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Research Article

The relationship between optic nerve sheath diameter and demographic and clinical findings in patients diagnosed with clinically isolated syndrome

Klinik izole sendromlu hastalarda optik sinir kılıfı çapının demografik ve klinik bulgularla ilişkisi

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Abstract

Aim: This study aimed to assess optic nerve sheath diameter (ONSD) levels in patients diagnosed with clinically isolated syndrome (CIS) who were being followed in the demyelinating diseases clinic, as well as to examine their relationship with demographic characteristics and clinical findings.

Material and Methods: In this cross-sectional prospective study, 14 patients diagnosed with CIS who underwent lumbar puncture for specific cerebrospinal fluid (CSF) analysis were included between January 2024 and August 2024. The ONSD were measured by transorbital sonography. All patients' demographic characteristics, clinical parameters (CSF protein, CSF albumin, serum albumin, immunoglobulin G index, and vitamin D) were recorded.

Results: The patients had a mean age of 39.4 ± 12.8 years, and the majority were women. Oligoclonal bands were positive in all patients. The mean disease duration was 23.5 ± 7.6 days. The ONSD measurements for all patients ranged between 3.1 and 5.9 mm in the sagittal and axial planes of both eyes. There was a strong negative correlation between ONSD levels and age, diseases duration, CSF protein, CSF albumin, serum albumin, and immunoglobulin G index.

Conclusion: This study demonstrated a significant relationship between ONSD and various clinical and laboratory parameters in patients diagnosed with CIS. These findings suggest that ONSD may serve as a valuable, non-invasive marker in assessing disease severity and progression in CIS patients.

Keywords: axonal degeneration, clinically isolated syndrome, demyelinating diseases, multiple sclerosis, optic nerve sheath diameter, transorbital sonography

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Öz

Amaç: Bu çalışma, demiyelinizan hastalıklar polikliniğinde takip edilen ve klinik izole sendrom (KİS) tanısı alan hastalarda optik sinir kılıfı çapı (OSKÇ) seviyelerini değerlendirmeyi ve bu seviyelerin demografik özellikler ve klinik bulgular ile ilişkisini incelemeyi amaçladı.

Gereç ve Yöntemler: Bu kesitsel prospektif çalışmaya, Ocak 2024 ile Ağustos 2024 tarihleri arasında spesifik beyin omurilik sıvısı (BOS) analizi için lomber ponksiyon uygulanan CIS tanısı almış 14 hasta dahil edildi. OSKÇ, transorbital sonografi ile ölçüldü. Tüm hastaların demografik özellikleri, klinik parametreleri (BOS proteini, BOS albümini, serum albümini, immünoglobulin G indeksi ve D vitamini) kaydedildi.

Bulgular: Hastaların ortalama yaşı 39,4 ± 12,8 yıl ve büyük çoğunluğu kadındı. Tüm hastalarda oligoklonal bantlar pozitif saptandı. Ortalama hastalık süresi 23,5 ± 7,6 gündü. Tüm hastalarda OSKÇ ölçümleri, her iki gözde de sagittal ve aksiyel düzlemlerde 3,1 - 5,9 mm arasında idi. OSKÇ ile yaş, hastalık süresi, BOS proteini, BOS albümini, serum albümini ve immünoglobulin G indeksi arasında güçlü bir negatif korelasyon saptandı.

Sonuçlar: Bu çalışma, KİS tanısı almış hastalarda OSKÇ ile çeşitli klinik ve laboratuvar parametreleri arasında anlamlı bir ilişki olduğunu göstermiştir. Bu bulgular, OSKÇ, KİS hastalarında hastalık şiddetini ve ilerlemesini değerlendirmede değerli ve non-invaziv bir biyomarker olarak kullanılabileceğini düşündürmektedir.

Anahtar Kelimeler: aksonal dejenerasyon, klinik izole sendrom, demiyelinizan hastalıklar, multipl skleroz, optik sinir kılıfı çapı, transorbital sonografi

Introduction

Multiple sclerosis (MS) is a chronic disease pathologically characterized by scattered areas of inflammatory demyelination in the central nervous system (CNS) [1]. Over time, 85% of patients who develop MS experience an acute or subacute neurological disorder characterized by a single white matter lesion at clinical onset. This condition is referred to as clinically isolated syndrome (CIS) [2]. In previous studies, the conversion rate from CIS to MS has been reported to vary from 30% to 82% [3].

