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Original Article / Özgün Araştırma

Investigation of Relationship of Stereoacuity with Retinal Nerve Fiber Layer Thickness and P100 Latency in Patients with Multiple Sclerosis with and Without Optic Neuritis

Optik Nöriti Olan ve Olmayan Multipl Sklerozlu Hastalarda Stereokeskinliğin Retinal Sinir Lifi Tabakası Kalınlığı ve P100 Dalgası ile İlişkisinin İncelenmesi

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Abstract

Objective: It was aimed to investigate the relationship of stereoacuity with retinal nerve fiber layer thickness (RNFLT) and P100 latency in multiple sclerosis (MS) patients with and without optic neuritis (ON).

Materials and Methods: Twenty-nine patients diagnosed with clinically definite MS with and without a history of ON were included in this prospective study. Patients without ON were classified into relapsing-remitting MS (RRMS) and single-attack MS (SAMS) subgroups. There were 11 patients in the RRMS group with ON (ON-RRMS), 11 patients with RRMS and 7 patients with SAMS in the MS group without ON, and 16 healthy subjects in the control group. Stereoacuity was determined by the TNO and Titmus tests. RNFLT was measured by spectral domain-optical coherence tomography and P100 latency was measured in pattern visual evoked potential recordings. The results were analyzed with the SPSS 20 statistical program. P<0.05 was considered significant.

Results: In ON-RRMS, RRMS, SAMS, and control groups, the TNO test scores were 151.5±175.8, 117.2±67.0, 197.1±141.6, and 49.2±29.0, respectively and Titmus test scores were 89±111.2, 59.0±48.2, 68.5±39.7 and 40.0±0.0, respectively. TNO test scores were significantly higher in ON-RRMS and SAMS groups than in controls (p=0.03 and p=0.006, respectively). There was no difference between the MS groups and the control group in terms of the Titmus test. Nasal-RNFLT decreased as Titmus test scores increased in the ON-RRMS group, and P100 latency was prolonged as TNO test scores increased in the SAMS group (r=-0.795, p=0.018 and r=0.761, p=0.047, respectively).

Conclusion: Stereoacuity was decreased in patients with MS with and without ON. Measurement of stereoacuity in patients with MS may be useful for diagnosis and monitoring.

Keywords: Multiple sclerosis, optical coherence tomography, stereoacuity, stereotest, visual evoked potentials

Öz

Amaç: Optik nöriti (ON) olan ve olmayan multipl sklerozlu (MS) hastalarda stereokeskinliğin P100 dalgası ve retinal sinir lif tabakası kalınlığı (RSLTK) ile ilişkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Bu prospektif çalışmaya klinik MS tanısı almış, hikayesinde ON olan ve olmayan 29 hasta dahil edildi. ON olmayan hastalar tekrarlayan-düzelen MS (TDMS) ve tek atak MS (TAMS) alt gruplarında incelendi. Çalışmada ON'li TDMS (ON-TDMS) grubunda 11 hasta, ON olmayan MS grubunda 11 TDMS'li ve 7 TAMS'li hasta ve üçüncü grup olarak kontrol grubunda 16 sağlıklı gönüllü yer aldı. Stereokeskinlik TNO ve Titmus testleri ile belirlendi. RSLTK, spektral-domain optik koherens tomografi ve P100 dalgası, patern görsel uyarılmış potansiyeller ile ölçüldü. Sonuçlar, SPSS 20 istatistik programı ile analiz edildi. P<0,05 anlamlı kabul edildi.

Bulgular: ON-TDMS, TDMS, TAMS ve kontrol gruplarında sırasıyla TNO test skorları 151,5±175,85, 117,27±67,00, 197,14±141,62 ve 49,29±29,00; Titmus test skorları 89±111,20, 59,09±48,26, 68,57±39,76 ve 40,00±0,00 saptandı. TNO test skorları ON-TDMS ve TAMS gruplarında kontrol grubundan

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anlamlı derecede daha yüksek idi (sırasıyla; p=0,03 ve p=0,006). Titmus test skorları MS gruplarında kontrol grubundan farklılık göstermedi. ON-TDMS grubunda Titmus test skorları arttıkça nasal-RSLTK azalmaktaydı ve TAMS grubunda TNO test skorları arttıkça P100 latansı uzamaktaydı (sırasıyla r=-0,795, p=0,018 ve r=0,761, p=0,047).

