fluid/serum albumin, multiple sclerosis, oligoclonal bands, periventricular lesion volume, volbrain.

Multiple sclerosis (MS) is a central nervous system (CNS) disease characterized by inflammation, demyelination, and axonal damage.[1,2] Common symptoms include weakness in the extremities, sensory issues, ataxia, bladder problems, fatigue, visual symptoms such as diplopia and blurred vision, dysarthria, and cognitive complaints such as memory, concentration, and attention impairments.[3,4] Conversely, movement disorders, epileptic seizures, headaches, severe cognitive impairment (dementia), cortical symptoms, hearing loss, and amyotrophy are rare symptoms and findings.[5,6] The fundamental principle in diagnosing MS is to demonstrate the temporal and spatial spread of CNS lesions causing the clinical symptoms and exclude other diseases with similar features through clinical or investigative

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methods.[7] Due to the absence of a single clinical or laboratory test for a definitive diagnosis of MS, researchers have worked to establish diagnostic criteria. In 1965, the Schumacher et al.[8] first developed these criteria, which were later updated and published as the McDonald criteria by McDonald et al.[9] The diagnostic criteria were updated in subsequent years, and revisions were published in 2005, 2010, and most recently in 2017.[10-12]

In MS, the primary laboratory evidence supporting the disease is the presence of oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF) and impaired evoked potentials.[13,14] The positivity of OCBs and an elevated immunoglobulin G (IgG) index indicate intrathecal IgG synthesis. Oligoclonal band positivity and a high IgG index can be observed in acute or chronic inflammation of the brain and meninges, infections, paraneoplastic diseases, and even in some noninflammatory neurological disorders. Thus, they are not specific to MS. The IgG index is calculated by dividing the ratio of CSF and serum IgG levels by the ratio of albumin levels in the CSF and serum. Generally, values above 0.70 indicate an increased ratio. Oligoclonal bands may be negative at the onset of MS but can become positive in later stages, and once positive, they tend to remain so. Analyzing OCBs in both CSF and serum using isoelectric focusing is an accepted and recommended method. Type 2 indicates the presence of OCBs in CSF but not in the serum, suggesting immunological activation in the CNS. Type 3 indicates the presence of more bands in CSF than in serum, also suggesting immunological activation in the CNS.[3,15-17] Type 4 indicates a systemic response, with identical bands in both CSF and serum. Finally, type 5 features identical OCBs in both CSF and serum, with additional bands found only in the CSF. In MS, types 2 and 3 are commonly observed; however, other types of OCBs have also been identified in MS.[18]

In this study, CSF albumin, which serves as an ideal parameter to evaluate the permeability of the blood-CSF barrier, was also examined. The cerebrospinal fluid/serum albumin quotient (Q-Alb) was used to correct for individual blood concentrations of albumin. Abnormal elevations in Q-Alb occur in various disorders, including inflammatory and noninflammatory neurological diseases. Mild to moderate elevations in Q-Alb are typical for diabetic and immune-mediated polyneuropathies or viral meningitis, while moderate to severe elevations are associated with CNS infections, immune-mediated polyradiculitis, or severe spinal canal stenosis.[19] For MS, normal Q-Alb values are recommended to be ≤6.5 (10^{-3}) for individuals younger than 40 years and ≤8.0 (10^{-3}) for those 40 years or older.[20]

The Expanded Disability Status Scale (EDSS) was developed to monitor disease progression and assess neurological impairment in MS. It combines grades from 0 (normal) to 5 or 6 (maximum impairment) within eight functional systems. The overall scale ranges from 0 (normal) to 10 (death due to MS). Later, the scale was expanded to include half steps (e.g., 1.0, 1.5, 2.0 to 9.5), increasing its usage. The functional systems evaluated include the pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and other systems.[21] Over the years, a better understanding of the disease has revealed that disability is broader than what the EDSS detects. Various symptoms, such as cognitive impairments (memory, concentration, and attention deficits), psychiatric symptoms (depression and anxiety), and other symptoms such as chronic fatigue can also be observed.