Axonal and neuronal damage in the CNS plays a crucial role in long-term disability in MS [4]. Recently, there has been a rising interest in cost-effective and accessible biomarkers for detecting this damage [5]. The optic nerve provides a valuable window into these processes, with optical coherence tomography (OCT) offering a precise, non-invasive method to measure retinal nerve fibre layer (RNFL) thickness [6]. A reduction in RNFL thickness has been observed in MS patients, and this has been linked to their level of disability [7]. On the other hand, it has been reported that the optic nerve diameter (OND) or optic nerve sheath diameter (ONSD) measured by ultrasound in MS patients shows a negative correlation with the level of disability and a positive correlation with RNFL thickness and the ganglion cell layer as measured by OCT [8]. Furthermore, it has been shown that there is a high degree of concordance between ultrasonography and magnetic resonance imaging in the measurement of ONSD [9]. However, ONSD and its relationship with clinical parameters in CIS patients have not yet been evaluated.

This study aimed to assess ONSD levels in patients diagnosed with CIS who were being followed in the demyelinating diseases clinic, as well as to examine their relationship with demographic characteristics, clinical and laboratory parameters.

Material and Methods

Following the principles set forth in the Declaration of Helsinki, this prospective study was conducted at the Bakırköy Dr. Sadi Konuk Training and Research Hospital Neurology Clinic from January 2024 to August 2024. The study received approval from the Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (Date: 15/02/2024- No: 2024/02). Informed consent was obtained from all patients prior to their participation in the study.

Study population

A total of 530 patients followed in the demyelinating diseases clinic were evaluated for eligibility according to the research criteria. The study inclusion criteria consisted of patients with a single attack who did not meet the McDonald's 2017 MS diagnostic criteria [10], and those who provided informed consent to participate. The exclusion criteria involved patients younger than 18 or older than 65, pregnant or breastfeeding patients, those who had a new attack and were diagnosed

with MS during follow-up, patients with eye pathologies from trauma or external causes, patients with a diagnosis of vasculitis or additional systemic findings that suggested vasculitis, those suffering from migraine [11], and those with any comorbid conditions. Following the exclusion criteria, 14 diagnosed CIS patients were included in the study.

Study protocol

A detailed physical and neurological examination was performed on the patients included in the study. The demographic, clinical, and imaging data of the patients were obtained at the time of admission. Biochemical parameters were analyzed using venous blood samples collected during outpatient evaluations after a 12-hour fasting period. All samples were analyzed in a single laboratory using the same methodology as described below.

Biochemical analysis

A Beckman Coulter LH 780 device (Mervue, Galway, Ireland) and Hitachi Modular P800 autoanalyzer (Roche Diagnostics Corp., Indianapolis, USA) were used to evaluate patients' venous blood samples. Levels of serum albumin (bromocresol green method) and Vitamin D (enzymatic colorimetric method) were measured.

Ultrasonography evaluation

All measurements were performed using transorbital ultrasonography by a certified neurologist trained in ultrasound, who was blinded to the subjects' clinical data for the duration of the study, in accordance with the ALARA (as low as reasonably achievable) principle. Ultrasonography was performed using the Samsung HM70EVO ultrasound system with a 5-12 MHz linear array B-mode transducer (Samsung Electronics GmBH, Schwalbach, Germany). Subjects were examined in the supine position with the upper part of the body and the head elevated 20º to 30º degrees to avoid any pressure on the eye. They were asked to keep their eyes in a mid-position and to suppress eye movements. For safety, the mechanical index was reduced to 0.2. The probe was placed on the temporal part of the closed upper eyelid using a thick layer of sonography gel. The anterior part of the optic nerve was depicted in an axial plane showing the papillae and the optic nerve in its longitudinal course. The measured parameters were the ONSD, which were measured 3 mm behind the posterior edge of the globe in a horizontal plane.

During the ultrasound examination, the optic nerve is identified by its characteristic appearance. It typically appears as a hyperechoic (bright) tubular structure surrounded by a hypoechoic (dark) rim, which represents the optic nerve sheath (Figure 1). Care is taken to obtain a clear and consistent image of the optic nerve in both transverse (axial) (Figure 1A) and longitudinal (sagittal) (Figure 1B) views. This dual-plane approach helps in ensuring the accuracy and reproducibility of the measurements.