Sonuç: Çalışmanın sonuçlarına göre, ON olan ve olmayan MS gruplarında stereokeskinlik azalmaktadır. MS'li hastalarda stereokeskinliğin ölçülmesi tanı ve takipte yardımcı olabilir.

Anahtar Kelimeler: Multipl skleroz, optik koherens tomografi, stereokeskinlik, stereotest, görsel uyarılmış potansiyeller

Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by axonal degeneration and demyelination (1,2). Visual system involvement is common in MS and optic neuritis (ON) has been reported with a frequency of 50-70%, which is also the first clinical sign in 20-30% of MS patients (2,3,4,5,6). Early diagnosis and careful monitoring of ocular findings are important in the differential diagnosis and follow-up of the disease (6). In previous studies, structural changes of the retina were investigated by optical coherence tomography (OCT) and functional involvement of the optic tracts by visual evoked potentials (VEPs) in MS patients with and without ON (5,6,7). Thinning of the peripapillary retinal nerve fiber layer (RNFL) in OCT, which is a non-invasive high-resolution method, has been reported as an indicator of axon loss in the optic nerve (8). Moreover, it has been recommended for diagnosis and follow-up in early MS, clinically isolated syndrome, radiologically isolated syndrome, and MS without a history of ON (5,6,7,8,9). VEP recording is a highly sensitive non-invasive method for demonstrating lesions in the anterior visual pathways (10,11,12). The most prominent component of VEP is the P100 wave that occurs around 100 ms in normal individuals. Prolonged P100 latency has been reported in approximately 90% of patients with a definite history of ON and is recommended as a standard method to confirm the presence of clinical or subclinical ON in MS (5,8).

It has been reported that visual functions are affected in 80% of patients with MS (13). Visual acuity, contrast sensitivity and color vision functions have been frequently investigated in patients with clinical and/or subclinical ON and are associated with the pathophysiology of MS (13,14,15). On the other hand, few studies have been reported on the relationship between MS and stereopsis.

Stereopsis is defined as depth perception resulting from binocular horizontal retinal disparity. Presence of stereopsis and stereoacuity ability can be evaluated with stereotests arranged according to different principles (16,17). The standard numerical measure of stereopsis is stereoacuity, which is the smallest depth interval between two stimuli that a person can detect using only stereoscopic cues (18). It is known that stereopsis is primarily affected by changes in eye movements. Additionally, it was reported in one study that MS had potential negative effects on stereoacuity (19). There is only minimal evidence and the issue has not been clarified yet.

Although it is known that visual functions are frequently affected in MS, its relationship with stereopsis is not clear yet. In this study, we aimed to examine stereopsis in patients with MS with ON (ON-MS) and without ON (non-ONMS). Unlike previous studies, we examined stereopsis both with the contour-based Titmus test and the random dot-based TNO test. Another difference from other studies was that the non-ONMS group was classified into two subgroups as relapsing-remitting MS (RRMS) and single-attack MS (SAMS) groups. Retinal nerve fiber layer thickness (RNFLT) and P100 latency values were analyzed by spectral domain (SD)-OCT and pattern visual evoked potential (PVEP) recordings, respectively.

Materials and Methods

Subjects

This prospective study was conducted in Antalya Training and Research Hospital. The study included 29 patients with clinically definite MS according to the McDonald criteria 2017 revisions with and without a history of ON (20). There were 11 patients in the ON-MS group including patients with RRMS with ON (ON-RRMS). There were 11 patients with RRMS and 7 patients with SAMS in the non-ON MS group. The control group consisted of 16 healthy individuals.

Exclusion criteria were; presence of strabismus, amblyopia or nystagmus, ocular surgery history, retinal pathology, systemic diseases such as diabetes mellitus and hypertension or other diseases that affect visual functions. Visual acuity testing and detailed ophthalmological examination (slit lamp biomicroscopy) were performed by an ophthalmologist in all participants. Best corrected visual acuity (BCVA) was provided before performing stereotests.