The other subject of this study is the examination of brain atrophy in patients who do not show cognitive dysfunction clinically or on any scale. In the literature, MS and clinically isolated syndromes suggestive of MS are compared to controls. It is observed that atrophy occurs over periods ranging from three months to several years.[22] Total brain atrophy, particularly prominent in the cerebral cortex, was found in patients with MS on follow-up imaging at a median of 3.2 (interquartile range, IQR: 2.0-4.9) years.[23]

Although postmortem studies on atrophy are limited, many magnetic resonance imaging (MRI)-based programs have been developed for patients, leading to significant research. Recently, automatic measurement methods have been found reliable in brain volumetric studies. Despite some criticisms, studies like volBrain demonstrated that the results of automatic segmentation programs were quite close to those of manual measurements.[24] Commonly used methods such as Freesurfer (Harvard University software), FSL-FIRST, and volBrain have been used for measuring the caudate nucleus, and volumes calculated with volBrain have been compared with manually calculated volumes. It was observed that volumes calculated with volBrain were the closest to those calculated manually.[25]

In this study, laboratory findings such as the presence of OCBs in the CSF, high IgG index, and Q-Alb were investigated using volBrain to determine their relationship with demyelinating lesions (number and volume) and brain atrophy. The goal was to identify more early-stage disease indicators, such as CSF biomarkers. Besides the spatial spread of the disease and blood-brain barrier (BBB) disruption, the study aimed to discuss brain atrophy, which is not adequately addressed in current disability and impairment criteria.

PATIENTS AND METHODS

This single-center retrospective study included 47 patients diagnosed with relapsing-remitting MS at the Erenköy Mental and Nervous Diseases Training and Research Hospital between July 2022 and July 2023, who had no additional neurological or autoimmune diseases and were followed up regularly. The patients had a definitive MS diagnosis based on follow-up visits, with at least one clinical history and criteria for spatial dissemination. Cerebrospinal fluid samples

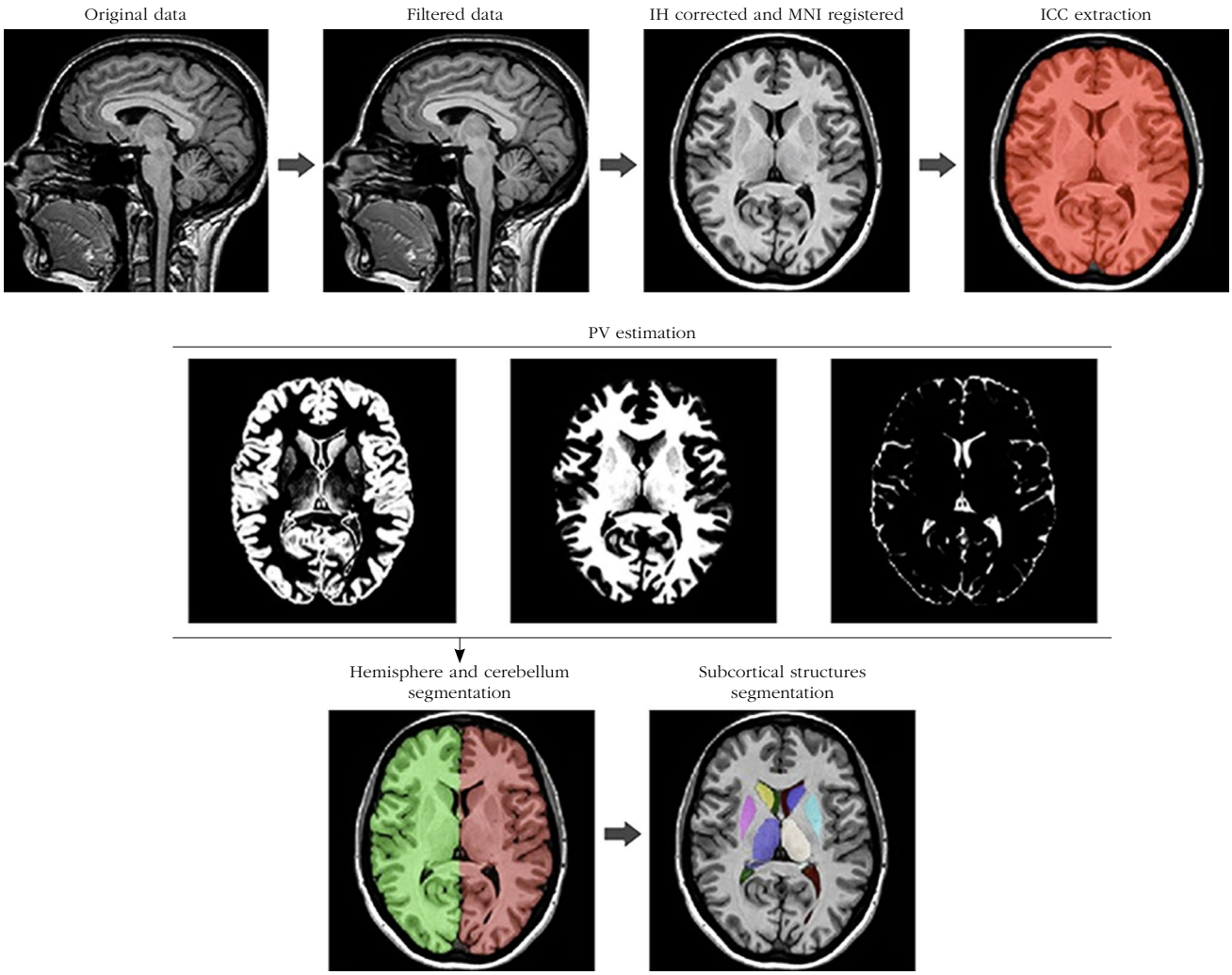
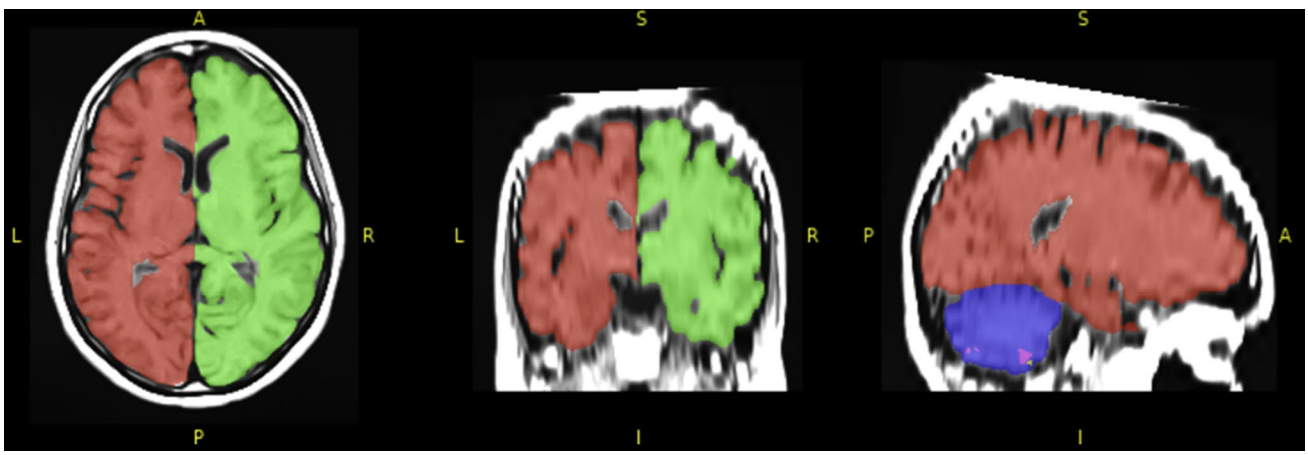