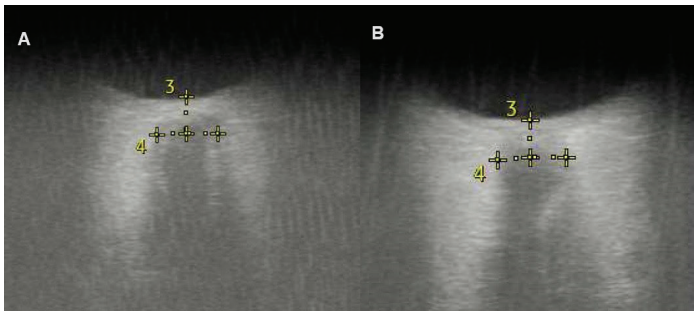

Figure 1. A. Axial plane optic nerve sheath diameter. **B.** Sagittal plane optic nerve sheath diameter

In the longitudinal view, the probe is oriented parallel to the long axis of the optic nerve, providing a sagittal image. In this view, the ONSD is measured at a standardized point, typically 3 mm posterior to the globe, which is considered a reliable site for assessing changes in intracranial pressure (ICP) (Figure 1). This specific measurement point is chosen because it has been shown to correlate well with changes in ICP [11-13].

Once the sagittal view was acquired and the ONSD measurement recorded, the procedure was repeated to capture a transverse (axial) view. In this view, the probe was oriented perpendicular to the long axis of the optic nerve. Measuring ONSD in both the sagittal and axial planes was done to minimize the likelihood of measurement errors and to enhance reliability and accuracy. Moreover, the same measurement procedure was performed on the other eye to ensure the reliability of the data. Bilateral measurements are essential in clinical practice to exclude any asymmetry that might indicate localized pathology. Hence, ONSD measurements were taken from both eyes in both sagittal and axial planes and recorded in millimeters (mm). Each measurement was repeated at least three times, and an average value was calculated to ensure accuracy.

Statistical analysis

All data were analyzed with STATA/MP v.16 software (StataCorp LLC, Texas, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-

Smirnov tests are given as mean ± standard deviation values, while non-normally distributed variables are given as median (25th-75th quartiles) values. Accordingly, Student t-test and Mann-Whitney U test were used for comparisons between two groups. Categorical variables were presented as numbers and percentages, and comparisons between groups were performed using Chi-square and Fisher exact tests. Pearson's and Spearman's correlation analyses were used to assess the associations between numerical variables. Significance was accepted at $P < 0.05$ (*) for all statistical analyses [12-14].

Results

The study included 14 patients, with a mean age of 39.4 ± 12.8 years, most of whom were women. Of the 14 patients, 8 had optic neuritis, 3 has paresthesia, 2 had mono/hemiparesis, and 1 patient was diagnosed with CIS with the clinical presentation of ophthalmoparesis. Oligoclonal bands were positive in all patients. The mean disease duration was 23.5 ± 7.6 days. The demographic and clinical features of the patients are shown in Table 1.

Table 1. Demographic and clinical findings.

Variables	All population n = 14	
	values	range
Demografic findings		
Age, years	39.4 ± 12.8	17 - 60
Gender, n (%)		
Female	9 (64.3)	-
Male	5 (35.7)	-
Smoking, n (%)	2 (14.3)	-
Laboratory findings		
CSF protein, mg/dL	39.1 ± 8.3	22.4 - 53.2
CSF albumin, mg/dL	17.2 ± 4.1	8.9 - 25.5
Serum albumin, mg/dL	38.0 ± 7.0	23.1 - 47.4
Vitamin D	43 (12.5-47.5)	3 - 74
Immunoglobulin G index	1 (0.8-1.2)	0.3 - 1.8
Oligoclonal band, n (%)		
Negative	-	-
Positive	14 (100.0)	-
Diseases duration, days	23.5 ± 7.6	12 - 40

Numerical variables were shown as mean ± SD or median (IQR). Categorical variables were shown as numbers (%). CSF, specific cerebrospinal fluid.

The ONSD measurements for all patients ranged between 3.1 and 5.9 mm in the sagittal and axial planes of both eyes (Figure 2, Table 2). The mean ONSD values were 4.9 ± 0.5 mm for the right sagittal, 4.6 ± 0.6 mm for the right axial, 5.0 ± 0.6 mm for the left sagittal, and 4.8 ± 0.4 mm for the left axial.

There was a strong negative correlation between ONSD levels and age, illness duration, CSF protein, CSF albumin, serum albumin, and immunoglobulin G index (Table 3).

