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STRUCTURAL AND FUNCTIONAL CHANGES OF OPTIC NERVE IN MULTIPLE SCLEROSIS PATIENTS

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ABSTRACT

Background: Transorbital ultrasound (TOS) is a promising tool for identification and monitor of structural changes in optic nerve in multiple sclerosis patients (MS).

Aim: To assess the functional and structural alterations of the optic nerve utilizing transorbital ultrasound (TOS) and visual evoked potentials (VEP), as potential neuroaxonal damage markers in RRMS.

Subjects and methods: This case-control comparative research has been performed on 90 Egyptian subjects, 50 of them were patients and 40 individuals were healthy controls. Optic nerve sheath diameter (ONSD), and optic nerve diameter (OND) their ratio have been determined using TOS. P100 latency was measured by VEP.

Results: A statistically significant variance has been observed among patients (whether they had a history of optic neuritis or not) and controls regarding OND, ONSD, OND/ONSD and P100 latency. There was a statistically significant variance among cases with EDSS ≤2 and patients with EDSS >2 regarding different study parameters.

Conclusion: VEP and transorbital ultrasound differentiated multiple sclerosis cases from control. They also discriminated patients with history of optic neuritis from those without it, proposing that these methods are sensitive enough to identify functional and structural alterations formed in the optic nerve in RRMS.

Key words: Visual Pathway Changes, Multiple Sclerosis, TOS,

INTRODUCTION

Multiple sclerosis is a chronic autoimmune illness of the central nervous system marked via demyelination, inflammation, axonal damage and gliosis.[1]

Visual symptoms are prevalent, with optic neuritis (ON) being the initial symptom in twenty-five percent of multiple sclerosis cases. Furthermore, optic neuritis manifests in around fifty percent of cases throughout the progression of the disease. Those without a history of ON are likely to exhibit lesions in their visual pathways, as post-mortem investigations revealed that over ninety percent of cases showed affection regardless of optic neuritis history.[2]

Before the introduction of magnetic resonance imaging (MRI), evoked potentials, particularly visual evoked potentials, have been utilized to identify both clinically evident and asymptomatic lesions in multiple sclerosis and were essential for conventional diagnostic procedures. Furthermore, VEP could provide information regarding the functional evaluation of axons, synapses, and myelin within the visual pathway, particularly it's prechiasmatic segment, and serves as a significant instrument for tracking the development and prognosis of MS. The N75/P100 amplitude indicates the quantity of functional axons transmitting signals to the visual cortex and is diminished because of temporary conduction block throughout acute optic neuritis and/or irreversible loss of the axon in the optic nerve. Visual evoked potentials delay indicates myelin integrity and may be valuable in assessing the degree of remyelination or demyelination in the visual pathway.[3]

Transorbital ultrasonography (TOS) may serve as an alternative to optical coherence tomography in the structural examination of the optic nerve. This approach has many advantages, including great reproducibility and low expense,

along with minimum inter- and intra-observer variability. The existing information further approves that TOS measures exhibit a strong correlation with those obtained using MRI.[1]

The optic nerve sheath diameter was identified as a prognostic indicator for assessing prognosis and the possibility of relapse. Detecting injuries to the optic nerve sheath and optic nerve before the clinical onset of optic neuritis may facilitate early diagnosis and improve ultimate outcomes through the prompt beginning of therapy.[4]

The purpose of this research was to assess the functional and structural alterations of the optic nerve by TOS and VEP as possible indicators of neuroaxonal damage in multiple sclerosis which will help in early detection of disability and disease progression.

SUBJECTS AND METHODS

This was a case – control comparative research. It has been carried out on 90 Egyptian subjects aged from (20-40) years, of both sexes (females and males), 50 of them were patients and 40 individuals were healthy controls. It was carried out during the duration among January 2022 and May 2024 and the cases have been selected from Neurology department of Al-Zahraa University Hospital and the outpatient clinic of Cairo Fatemic Hospital.