Figure 1. VolBrain Working Principle: The first row illustrates the preparation steps for any new MRI. This stage includes non-local noise reduction filters to mitigate issues arising from imaging protocol differences, MNI space registration for normalization of the image in other axes, intensity normalization, and ICC extraction. In the second row, the results of global tissue estimation (gray and white matter, CSF) are shown. The third row displays the segmentation results of macrostructures and subcortical structures.

IH: Inhomogeneity; MNI: Montreal Neurological Institute; ICC: Intracranial Cavity Extraction; PV: Partial volume. MRI: Magnetic resonance imaging; CSF: Cerebrospinal fluid.

taken from the patients at the time of initial admission were examined retrospectively. Patients were divided into two groups according to the results of the CSF examination: Group 1 consisted of 21 patients (7 males, 14 females; median age: 34 years; range, 21 to 58 years) compatible with OCB type 1, and Group 2 consisted of 26 patients (6 males, 20 females; median age: 31 years; range, 20 to 53 years) compatible with OCB type 2. The CSF IgG index ([CSF IgG/serum IgG]/[CSF albumin/serum albumin]) and the Q-Alb of each patient in both groups were calculated. Additionally, the EDSS scores of the patients at initial admission were noted. A written informed consent was obtained from each patient. The study protocol was approved by the Erenköy Mental and Neurological Diseases Training and Research Hospital Clinical Research Ethics Committee (date: 15.09.2023, no: 63). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The brain MRIs of the patients, used for volume calculations of brain regions and demyelinating lesions, were downloaded from the hospital system in DICOM (Digital Imaging and Communications in Medicine) format. These MRIs were taken no more than one month before the lumbar puncture. The brain MRIs in DICOM format were then