The Clinical Research Ethics Committee of Antalya Education and Research Hospital approved the study (date: 20.06.2019, approval number: 15/20). All procedures were performed according to the Declaration of Helsinki and informed consent was obtained from all participants.

Structural Assessment of the Optic Pathways

The RNFLT, which is one of the topographic optical disc parameters, was assessed using SD-OCT (Cirrus HD OCT, Carl Zeiss Meditec, Dublin, CA, USA). RNFLT measurements (RNFLT-average, -superior, -inferior, -temporal and -nasal) were made using a circular sweep of a fixed diameter of 3.45 mm around the optic disc.

Functional Assessment of the Optic Pathways

The PVEP recordings were performed using a Nihon Kohden device. An active electrode was placed on the scalp over the visual cortex at Oz. The reference and ground electrodes were positioned at Fz and Cz (vertex), respectively. The subject stayed one meter in front of the video monitor, and a 16×12 checkerboard pattern reversed (black to white and white to black) stimulation was applied. The subjects fixed their gaze on a red marker at the center of the screen. Monocular stimulation was given to both eyes, separately. The stimulus rate was 2 Hz. The filter bandpass was 0.5 Hz-1 kHz, sensitivity was 5 mV/division (lV/D), and sweep was 30 ms/division (ms/D). N75, P100 and N135 latencies, and N75/P100 amplitudes were measured. At least 100 artifact-free

responses were averaged and the waveform was recorded twice for the right and left eye of each patient (21). The measurements were performed in a dark and quiet room at a neurophysiology laboratory.

Assessment of Stereoacuity

Existence of stereopsis and stereoacuity were investigated using the TNO and Titmus stereotests which were in the form of a booklet. During these tests, the subjects wore the test-specific eye glasses.

The TNO test (TNO test for stereoscopic vision; Schairer Frank Ophthal-Technik, Stuttgart, Germany) was used to measure global stereopsis and the Titmus test [(Original stereo-fly test, Stereo Optical Co. Inc. 3539) N. Kenton Avenue Chicago, IL, USA] was used to measure local stereopsis. In these tests, subjects were asked to discriminate the three-dimensional images in the tables shown to them. The TNO test consists of colorful plates containing random-dot stereograms. These colorful plates hide three-dimensional test elements that can be seen only by binocular individuals. The TNO test includes seven plates. The first three plates are used to determine the presence of gross stereopsis. The fourth plate (the suppression test) confirms binocularity. The last three plates measure stereoacuity from 480 to 15 arc sec. The Titmus test also consists of three-dimensional test images. During the Titmus test, first, the subject is shown a big image of a housefly to determine the presence of stereopsis. Thereafter, the subject is expected to discriminate the 3D picture in each set consisting of 3 animal pictures and 9 circles. The 9 circles measure stereoacuity from 800 to 40 arc sec. Stereoacuity increases with decreasing test scores and ≤60 arc seconds is considered normal (22).

Stereotests were performed binocularly and with BCVA from a reading distance of approximately 40 cm without time restriction in a silent room where standard daylight illumination and heat (22 °C) were provided. The subjects were asked to check the image shown. The test was performed by the same researcher.

Statistical Analysis

For discrete and continuous variables, descriptive statistics [mean, standard deviation (SD), median, minimum value, maximum value, and percentile] were given. In addition, the homogeneity of the variances, which is one of the prerequisites of parametric tests, was checked through Levene's test. The hypothesis of normality was tested via the Shapiro-Wilk test. To compare the differences between the two groups, the Student's t-test was used when the parametric test prerequisites were fulfilled, and the Mann-Whitney U test was used when such prerequisites were not fulfilled. To compare the differences between three or more groups, One-Way analysis of variance was used when the parametric test prerequisites were fulfilled, and the Kruskal-Wallis test was used when such prerequisites were not fulfilled. The Bonferroni correction method, which is a multiple comparison test, was used to evaluate the significant results concerning three or more groups. The data were evaluated with SPSS 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Results are given as mean ± SD $p<0.05$ and $p<0.01$ were considered as statistically significant.

Results

Twenty nine patients with MS (mean age, 35.8±9.9 years; median, 36.5 years; range, 19-53 years) and 16 healthy controls (mean age, 35.9±8 years; median, 37.8 years; range, 20-46 years), a total of 45 individuals, participated in the study. There was no significant difference between the groups in terms of age ($p>0.05$). The female/male ratio in patients with MS was 3/1. The demographic data of the individuals participating in the study are shown in Table 1.