Cases group: This group involved fifty cases identified as relapsing remitting multiple sclerosis (RRMS) patients based on McDonald et al criteria 2017 [5] with age ranged from 20 to 40 years. Out of them, 17 patients (34%) had a history of previous optic neuritis; two cases had bilateral ON, 5 patients had left ON, and 10 patients had right ON. While 33 patients were free of visual manifestations suggesting history of optic neuritis.

Control group: Involved 40 age and gender matched apparently healthy individuals. They were selected from volunteers of friends and hospital workers.

Inclusion criteria: Relapsing remitting MS patients, Age range from 20 to 40y, patients free from clinical criteria of relapse for the last 3 months and patients free from optic neuritis attacks for the last 6 months before to the study.[1,4]

Exclusion criteria: Other medical conditions such as hypertension and diabetes, neurological disorders like myelin oligodendrocyte glycoprotein antibodies (anti-MOG) disorder and neuromyelitis optica spectrum disorder (NMOSD), cases with prior ocular pathology that may influence optic nerve measurement (such as glaucoma, high myopia) and patients with progressive multiple sclerosis (primary or secondary).

METHODS:

All patients were subjected to: Complete medical history, General medical assessment, neurological evaluation involving; history and neurological investigation and evaluation of disability through expanded disability status scale (EDSS).[2]

Pattern reversal visual evoked potentials:

The test was done for each eye separately using black and white check board pattern using (2 channel NCS/EMG Neuropack S1, Nihon Koden) machine according to recent standard protocols. Electrodes were located based on 10-20 International system. Active electrode was placed over Oz at approximately two centimeters above the inion. Reference electrode has been located over FZ at the forehead and the ground electrode has been positioned over Cz at the vertex. The distance between the subjects and checkboard was 100 cm. The latency of P100 was recorded from both eyes of participants.[6]

Transorbital ultrasonography (TOS):

Our sonography apparatus was a Samsung HS60 equipped with a LA3-14 AD linear array transducer. TOS has been conducted in B-mode for all controls as well as cases. Participants have been assessed in a supine position with the upper body raised, maintaining an angle of head of twenty to thirty degrees to prevent ocular pressure. To inhibit eye movements, all participants have been instructed to maintain their eyes in the central location. To minimize potential biomechanical side effects on patients, we decreased the mechanical index to 0.2. Following the application of a significant quantity of sonography gel, the probe has been positioned on the temporal aspect of the closed upper eyelids. The anterior segment of optic nerve has been illustrated in a transverse plane, highlighting the optic nerve and papilla in it's longitudinal trajectory. The the optic nerve diameter and optic nerve sheath diameter, were determined three millimeters posterior to the globe's border in a horizontal plane. To reduce bias, we assessed each bulb twice and provided the average measurements. The optic nerve appeared as a hypoechoic structure beyond the retina, encased through hypoechoic dura matter and hyperechoic subarachnoid space. The distance between the exterior margins of the hyperechoic region encircling the optic nerve has been measured as the ONSD.[4]