Structure	Total (cm^3 / %)	Right (cm^3 / %)	Left (cm^3 / %)	Asymmetry (%)
Cerebrum	1025.23 / 73.918 [74.213, 79.990]	514.80 / 37.116 [37.096, 40.043]	510.43 / 36.801 [37.063, 39.999]	0.8525 [–1.296, 1.568]
Cerebrum WM	403.93 / 29.123 [29.829, 34.031]	205.36 / 14.806 [14.914, 17.021]	198.57 / 14.317 [14.896, 17.030]	3.3638 [–1.899, 1.837]
Cerebrum GM	621.30 / 44.795 [43.722, 47.107]	309.44 / 22.310 [21.876, 23.592]	311.86 / 22.485 [21.818, 23.535]	–0.7801 [–1.233, 1.809]
Cerebellum*	126.64 / 9.130 [8.148, 10.288]	63.88 / 4.605 [4.093, 5.179]	62.76 / 4.525 [4.040, 5.116]	1.7653 [–1.764, 4.522]
Cerebrum WM	32.68 / 2.357 [1.639, 2.230]	18.71 / 1.349 [0.815, 1.126]	13.97 / 1.007 [0.819, 1.107]	29.0110 [–4.128, 6.350]
Cerebrum GM	93.95 / 6.774 [6.507, 8.110]	45.16 / 3.256 [3.261, 4.095]	48.79 / 3.517 [3.220, 4.032]	–7.7132 [–1.923, 4.918]
Vermis	10.78 / 0.777 [0.709, 0.958]			
Brainstem	16.08 / 1.159 [1.156, 1.496]			

Figure 2. Segmentation of Macro Structures: The volumes of the total cerebrum (gray and white matter), cerebellum, vermis, and brainstem in the patient's brain MRI are shown as total, right, and left (if asymmetrical) volumes. The ratio of the current region to the total brain is indicated after the '/' symbol, and if there is a decrease in this ratio compared to healthy individuals, it is highlighted in red. In healthy individuals, this ratio is reported as a range in square brackets at the bottom row.

WM: White matter; GM: Gray matter; MRI: Magnetic resonance imaging

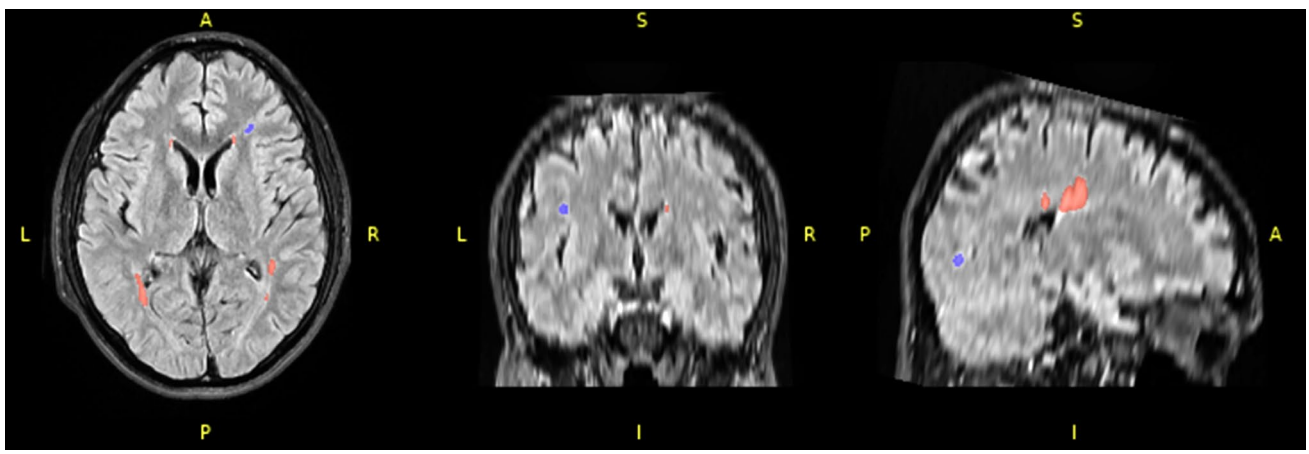
converted to NIfTI (Neuroimaging Informatics Technology Initiative) format, which is necessary for the volBrain calculations used in the study. Subsequently, the numbered MRIs were uploaded to the volBrain platform. T1-weighted sequences were used for total volume calculations, and T2-weighted FLAIR (fluid-attenuated inversion recovery) sequences were used for lesion volume calculations while keeping all information other than patient age and sex confidential. The working principle of volBrain is briefly shown in Figure 1.[26]