In the ON-RRMS group, 6 patients (54.5%) had involvement in the right eye and 5 patients (46.4%) had involvement in the left eye. RNFTL, P100 latency and P100 amplitude measurements of the eyes with ON and fellow eyes are given in Table 2. According to the results, although the RNFLT were thinner and P100 latencies were longer in the eyes with ON than in the fellow eyes, there was no statistically significant difference between them. No significant differences were found between eyes with ON and non-ON eyes in terms of P100 amplitudes.

The RNFLT, P100 latency and P100 amplitude measurements in patients and controls are shown in Table 3. Temporal RNFLT was significantly thinner in the ON-RRMS and RRMS groups than the control group. Superior RNFLT was significantly thicker in the SAMS group than the control group; nasal-RNFLT was thicker in the ON-RRMS and SAMS groups than the control group. P100 latencies were significantly prolonged in all MS groups compared to the control group. P100 amplitudes were decreased in all MS groups compared to the control group, but the difference was not statistically significant.

The stereotest scores of the patients and controls are given in Table 4. In the comparisons between the groups, the mean TNO test scores were found to be significantly higher in the ON-RRMS and SAMS groups than the control group. According to the Titmus test, it was observed that the scores of the patients were higher than controls, but these differences were not statistically significant.

Table 1. Demographic data of subjects

	Patients with MS with ON	Patients with MS without ON		Healthy subjects
	ON-RRMS n=11	RRMS n=11	SAMS n=7	Controls n=16
Age (mean ± SD)	37.55±7.51	37.19±9.60	34±10.83	35.94±8
Median	35	36	36	37.88
Age range	27-47	27-53	19-49	20-46
Gender				
Female	10	9	4	11
Male	1	2	3	5

MS: Multiple sclerosis, ON: Optic neuritis, RRMS: Relapsing-remitting multiple sclerosis, SAMS: Single-attack multiple sclerosis, SD: Standart deviation

The correlation analyses between the patients' stereotest scores, RNFLT and P100 latencies were presented in Table 5. A negative correlation was found between Titmus test scores and nasal-RNFLT in the ON-RRMS group, and a positive correlation was found between TNO test scores and P100 latency in the SAMS group.

Discussion

In this study, stereoacuity was examined with two different stereotests in patients with MS and it was affected to varying degrees in the patient groups. Moreover, we found with TNO test that stereoacuity was decreased significantly in ON-RRMS and SAMS groups. In addition, it was found that nasal-RNFLT decreased as Titmus test scores increased in the ON-RRMS group and that P100 latencies were prolonged as TNO test scores increased in the SAMS group (p=0.018 and p=0.047, respectively).

It has been reported that abnormal VEP findings are common in MS consistent with the involvement of afferent visual pathways.

Table 2. Retinal nerve fiber layer thicknesses and VEP parameters of patients with multiple sclerosis with optic neuritis

	ON (+) eyes mean ± SD (n=eyes)	Fellow eyes mean ± SD (n=eyes)
Average RNFLT	83.1±15.8 (11)	86.9±18.6 (11)
Superior RNFLT	104.8±21.1 (11)	109.6±24.0 (11)
Inferior RNFLT	99.7±31.0 (11)	106.8±35.5 (11)
Temporal RNFLT	53.4±11.6 (10)	55.5±12.9 (11)
Nasal RNFLT	73.6±10.9 (10)	79.3±16.8 (11)
P100 latencies	123.8±16.2 (11)	115.6±8.3 (11)
P100 amplitudes	8.9±4.1 (11)	6.6±3.2 (11)

VEP: Visual evoked potentials, ON: Optic neuritis, RNFLT: Retinal nerve fiber layer thickness, SD: Standart deviation

Also it has been recommended as a sensitive and specific tool to detect demyelinating ON (5). Approximately in 90% of patients with MS with and without ON, P100 latency was prolonged and this prolongation was not always accompanied by a decrease in amplitude (5,23). We found significantly longer P100 latencies and P100 amplitudes were decreased without reaching statistical significance in the MS groups with and without ON than the control group. Prolongation of P100 latency in MS is due to impaired saltatory conduction caused by demyelination, and the decrease in P100 amplitude is due to the decrease in the number of axons carrying impulses.