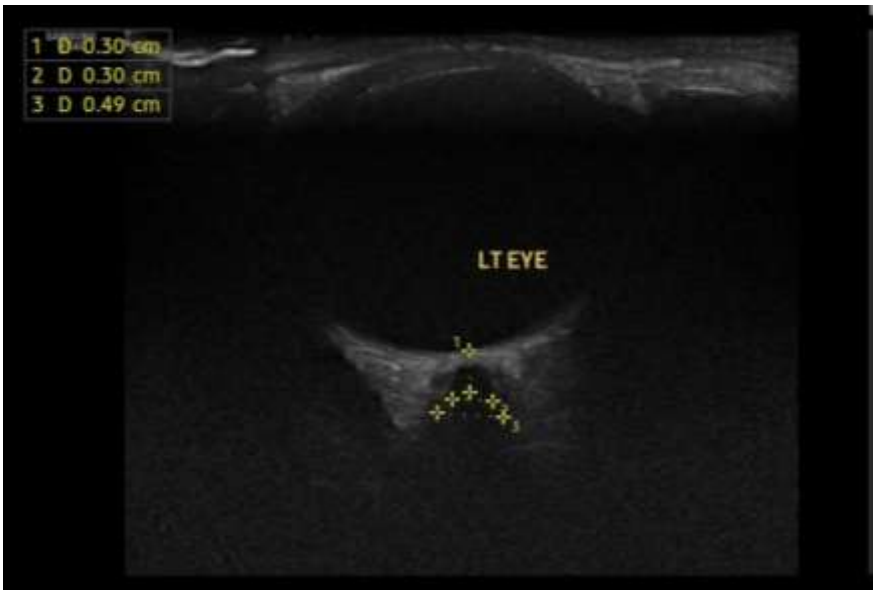

Figure (1): Optic nerve sheath diameter and the optic nerve diameter determined through transorbital ultrasound.

Statistical analysis:

The recorded information has been examined utilizing the Statistical Package for the Social Sciences, version 26.0 (SPSS Inc., Chicago, Illinois, United States of America). Quantitative information has been represented as mean ± standard deviation and ranges for parametric distributions, whereas non-parametric variables have been represented as median with inter-quartile range (IQR). Qualitative parameters have been expressed as numbers and percentages. The information has been explored for normality utilizing the Shapiro-Wilk and Kolmogorov-Smirnov tests. A P-value below 0.05 has been regarded as significant. A P-value below 0.001 has been regarded as greatly significant. A P-value greater than 0.05 has been regarded as insignificant.

RESULTS

Demographic data and clinical characteristics:

The research involved fifty RRMS cases, 33 without previous history of ON and 17 with a previous history of optic neuritis. Out of them, two cases had bilateral optic neuritis, 5 cases had left optic neuritis, and 10 patients had right optic neuritis. (**Table 1).**

EDSS score varied from 0.5 to 3 with a mean of (1.61±0.52). Forty-two patients had EDSS ≤2, and 8 had EDSS >2. (**Table 1).**

Table (1): Demographic data and clinical features of the examined groups.

Demographic data	**Patients Group (number=50)**	**Control Group (number=40)**
Age "years"		
Mean ±SD	28.73±6.41	30.88±5.94
Sex		
Female	47 (94.0%)	34 (85.0%)
Male	3 (6.0%)	6 (15.0%)
Optic neuritis (ON) history		
Non optic neuritis	33 (66.0%)	-
Optic neuritis	17 (34.0%)	-
Bil ON	2 (4.0%)	-
Lt ON	5 (10.0%)	-
Rt ON	10 (20.0%)	-
EDSS Score		

Mean ±SD	1.61±0.52	-
Range	0.5-3	-
EDSS ≤2	42 (84.0%)	-
EDSS >2	8 (16.0%)	-

Utilizing: t-Independent Sample t-test for Mean ±SD; Utilizing: x^2: Chi-square test for Number (%) or Fisher's exact test, when appropriate, S: Significant; NS: Non-significant; HS: Highly significant

The patient's group had significantly lower mean ONSD (4.93 ± 0.45), OND (2.90 ± 0.39), and OND/ONSD ratio (0.59 ± 0.03) compared to the control group (5.48 ± 0.19, 3.35 ± 0.21, 0.61 ± 0.03, respectively), with p-values of 0.001. Patients group also showed significantly higher mean P100 latency (115.60 ± 13.50) compared to controls (104.30 ± 5.89), p-value equal to 0.001. (**Table 2)**

Table (2): Comparison among cases Group and control Group concerning P100 latency, OND, ONSD, OND/ ONSD ratio