In this platform, the total volumes of the cerebrum, cerebral gray matter, cerebellum, and brainstem obtained from the T1-weighted MRIs of patients were calculated in cm^3 and as a percentage of the total brain volume. Additionally, this platform analyzed brain images based on a database of healthy individuals with similar age and sex characteristics (including approximately 600 images of healthy individuals aged 24 to 75 years randomly selected from the IXI dataset available at http://www.brain-development.org) and indicated whether there was any atrophy in the individual's brain regions.[24] In this system, any change in the ratio of a brain region to the total brain volume, indicating atrophy, appeared in red (Figure 2). Atrophy in the total cerebrum, cerebral gray matter, cerebellum, and brainstem volumes relative to healthy individuals was noted for each patient. The number, distribution, and burden of demyelinating lesions in the periventricular, subcortical, juxtacortical, and infratentorial regions were automatically calculated using the program's segmentation method (Figure 3).

Statistical analysis

All univariate statistical analyses were conducted using the IBM SPSS version 29.0 software (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were presented as median (IQR). The distribution type of sociodemographic data and routine biochemical measurement results were examined using the Shapiro-Wilk test (for sample sizes <30), and the homogeneity of variances was assessed using the Levene test. Differences in means of parameters with normal distribution among groups were analyzed using two-way analysis of variance, and post hoc Tukey's tests were used for multiple comparisons. Median values of nonparametric measurements between groups were compared using the Kruskal-Wallis test. A p-value <0.05 was considered statistically significant.

Lesion segmentation



Lesion	Count	Volume (cm^3 / %)	Lesion burden (%)
Total lesions	29	5.6466 / 0.3578	1.1478
Periventricular	16	4.2785 / 0.2711	0.8697
Deepwhite	5	0.1927 / 0.0122	0.0392
Juxtacortical	8	1.1755 / 0.0745	0.2389
Infratentorial	0	0.0000 / 0.0000	0.0000

Figure 3. Lesion segmentation: The number and distribution of demyelinating lesions (marked in red and blue) in the periventricular, subcortical, juxtacortical, and infratentorial regions, along with lesion load, are shown in patients.

TABLE 1
Statistical data regarding patients' demographic information, CSF results, demyelinating lesion volumes, and distributions

	OCB 1						OCB 2					
	n	%	Mean±SD	Median	Min-Max	IQR	n	%	Mean±SD	Median	Min-Max	IQR
Age (year)				34	21-58	19				31	20-53	16
Sex												
Female	21	66.6					26	80.1				
Lesion burden (%)				1.09	0.26-3.06	1.46				0.64	0.003-7.96	1.11
Total lesion count				8	12-74	6				5	2-74	7
Periventricular lesion count			9.37±3.97		3-17				10.28±4.81		0-22	
Subcortical lesion count				9	1-27	6				5	0-16	7
Juxtacortical lesion count				8	1-29	9				8	1-31	12
Infratentorial lesion count total				1	0-7	4				1	0-6	2
Lesion volume (cm^3)				5.2	1.08-13.62	7.18				3.16	0.016-34.2	5.23
Periventricular lesion volume (cm^3)				3.98	0.38-12.15	5.82				2.73	0-32.77	5.02
Subcortical lesion volume (cm^3)				0.23	0.02-0.88	0.26				0.13	0-0.61	0.25
Juxtacortical lesion volume (cm^3)				0.49	0.02-2.32	0.52				0.58	0-4.09	0.99
Infratentorial lesion volume (cm^3)				0.07	0-0.46	0.15				0.03	0-0.62	0.14
EDSS				1	0-2	0.5				1.5	0-3	1
Q-alb (10^{-3})				5.72	2.04-8.98	3.03				4.01	2.87-24.52	2.07
IgG index				0.48	0.30-1.36	0.22				1.01	0.65-5.70	0.59

CSF: Cerebrospinal fluid; OCB: Oligoclonal bands; SD: Standard deviation are used for parametric tests; Median and Interquartile range (IQR) are used for nonparametric tests; EDSS: Expanded Disability Status Scale; Q-alb: Serum albumin ratio; IgG: Immunoglobulin G.