In our study, although the RNFLT was thinner and P100 latency was prolonged in the eyes with ON than in the fellow eyes, there was no statistically significant difference between them. No significant differences were found between ON eyes and non-ON eyes in terms of P100 amplitudes. Alshuaib (24) reported that there was a progression of the P100 latency delay and of the P100 amplitude decrement in ON, confirmed MS, and ON combined with confirmed MS, indicating a progression of demyelination in them. On the other hand, evoked potentials, including VEPs, may change according to the natural history of MS and the potential effect of therapeutic interventions (4). The study of Chatziralli et al. (25) suggests that there is a progressive decrease in RNFL over time in eyes with ON associated with MS. The P100 amplitude and P100 latency in VEP examination returned to normal ranges over time in their study (25). The lack of any significant differences in P100 latencies and amplitudes between eyes with ON and fellow eyes in our study might be related to the severity of ON and the time elapsed since diagnosis. The low number of patients might also be another factor.

Measurement of RNFLT in OCT is one of the accepted parameters to evaluate retinal axonal damage in patients with MS. It is not clear yet whether RNFL thinning is a part of diffuse neurodegeneration affecting all quadrants or is an indicator of local damage varying according to the quadrants and whether it is an appropriate method for monitoring disease progression. Studies

Table 3. Retinal nerve fiber layer thicknesses and VEP parameters of subjects

	Patients with MS with ON	Patients with MS without ON		Healthy subjects	
	ON-RRMS mean ± SD (n=eyes)	RRMS mean ± SD (n=eyes)	SAMS mean ± SD (n=eyes)	Controls mean ± SD (n=eyes)	p
Average RNFLT	83.1±15.8 (11)	82.1±15.3 (22)	93.2±10.6 (14)	88.6±11.2 (32)	**>0.05**
Superior RNFLT	104.8±21.1 (11)	106.7±20.1 (22)	126.1±24.4[a] (14)	112.1±15.5[a] (32)	**0.028[a]**
Inferior RNFLT	99.7±31.0 (11)	118.5±76.3 (22)	120.9±11.8 (14)	116.9±17.0	**>0.05**
Temporal RNFLT	53.4±11.6[a] (10)	52.5±11.6[b] (22)	62.2±9.5 (14)	69.6±13.9[a,b] (32)	**0.001[a]** **0.000[b]**
Nasal RNFLT	73.6±10.9[a] (10)	66.0±9.7 (22)	69.5±13.1[b] (14)	60.3±12.6[a,b] (32)	**0.003[a]** **0.018[b]**
P100 latencies	123.8±16.2[a] (11)	122.9±15.7[b] (22)	117.8±11.4[c] (14)	105.6±6.0[a,b,c] (32)	**0.000[a]** **0.000[b]** **0.002[c]**
P100 amplitudes	8.9±4.1 (11)	8.7±3.4 (22)	9.9±2.6 (14)	10.0±9.3 (32)	>0.05

[a]There is a statistically significant difference between groups containing letters (p<0.05), [b]There is a statistically significant difference between groups containing letters (p<0.05), [c]There is a statistically significant difference between groups containing letters (p<0.05). VEP: Visual evoked potentials, MS: Multiple sclerosis, ON: Optic neuritis, RNFLT: Retinal nerve fiber layer thickness, RRMS: Relapsing remitting multiple sclerosis, SAMS: Single attack multiple sclerosis, SD: Standart deviation

Table 4. TNO and Titmus tests scores of subjects

	Patients with MS with ON	Patients with MS without ON		Healthy subjects	
Parameters	**ON-RRMS mean ± SD (n=patients)**	**RRMS mean ± SD (n=patients)**	**SAMS mean ± SD (n=patients)**	**Controlls mean ± SD (n=subjects)**	**p**
TNO test, arc sec	151.5±175.8[a] (10)	117.2±67.0 (11)	197.1±141.62[b] (7)	49.2±29.0[a,b] (14)	**0.030[a]** **0.006[b]**
Titmus test, arc sec	89±111.2 (10)	59.0±48.2 (11)	68.5±39.7 (7)	40±0 (16)	**0.25**