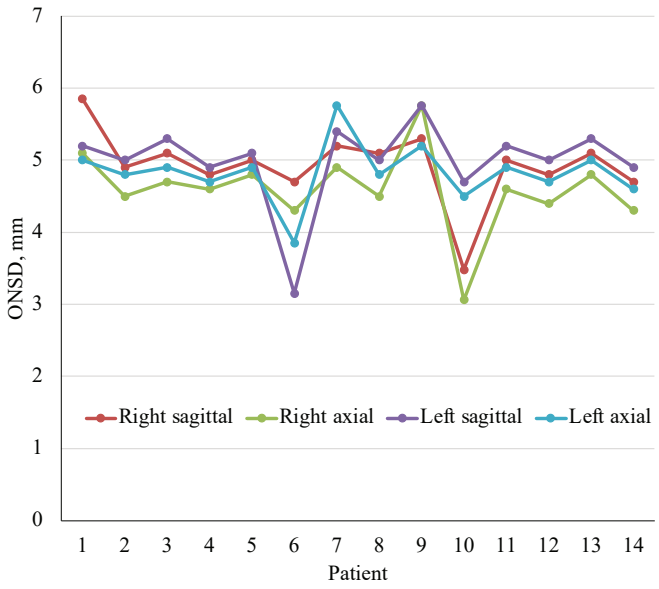

Figure 2. Levels of optic nerve sheath diameter (ONSD) in the patients group

Table 2. Transorbital sonography findings

ONSD, mm	range	mean ± SD	95% CI	median (IQR)
Right sagittal	3.5 - 5.9	4.9 ± 0.5	4.6 - 5.2	5.0 (4.8 - 5.1)
Right axial	3.1 - 5.8	4.6 ± 0.6	4.3 - 4.9	4.6 (4.4 - 4.8)
Left sagittal	3.2 - 5.8	5.0 ± 0.6	4.7 - 5.3	5.1 (4.9 - 5.3)
Left axial	3.9 - 5.8	4.8 ± 0.4	4.6 - 5.1	4.9 (4.7 – 5.0)

CI: confidence interval; IQR, interquartile range; ONSD, optic nerve sheath diameter; SD, standard deviation.

Discussion

To the best of our knowledge, this was the first study to present preliminary findings on the relationship between ONSD and inflammation markers in CIS patients. In CIS patients, ONSD measurements, ranging from 3.1 to 5.9, were negatively correlated with both CSF and serum inflammatory parameters. A strong negative correlation was also observed between ONSD levels and age or illness duration.

The correlation between ONSD measurements and CSF protein and albumin levels suggests that ONSD may serve as a potential marker for increased ICP. Elevated ICP is rarely observed in MS patients due to the inflammatory processes affecting the optic nerve. When ICP increases, it exerts greater pressure on the optic nerve sheath, consequently leading to an increase in the ONSD. This relationship has been supported by various studies indicating that ONSD measurements

Table 3. Relationship between optic nerve sheath diameter and demographic and clinical findings

Variables	Right sagittal		Right axial		Left sagittal		Left axial	
	r	p	r	p	r	p	r	p
Age	-0.895	<0.001*	-0.938	<0.001*	-0.873	<0.001*	-0.926	<0.001*
Gender								
Female	5.0±0.4	0.420	4.6±0.3	0.820	4.9±0.7	0.477	4.8±0.5	0.846
Male	4.8±0.7		4.5±1.0		5.2±0.4		4.9±0.3	
CSF protein	-0.904	<0.001*	-0.923	<0.001*	-0.901	<0.001*	-0.913	<0.001*
CSF albumin	-0.893	<0.001*	-0.923	<0.001*	-0.886	<0.001*	-0.901	<0.001*
Serum albumin	-0.908	<0.001*	-0.914	<0.001*	-0.897	<0.001*	-0.910	<0.001*
Vitamin D	0.257	0.255	0.210	0.314	0.270	0.367	0.246	0.268
Immunoglobulin G index	-0.917	<0.001*	-0.930	<0.001*	-0.870	<0.001*	-0.917	<0.001*
Diseases duration	-0.755	0.002*	-0.791	0.001*	-0.734	0.003*	-0.786	0.001*

CSF, specific cerebrospinal fluid.

can reflect changes in ICP, providing a non-invasive means to monitor this critical parameter in MS patients [15, 16]. Furthermore, it has been documented that the optic nerve sheath thickness can increase in patients experiencing acute optic neuritis, a common manifestation of MS. This condition involves acute inflammation of the optic nerve, which contributes to the thickening of the ONS. However, the sensitivity and specificity of ONSD measurements in detecting acute optic neuritis remain areas of ongoing research and are not yet fully established [17, 18].