RESULTS

Both groups had a high proportion of females, with 66.6% in Group 1 and 80.1% in Group 2. Detailed demographic and statistical data for other parameters of the patient groups are provided in Table 1.

The median IgG index was 0.48 in Group 1 and 1.01 in Group 2. The IgG index was statistically significantly higher in Group 2 compared to Group 1, regardless of whether it exceeded the clinically significant threshold of 0.70 ($p<0.05$). A significant relationship was found between having OCB type 2 and an elevated IgG index ($p<0.05$). The median values of the Q-Alb × 10^3) were 5.72 in Group 1 and 4.01 in Group 2. Contrary to expectations, the medians were close to each other, and there was no statistically significant difference between the two groups in this aspect ($p>0.05$).

There were no significant differences between the patient groups in terms of lesion burden (%), total lesion count, volume, and distribution (periventricular, subcortical,

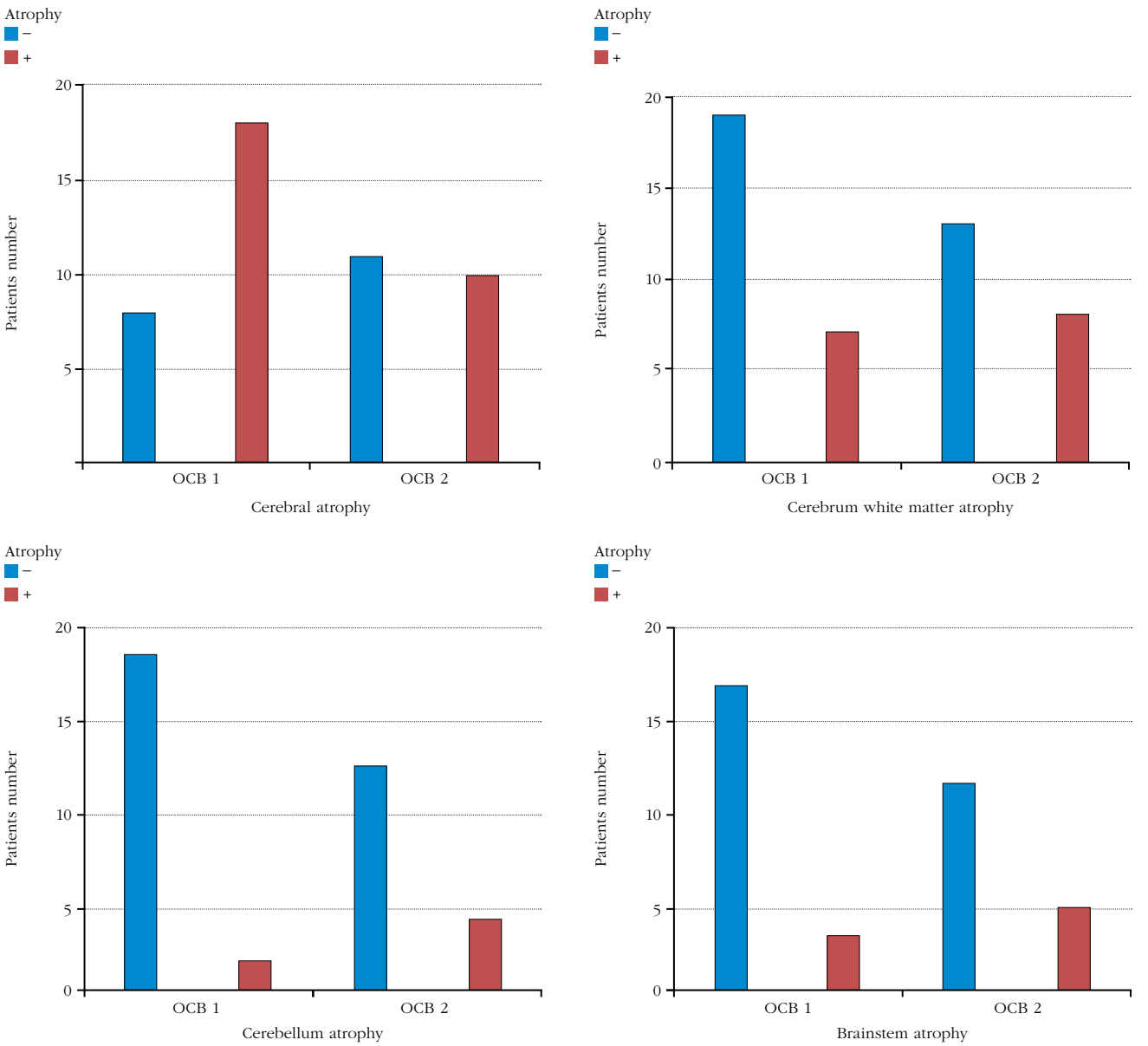


Figure 4. The percentage of individuals with atrophy in brain regions within the groups according to OCB types among patients.