Parameters	**cases Group (number=fifty)**	**Control Group (number=forty)**	**Test value**	**p-value**	**Sig.**
Average P100 latency Mean ±SD	115.60±13.50	104.30±5.89	4.927	0.001	HS
Average of OND (mm) Mean ±SD	2.90±0.39	3.35±0.21	-6.528	0.001	HS
Average of ONSD (mm) Mean ±SD	4.93±0.45	5.48±0.19	-7.269	0.001	HS
Average of OND/ ONSD ratio Mean ±SD	0.59±0.03	0.61±0.03	-3.824	0.001	HS

There was a statistically significant variance among cases without history of optic neuritis and control group regarding P100 latency, OND, ONSD, OND/ ONSD ratio, P-value **(P-value below 0.05). (Table 3), (Figures 2,3).**

Table (3): Comparative analysis among cases without history of optic neuritis and control group regarding P100 latency, OND, ONSD, OND/ ONSD ratio

Parameters	**None Optic neuritis (n=33)**		**Control group (number=40)**		**Test value**	**p-value**	**Sig.**
	Mean	**±SD**	**Mean**	**±SD**			
P100 latency							
Average	110.42	12.27	103.31	5.43	3.298	0.002	S
OND (mm)							
Average	3.00	0.41	3.35	0.21	4.707	<0.001	HS
ONSD (mm)							
Average	5.06	0.46	5.48	0.19	5.262	<0.001	HS
OND/ ONSD ratio							
Average	0.59	0.03	0.61	0.03	2.835	0.006	S

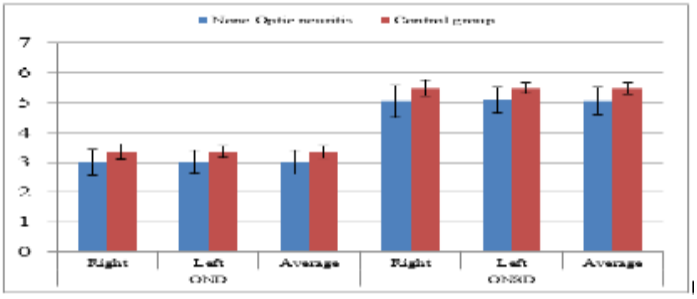

Figure (2): Comparison between cases without history of optic neuritis and control group based on OND, ONSD.

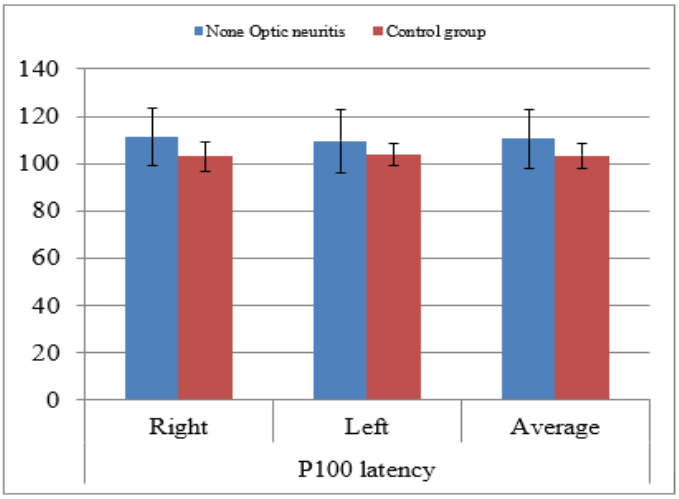

Figure (3): Comparison among cases without history of optic neuritis and control group based on P100 latency.

The mean value of P100 latency has been significantly delayed in cases had history of optic neuritis in comparison with non-optic neuritis cases, **P-value (P-value below 0.05).** There was a statistically significant reduction in ONSD as well as OND in cases had history of optic neuritis in comparison with non-optic neuritis patients, **P-value (P-value below 0.05). (Table 4)**

Table (4): Comparison among cases had history of ON and none-ON according to P100 latency, OND, ONSD, OND/ ONSD ratio.