In the context of elevated ICP, the expansion of the subarachnoid space surrounding the optic nerve leads to an increased ONSD [19]. This is expected as the increased pressure causes the sheath to distend. However, our study presents an intriguing finding of a negative correlation between ONSD and CSF protein and albumin levels. This finding may suggest that the relationship is more complex, particularly in the chronic stages of the condition. Following acute inflammation, there may be significant axonal damage leading to axonal loss [20]. This neurodegenerative process could result in a subsequent decrease in ONSD over time. The chronic inflammatory state in MS, characterized by ongoing neurodegeneration and axonal loss [21], could thus contribute to a reduced ONSD despite the initial increases associated with acute inflammation. The negative correlation observed in our study may be explained by the chronic stage of disease progression in our patient cohort. In chronic MS, prolonged inflammation and sustained neurodegeneration can lead to the thinning of the ONS due to axonal loss, overshadowing the initial increases in ONSD seen during acute inflammatory episodes [22]. This finding highlights the importance of considering the disease stage when interpreting ONSD measurements in MS patients.

In a study, it was suggested that ONSD measurements could be used as a criterion for temporal dissemination when evaluating MS diagnostic criteria [23]. In our study, the negative correlation between disease duration and ONSD suggests that, given that patients are not in the acute phase, ONSD may decrease due to axonal damage after inflammation. On the other hand, Moreover, the relationship between CSF protein and albumin levels and ONSD suggests that these biomarkers could reflect different aspects of disease pathology. Elevated CSF protein and albumin levels are indicative of blood-brain barrier disruption and inflammation, common features in MS. However, their inverse relationship with ONSD in our study suggests that, in chronic stages, these markers may be more reflective of ongoing neurodegenerative processes rather than acute inflammatory changes. The negative correlation between ONSD measurements and serum albumin levels may be due to the fact that albumin is a major protein in the blood that helps to maintain the integrity of the blood-brain barrier [24]. When albumin levels are low, more fluid and other molecules can leak from the blood vessels into the brain [25], including the ONS. This can lead to an increase in ONSD. The negative correlation between ONSD measurements and the IgG index suggests that ONSD may be a marker of humoral immune response in CIS patients. The IgG index is a measure of the concentration of IgG antibodies which are produced by B cells [26]. An increased IgG index provides insights into disease severity and also the potential for conversion to MS (18) Increased disease severity can lead to axonal damage in the optic nerve [18, 27], which can result in a decrease in ONSD. The negative correlation we observed in our study has suggested that ONSD measurements in CIS patients may provide information about disease severity.

This study has several limitations. First, the sample size was relatively small, with only 14 patients, which may limit the generalizability of our findings. A larger cohort would be needed to confirm the strength and consistency of the observed correlations. Additionally, the cross-sectional design of the study limits our ability to infer causal relationships or track changes in ONSD and inflammatory markers over time. Longitudinal studies are required to evaluate how ONSD evolves with disease progression and its potential role as a predictive marker. Finally, the absence of OCT measurements in our study prevents direct comparison between ONSD and retinal structural changes, which would have provided a more comprehensive view of optic nerve and retinal degeneration.

Conclusion

Our study demonstrated a significant relationship between ONSD and inflammatory markers in patients diagnosed with CIS. ONSD was found to be negatively correlated with CSF and serum parameters of inflammation, suggesting that ONSD may serve as a valuable non-invasive biomarker for assessing neuroinflammation in CIS. These findings provide preliminary evidence that ONSD could be a useful tool in monitoring disease activity and progression in CIS patients. However, further large-scale and longitudinal studies are necessary to validate these findings and explore the combined use of ONSD and OCT in guiding clinical management.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Ethics Committee (Date: 15/02/2024- No: 2024/02).

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author.

Authors' contribution

Concept – İ.A., Design – İ.A., Data collection and/or processing – İ.A., B.Y., A.S., and V.Y., Analysis and/or interpretation – İ.A., B.Y., A.S., and V.Y., Literature search – İ.A., B.Y., A.S., and V.Y., Writing – İ.A., Critical review – B.Y., A.S., and V.Y. All authors read and approved the final version of the manuscript.

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