OCB: Oligoclonal bands.

juxtacortical, infratentorial), indicating similarity in these parameters (p>0.05). There was no significant relationship between baseline EDSS scores among the groups (p>0.05). In both groups, some patients showed age-related brain region atrophy. The percentage of patients with brain region atrophy compared to healthy individuals was as follows: in Group 1, atrophy was observed in the total cerebrum (47%), total cerebral gray matter (38%), cerebellum (4.7%), and brainstem (28.5%); in Group 2, atrophy was noted in the total cerebrum (69%), total cerebral gray matter (26%), cerebellum (4.7%), and brainstem (15.3%) (Figure 4). However, no direct relationship was found between individuals with brain region atrophy and CSF biomarkers or EDSS scores (p>0.05).

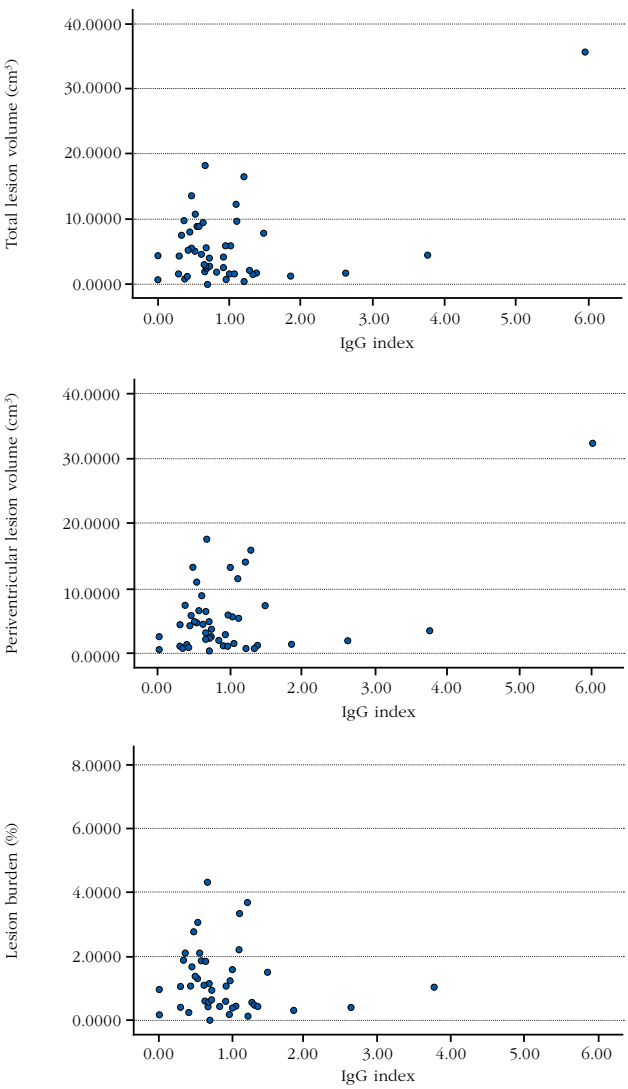


Figure 5. Moderate positive correlation of IgG index with total lesion volume, periventricular lesion volume, and lesion burden, respectively.

IgG: Immunoglobulin G.

All CSF biomarkers, OCB types, EDSS scores, the number and distribution of brain lesions, and the presence of atrophy were examined for correlations in the patients. A high correlation (r=0.728; p<0.05) was found between having OCB type 2 and the IgG index. No relationship was found between OCB type and brain atrophy (p>0.05). There was a moderate positive correlation between the IgG index and total lesion volume (r=0.466, p<0.05) and periventricular lesion volume (r=0.507, p<0.05). A positive correlation was also observed between the IgG index and lesion burden (r=0.469, p<0.05). Additionally, a moderate positive correlation was found between brainstem atrophy and cerebellar atrophy (r=0.513, p<0.05). No significant correlations were found between other parameters (Figure 5).