Parameters	Optic neuritis (n=17)		None (n=33)		Test value	p-value	Sig.
	Mean	±SD	Mean	±SD			
P100 latency							
Average	125.65	9.73	110.42	12.27	4.439	0.001	HS
OND (mm)							
Average	2.71	0.27	3.00	0.41	-2.620	0.012	S
ONSD (mm)							
Average	4.67	0.28	5.06	0.46	-3.227	0.002	S
OND/ ONSD ratio							
Average	0.58	0.03	0.59	0.03	-1.423	0.161	NS

Patients with EDSS > 2 showed a statistically significant elevation in the mean of P100 latency in both eyes in comparison with patients with EDSS ≤ 2. However, optic nerve sheath diameter, optic nerve diameter and OND/ONSD ratio were reduced in cases with EDSS >2 in comparison with patients with EDSS ≤2, with **p-value (P-value below 0.05). (Table 5)**

Table (5): Comparative analysis between cases with EDSS ≤ 2 and cases with EDSS >2 regarding P100 latency, TOS parameters.

Parameters	EDSS ≤2 (n=42)		EDSS >2 (number=8)		Test value	p-value	Sig.
	Mean	±SD	Mean	±SD			
P100 latency							
Average	111.76	10.64	135.75	7.82	-6.052	0.001	HS
OND (mm)							
Average	2.98	0.37	2.51	0.22	3.398	0.001	HS
ONSD (mm)							
Average	5.00	0.45	4.59	0.24	2.496	0.016	S
OND/ ONSD ratio							
Average	0.59	0.03	0.55	0.02	4.697	0.001	HS

OND and ONSD both showed strong and statistically significant ability to predict disability, with high AUCs (0.83) and good sensitivity and specificity. The OND/ONSD ratio also showed fair predictive value (AUC 0.74), (**Figure 4).**

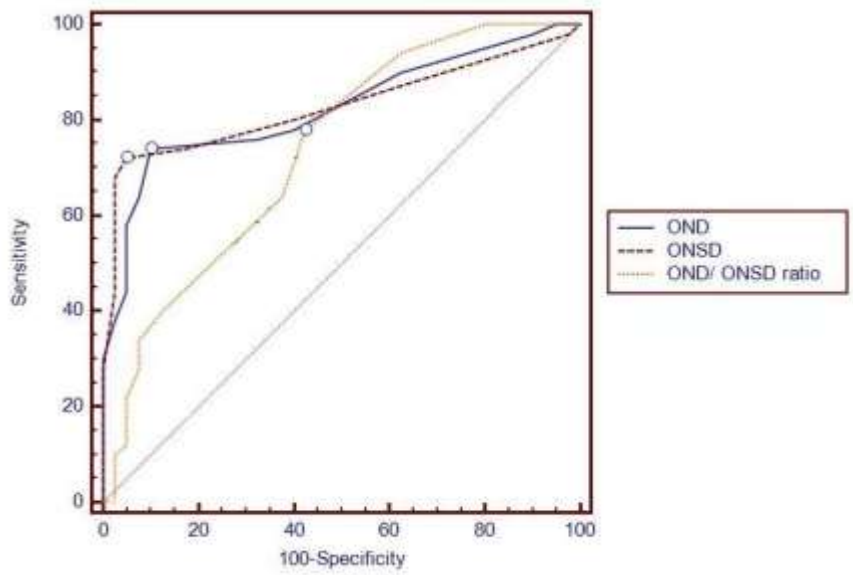

Figure (4): Receiver-operating characteristic (ROC) curve for expectation of early detection of disability, using the optic nerve sheath diameter, optic nerve diameter, OND/ ONSD ratio

DISCUSSION

The visual pathway, particularly the optic nerve, is frequently affected in multiple sclerosis and is often one of the first locations for inflammation to occur. The optic nerve and retina are functionally eloquent structures, recognized as critical targets of multiple sclerosis, especially in cases without history of optic neuritis. [7]

The involvement of the optic nerve may be determined either clinically or through paraclinical tests, like optical coherence tomography (OCT), visual evoked potentials (VEPs), and MRI. [8]

Transorbital ultrasonography, is a promising, non-invasive bedside method to assess the optic nerve changes. It shows great interobserver and intraobserver reliability, and is a cost-effective technique that may be easily mastered through any clinician. [9]

The present study revealed a statistically significant increase in P100 latency in patients group (115.60±13.50) compared to control group (104.30±5.89).