The tests were performed with BCVA and under binocular condition. [a]There is a statistically significant difference between groups containing letters ($p<0.05$), [b]There is a statistically significant difference between groups containing letters ($p<0.05$), MS: Multiple sclerosis, ON: Optic neuritis, RRMS: Relapsing-remitting multiple sclerosis, SAMS: Single-attack multiple sclerosis, SD: Standard deviation, BCVA: Best corrected visual acuity

Table 5. Correlation analysis between stereotest scores and retinal nerve fiber layer thickness, and P100 latency in patients

Parameters	Average RNFLT	Superior-RNFLT	Inferior-RNFLT	Temporal-RNFLT	Nasal-RNFLT	P100 latency
ON-RRMS						
TNO, arc sec	-	-	-	-	-	-
Titmus, arc sec	-	-	-	-	**r=-0.795 p=0.018**	-
P100 latency	r=-0.716 p=0.030	-	-	r=-0.834 p=0.005	r=-0.721 p=0.028	-
RRMS						
TNO, arc sec	-	-	-	-	-	-
Titmus, arc sec	-	-	-	-	-	-
P100 latency	-	-	-	-	-	-
SAMS						
TNO, arc sec	-	-	-	-	-	**r=0.761 p=0.047**
Titmus, arc sec	-	-	-	-	-	-
P100 latency	-	r=-0.602 p=0.023	-	-	-	-

ON: Optic neuritis, RNFLT: Retinal nerve fiber layer thickness, RRMS: Relapsing-remitting multiple sclerosis, SAMS: Single-attack multiple sclerosis

measuring RNFLT in four quadrants have reported different results in terms of the affected quadrant. In our study, average RNFLT and RNFLT in four quadrants were measured. Temporal RNFLT was found significantly thinner in the ONMS and RRMS groups than the control group, but non-significant thinning was found in the SAMS group. Although our results are consistent with a study reporting that temporal quadrant thinning may indicate a selective susceptibility to damage of the papillomacular bundle, the need for clarification remains (21,26).

The SAMS group did not show significant thinning in RNFL compared to the control group, but P100 latencies were significantly prolonged. This finding appeared to be consistent with the study reporting that VEPs showed higher sensitivity for the diagnosis of the disease and that thinning of the RNFL was associated with disease severity and duration in all eyes with and without ON (27). The 2017 revisions to the McDonald criteria were intended to facilitate earlier diagnosis when MS was likely but not diagnosable with 2010 McDonald criteria. The panel recommends that in a typical clinically isolated syndrome; fulfillment of clinical or magnetic resonance imaging (MRI) criteria for dissemination in space, and demonstration of cerebrospinal fluid oligoclonal bands in the absence of atypical cerebrospinal fluid findings allow a diagnosis of MS to be made, even if the MRI findings on the baseline scan do not meet the criteria for dissemination in time or in the absence of either a second attack or MRI evidence of a new or active lesion on serial imaging (20). Therefore, we chose to use the term "SAMS". After all, we did not observe any RNFLT changes suggesting early MS in this group of patients. We may observe changes in the later stages of the disease in this group of patients.

Unlike previous studies, in this study, stereoacuity was examined with both TNO and Titmus tests. TNO test is a random dot-based test and Titmus test is a contour-based test. In these tests, if the stereoacuity is above 60 arc sec, it is accepted that the stereopsis of the patients is impaired. Accordingly, the rates of patients with impaired stereopsis are presented in Table 6. It was observed that stereopsis was affected at different rates in the MS groups. Impairment rates of stereopsis have also been reported in other studies. Gil-Casas et al. (19) used RST, a random dot-based test such as TNO, and showed that stereopsis was impaired by 70-80% in patients with MS with ON in one eye and by 53% in patients with MS without ON. Sobaci et al. (28) also reported that stereopsis was impaired by 73.9% in patients with MS without ON in their study using random stereotest. According to our

Table 6. Distribution of patients with MS affected by stereopsis

Parameters	ON-RRMS	Patients with MS without ON		Controls
TNO, >60 arc sec	4/10 (40%)	13/18 (72.2%)	RRMS 7/11 (63.6%) SAMS 6/7 (85.7%)	1/14 (7.1%)
Titmus, >60 arc sec	3/10 (30%)	5/18 (27.7%)	RRMS 2/11 (18.1%) SAMS 3/7 (42.8%)	0/14 (0%)