DISCUSSION

The BBB is a complex network of blood vessels that creates a continuous cellular barrier between the CNS and the rest of the body's circulation.[27] The disruption of the BBB, identified by Poser[28] in 1986 as one of the four key factors in the pathophysiology of MS, is still a crucial target for diagnosis and treatment. The ratio of albumin in CSF to serum is a simple and reliable biomarker for estimating BBB permeability. An increase in this ratio indicates a compromised BBB.[29] In this study, normal levels of Q-Alb in both groups suggested that the BBB was not disrupted or there was no detectable disruption in these patients. However, positivity for OCB and an elevated IgG index (>0.7) indicated intrathecal IgG synthesis. The high correlation between OCB positivity and elevated IgG index, regardless of the group, supported the findings. Intrathecal IgG synthesis is a humoral immune response and is thought to be a possible result of BBB damage.[30] The limitation of this study was the absence of healthy individuals for comparison. Therefore, the Q-Alb values of the MS patients in the study were found to be within the normal range when compared to the reference range for healthy individuals in the literature. This suggested that the Q-Alb value was less effective than OCBs and the IgG index in indicating BBB disruption in MS.

Examining the number and volume of lesions in different brain regions does not significantly aid in interpreting CSF biomarkers for disease diagnosis.

In general, minimizing invasive procedures for diagnosis and treatment is important in MS. Initially, CSF examination was a key diagnostic parameter, but it has gradually been supplemented by MRI criteria. One of the main objectives of this study was to determine whether OCB positivity or an elevated IgG index, observed during disease diagnosis and temporal dissemination, correlated with less invasive methods such as MRI criteria. A similar study demonstrated that OCB-positive patients had higher cranial lesion burdens compared to OCB-negative patients, although no statistical difference was found.[31] In the present study, the volume and number of demyelinating lesions were calculated using the volBrain automatic segmentation program. The moderate correlation between periventricular lesion volume and the IgG index suggests that these lesions may be associated with their proximity to CSF. However, the lack of a relationship with the number of periventricular lesions emphasizes that lesion size is more informative than the number of lesions. This result also highlights the importance of the total surface area in contact with the CSF. Therefore, it is suggested that the presence of classical periventricular lesions for MS diagnosis is supported when correlated with the IgG index, raising the question of whether these spatial criteria are superior. According to this study, no specific lesion location is superior for diagnosis. However, periventricular lesion volumes may be associated with temporal criteria, potentially representing a parameter that shows both temporal and spatial dissemination simultaneously. This challenges the literature that suggests diagnosing MS based on three or more periventricular lesions, and more studies are needed to determine how much periventricular lesion volume is required to elevate the IgG index. The lack of a relationship between periventricular lesions and OCB positivity, despite the strong correlation between OCB positivity and the IgG index, may be due to the IgG index being a more linear parameter. However, further studies with a larger number of patients are still needed to make definitive conclusions.

No relationship was found between OCB subtypes and regional brain volume loss. More studies are needed to determine whether the presence of OCBs in CSF, which is considered an indicator of BBB damage, is related to brain atrophy.

In this study, no correlation was found between disease severity and CSF biomarkers, which is likely due to using patients' baseline EDSS scores. In a study by Akaishi et al.[32] on 38 patients, it was found that baseline CSF albumin and IgG index were correlated with EDSS scores one year later, indicating that these biomarkers are associated with disease progression.

The patients' brain volumes at baseline were evaluated in terms of brain atrophy in this study. The volBrain program used in this study provides fully automatic brain volume analysis without human interaction in a very short time, and its reliability is well-supported in the literature.[24] Accepting these results as reliable, the high incidence of atrophy in a significant proportion of patients is noteworthy for its relevance to MS. Atrophy remains under-evaluated in diagnostic criteria and as a parameter of disability. This study emphasizes the need for further evaluation of this biomarker, which is also being discussed as a treatment target, using more comprehensive scales.

In conclusion, while the IgG index was associated with periventricular lesion volume, the lack of association with the number of lesions suggests that lesion volume is more important for diagnosis. The correlation between periventricular lesion volume and the IgG index may be due to their proximity to CSF. The fact that the number of periventricular lesions did not add diagnostic value raises the question of whether they differ from lesions in other locations. The detection of brain atrophy in most patients highlights the need for more comprehensive disease severity scales to better evaluate the role of atrophy in MS and its impact on clinical outcomes.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Surgical and medical practices: S.F.D., G.T., B.A.K., A.M.A., Y.B.Y.; Concept, design, writing: G.T., B.A.K.; Data collection or processing: A.M.A., Y.B.Y.; Analysis or Interpretation, literature search: G.T.

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