Papadopoulou et al.[10] and Orabi et al.[9] studies demonstrated that MS cases exhibited prolonged P100 latency compared to the control group and that P100 latency delay has been related to retinal degeneration in cases with relapsing-remitting multiple sclerosis.

Our research revealed a statistically significant variance was found among cases without and with previous history of optic neuritis and control group regarding P100 latency. In the same line, **Carcelen et al. [11]**study illustrated that in cases without history of optic neuritis, there was a statistically significant prolongation in the visual evoked potential-latency than control.

P100 latency in our study was more prolonged in cases had history of ON than those without history of ON. Similar to our results, **Papadopoulou et al**.[10] found that P100 latency was higher in cases with history of ON (123.8±30.6 ms) than cases without history of optic neuritis (109±11.9 milliseconds)**.**

Prior research in cases with multiple sclerosis examined the association among P100 latency and measures of damage to the posterior and anterior visual pathways. The P100 latency is influenced by both remote and acute optic neuritis and relates to measures of neuro-axonal integrity in the retina. The P100 latency is influenced by both non-lesional and lesional damage in the optic radiation (OR), as demonstrated in eyes unaffected by optic neuritis. This result aligns with the concept of retrograde transsynaptic degeneration occurring from the posterior visual pathway through the lateral geniculate nucleus (LGN) to retinal structures. [12,13]

In our research, the OND was significantly reduced in the patients group (2.90±0.39) in comparison with control group (3.35±0.21).

In accordance with our findings, **Candeliere Merlicco et al.**[1] observed that the diameters of both the right (2.69 ± 0.30 millimeters in patients; 3.20 ± 0.16 millimeters in controls, P-value below.0001) and left (2.71 ± 0.26 millimeters in patients; 3.21 ± 0.17 millimeters in controls, P-value below .0001) optic nerves in the examined cases were smaller than those of the controls.

In the research by **Antal et al.,**[7] the OND in multiple sclerosis cases was considerably reduced compared to healthy controls (HC = 3.174 ± 0.376 millimeters, number = fifty; MS = 2.974 ± 0.407 millimeters, number = ninety; p-value below 0.0178).

The recent research revealed a statistically significant reduction in the mean value of ONSD in the cases group (4.93±0.45) compared to control group (5.48±0.19).

Consistent with our findings, **Carraro et al.**[14] detected a statistically significant reduction in optic nerve sheath diameter in RRMS relative to the control group.

Furthermore, **Orabi et al.**[9] demonstrated that the ONSD values at three millimeters, five millimeters, and the myelination index decreased significantly in multiple sclerosis cases in comparison with controls (p-value below 0.001). They determined that transorbital ultrasonography is a readily available technique for evaluating optic nerve atrophy in multiple sclerosis. It can indirectly assess loss of the axon and cerebral atrophy, serving as a dependable paraclinical diagnostic instrument, indicating that optic nerve sheath diameter may function as a biomarker for illness activity.

The patients group exhibited a statistically significant reduced mean OND/ONSD ratio (0.59±0.03) than control group (0.61±0.03).

In line with our outcomes, **Raeesmohammadi et al.**[4] documented that the optic nerve diameter / optic nerve sheath diameter ratio in cases was 0.70 ± 0.078 (ninety-five percent confidence interval: 0.69–0.72), whereas in healthy people it was 0.73 ± 0.067 (CI 95%: 0.71–0.74), showing a statistically significant variance among the 2 groups (P-value equal to 0.012).