ON: Optic neuritis, RRMS: Relapsing-remitting multiple sclerosis, SAMS: Single-attack multiple sclerosis

results, stereopsis was affected less in the Titmus test than the TNO test in the patients. This result may be related to the fact that the contour-based Titmus test provides monocular clues and produces better stereoacuity (16,29). The Titmus test is frequently used in clinics to evaluate stereopsis. Impaired stereopsis was also observed with the Titmus test in our study. To our best knowledge, our study is the first study examining stereopsis in MS with the Titmus test.

In our study, stereoacuity was found to be significantly decreased in ON-RRMS and non-ON SAMS groups with TNO test compared to the control group (p=0.03 and p=0.006, respectively). Saxena et al. (7) found with the TNO test that stereoacuity was decreased in patients with MS with and without ON. They reported for the first time that it was valuable to detect such a decrease in patients with normal visual acuity and that the decrease in stereoacuity in patients without ON might be associated with subclinical optic nerve involvement. In our study, TNO test was applied binocularly and with BCVA.

Unlike studies reporting decreased stereoacuity in patients with RRMS, stereotest score averages in patients with RRMS did not differ from the control group in our study. This may be related to residual damage in patients with RRMS as a result of different inflammation patterns in each patient (21,28,30).

In our study, correlation analyses were performed to show the relationship between TNO and Titmus test scores and RNFLT. A negative correlation was found between Titmus test scores and nasal-RNFLT in the ON-RRMS group (r=-0.795, p=0.018) and no correlation was found with RNFLT in any quadrant in the non-ONMS group. Unlike our results, Saxena et al. (7) reported a negative correlation between stereoacuity and average RNFLT and temporal RNFLT quadrant, and a positive correlation between superior and inferior RNFLT quadrants in patients with MS without ON.

Correlation analyzes were performed to investigate the relationship between TNO and Titmus test scores and P100 latency in our study. A positive correlation was found between TNO test scores and P100 latency in the SAMS group (r=0.761, p=0.047). This result was consistent with the results of the study conducted by Sobaci et al. (28). They found decreasing stereoacuity as P100 latency was prolonged in patients with MS without ON. They reported that this finding might be associated with subclinical involvement.

In MS, impairment of stereopsis has been mainly associated with ocular motor deficits (8,17). Examining relationship between stereoacuity, OCT and VEP parameters in MS patients is a new area of research. There are a few studies in the literature clarifying the relationship between these parameters. In these studies, stereoscopic visual defects in MS were associated with clinical and subclinical optic nerve involvement, and it was reported that the disease might occur in relation to the demyelination process (19,23,28). All of these possibilities might be true for our patients. The underlying mechanism is not clear yet.

Study Limitations

The small number of patients participating in the study was an important limitation of the study. The patients in the SAMS group were patients who presented with their first attack and were diagnosed as having MS according to the McDonald criteria 2017 revision. Although the number of patients was small, we thought that it was important to detect decrased stereoacuity in the SAMS group.

Another important limitation of the study was that it could not explain the underlying neurophysiological mechanism. Future comprehensive studies might clarify this issue.

Conclusion

In our study, it was observed that stereopsis was impaired at different rates and stereoacuity decreased in patients with MS with and without ON. Differences in testing principles should also be taken into account when assessing the stereoacuity of patients with MS.

Ethics

Ethics Committee Approval: Ethical approval was taken from the Clinical Research Ethics Committee of University of Health Sciences Turkey, Antalya Training and Research Hospital (date: 20.06.2019, approval number: 15/20).

Informed Consent: Informed consent of all participants was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.K., B.Y., D.D., M.A.Ç., D.T.Ç., Concept: B.K., B.Y., D.T.Ç., Design: B.K., B.Y., D.T.Ç., Data Collection or Processing: B.K., B.Y., D.D., M.A.Ç., M.A.T., Analysis or Interpretation: B.K., B.Y., D.D., M.A.T., Literature Search: B.K., B.Y., D.D., Writing: B.K., B.Y.

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