The current research demonstrated that there was a statistically significant variance among cases without history of previous optic neuritis and control group regarding optic nerve diameter, optic nerve sheath diameter, OND/ ONSD ratio, P-value ($P<0.05$).

Histopathological examination has detected lesions of the optic nerve and optic pathway in a high proportion of cases with MS, involving individuals who have never had acute optic neuritis. Additional types of visual function impairment, like subclinical optic neuritis, were documented in cases with multiple sclerosis. In contrast to the acute type, subclinical optic neuritis is marked by gradual development and bilateral involvement, rendering it undetected by the case.[15]

Previous studies confirmed that multiple sclerosis cases have loss of retinal ganglion cells and thus thinning of the RNFL and optic atrophy because of axonal loss, even in the absence of ON. Numerous hypotheses were suggested to clarify this phenomenon, involving trans-synaptic retrograde degeneration resulting from lesions impacting the posterior visual pathways, primary retinal damage, and subclinical demyelination of the optic nerve.[11]

However, throughout acute optic neuritis, axonal damage to retinal ganglion cells (RGCs) occurs predominantly due to demyelination and/or inflammatory transection, leading to retrograde degeneration of the axons and then the cell bodies of neurons from which these axons arise (i.e., retinal ganglion cells). These processes lead to the thinning of the retinal nerve fiber layer (retinal nerve fiber layer—comprising the axons of the retinal ganglion cells that coalesce to create the optic nerve) and the ganglion cell layer (comprising the cell bodies of the retinal ganglion cells) [16]

Our research shown that cases had EDSS > 2 showed a statistically significant elevation in the mean of P100 latency in both eyes in comparison with patients with EDSS ≤ 2. However, optic nerve sheath diameter, optic nerve diameter and optic nerve diameter/optic nerve sheath diameter ratio were reduced in cases with EDSS >2 in comparison with patients with EDSS ≤2, with p-value ($P<0.05$).

Similar to our study, **Koraysha et al.** [17] demonstrated that, cases with an EDSS score above two had significantly thinner optic nerve diameter (p-value equal to 0.014, p-value equal to 0.010 correspondingly) compared to cases with an EDSS score ≤ two.

A multicenter study by **Candeliere Merlicco et al.** [1] 1on 59 patients with RRMS demonstrated that the optic nerve thickness determined with transorbital ultrasonography has been related to the expanded disability status scale without interference from an earlier history of optic neuritis. Also, Raeesmohammadi **et al.** [4] study showed that there were statistically significant associations between expanded disability status scale in addition to p100 Latencies and both ONSD and OND variables.

In the current study, optic nerve sheath diameter, optic nerve diameter and optic nerve diameter/optic nerve sheath diameter ratio were predictors for detection of disability. OND ≤3.1 predicted disability with seventy-four percent

sensitivity and 90% specificity. Optic nerve sheath diameter ≤5.2 predicted disability with 72% sensitivity and 95% specificity. OND/ ONSD ratio ≤0.61 predicted disability with 78% sensitivity and 58% specificity.
Consistent with our findings, **Koraysha et al.**[17] explored the possibility of optic nerve diameter determined using ultrasonography as a biomarker for early impairment in cases with RRMS. They determined that OND may serve as a biomarker for the early identification of impairment in cases with relapsing-remitting multiple sclerosis.
Furthermore, **Sánchez et al.**[18] established that ultrasonography assessment of optic nerve diameter serves as a valuable predictive indicator for evaluating individuals with MS. Reduced diameters correlated with clinical progression and increased disability.

CONCLUSION

VEP and transorbital ultrasonography distinguished multiple sclerosis cases from control. They also discriminated patients with history of optic neuritis from those without it, proposing that these methods are sensitive enough to identify functional and structural alterations formed in the optic nerve in RRMS. Functional and structural alterations of optic nerve occur regardless of optic neuritis history.

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