ÖZGÜN ARAŞTIRMA / ORIGINAL RESEARCH

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Is there a relationship between the ganglion cell complex thickness and macular thickness in patients with multiple sclerosis?

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Abstract

Is there a relationship between the ganglion cell complex thickness and macular thickness in patients with multiple sclerosis?

Objective: Optic neuritis (ON) is the most common ocular finding of multiple sclerosis (MS). ON can cause axonal loss and abnormalities in both optical coherence tomography (OCT) parameters and visual evoked potentials (VEPs). In this study, the retinal fiber layer (RNFL), ganglion cell complex (GCC) and macular thicknesses were measured with OCT and compared between MS cases with and without a clinical history of ON and healthy individuals. In addition, it was examined whether these values were correlated with VEP and clinical findings and whether they could be used as a marker of axonal loss.
Method: The study included 49 patients with MS (98 eyes) and 30 healthy controls (60 eyes) aged 18-55 years. Visual acuity, color vision, VEP, and OCT measurements were evaluated.
Results: RNFL, GCC, macula (except the superior outer layer), and foveal thickness measurements were statistically significantly thinner in all MS patients, especially in eyes with a history of ON.
Conclusion: Due to the detection of deterioration in these values in non-ON eyes, it was concluded that the use of OCT in all patients, not only in MS patients with ON, would be beneficial, and as the number of parameters measured in OCT is increased, its distinctive feature will improve and axonal damage can be better evaluated in MS patients.
Keywords: Multiple Sclerosis, Macula, Retinal Ganglion Cell

Öz

Multipl skleroz hastalarında ganglion hücre kompleks kalınlığı ile maküler kalınlık arasında ilişki var mı?

Amaç: Optik Nörit (ON), Multipl Skleroz'un (MS) en sık saptanan göz bulgusudur. ON, aksonal kayba yol açıp hem Optik Koherens Tomografi (OCT) ve hem de görsel uyarılmış potansiyallerde (VEP) anormalliklere neden olabilmektedir. Bu çalışmada OCT ile Retina Sinir Lifi Tabakası (RSLT), Ganglion Hücre Kompleksi (GCC) ve maküler kalınlığı ölçülerek, bu parametreler, klinik olarak ON öyküsü olan ve olmayan MS hastaları ve sağlıklı bireylerle karşılaştırıldı. Ayrıca bu değerlerin VEP bulguları ve klinik bulgularla korelasyonunun olup olmadığı incelendi, aksonal kaybın bir belirteci olarak kullanılıp kullanılamayacağını değerlendirme hedeflendi.
Yöntem: Çalışmaya 18-55 yaşları arasında, 49 MS hastası (98 göz) ve 30 sağlıklı kontrol grubu (60 göz) dahil edildi. Görme keskinliği, renkli görme, VEP ve OCT ölçümü yapıldı.
Bulgular: ON öyküsü olan gözlerde daha fazla olmak üzere tüm MS hastalarında RNFL, GCC, makula (süperior dış katman hariç) ve fovea kalınlığı ölçümleri istatistiksel olarak anlamlı olarak daha ince bulundu.
Sonuç: ON olmayan gözlerde de bu değerlerde bozulma tespit edilmesi OCT'nin sadece ON geçiren MS hastalarında değil tüm hastalarda kullanılmasının fayda sağlayacağını ve OCT de bakılan parametre sayısı artırıldıkça ayırt edici özelliğinin artacağını ve aksonal hasarın MS hastalarında daha iyi değerlendirebileceğini düşündürdü.
Anahtar Kelimeler: Multipl Skleroz, Maküla, Retina Ganglion Hücresi

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INTRODUCTION

Multiple sclerosis (MS) is a chronic disease that causes axonal loss and demyelination in the central nervous system (CNS) and manifests with attacks, mostly affecting young adults. Optic neuritis (ON) is the inflammation of the optic nerve that usually results in a rapid and temporary reduction in visual function. ON can occur alone or as a manifestation of clinically isolated syndrome or MS. ON is the most common ocular manifestation of MS and is seen as the initial symptom in approximately 20% of cases (1,2).

Although the normal visual function is determined to be improved with standard methods after ON, patients generally complain of visual dysfunction subjectively (3). The presence of optic nerve involvement in MS has been tried to be demonstrated with VEP parameters for a long time and later with OCT (4,5).

In addition to axonal loss, ON can cause the thinning of the retinal nerve fiber layer (RNFL) and abnormalities in visual evoked potentials (VEPs) (6). Due to its high axial resolution, optical coherence tomography (OCT) provides cross-sectional images without damaging tissues (7). OCT allows for the examination of intraretinal structures, such as RNFL, photoreceptors, and retinal pigment epithelium, as well as anatomical structures, including the optic disc and macula. RNFL is reported to be thinner in all MS types (8).

The ganglion cell complex (GCC) is a structure comprising RNFL, the ganglion cell layer, and the inner plexiform layer, and has also been measured by OCT separately from RNFL. RNFL consists of the unmyelinated axons of retinal ganglion cells and is the most proximal of afferent visual pathways. In the presence of the destruction of backwards axonal degeneration, anomalies are detected in the optic nerve and RNFL (9).

In glaucoma, an increase in the cup-to-disc (c/d) ratio, obtained from the topographic images of the optic disc, is generally defined. It should be kept in mind that there may also be an increase in optic neuropathies. An increase in the c/d ratio has also been described in eyes with associated ON (10).

RNFL measurement in MS varies according to the type and stage of the disease and is used in the follow-up of patients (8). The use of GCC and macular thickness measurements in MS patients was later investigated and demonstrated to contribute to follow-up (11).

In the current study, the ocular findings of patients with MS and healthy controls were comparatively evaluated by measuring the RNFL, GCC and macular thicknesses with OCT. Therefore, the present study aimed to evaluate more detailed parameters by examining the GCC and macular thicknesses in addition to RNFL in many sections. In addition, it was intended to evaluate whether these parameters could be used as markers of axonal loss by investigating their correlation with VEP and clinical findings.

OCT use in MS patients has become more common daily, and these studies remain up to date with the developing technology.

METHOD

A total of 49 relapsing remitting MS patients (33 women and 16 men) aged 18-55 years that were followed up at the Multiple Sclerosis Outpatient Clinic of the Neurology Department of Gaziantep University Faculty of Medicine and 30 healthy individuals (13 women and 17 men) were included in the study. For the healthy control group, being between the age of 18-55, willing to participate in the study, and an absence of known severe visual problems, such as myopia were determined as the inclusion criteria. All the patients and healthy volunteers included in the sample were informed about the study and their written consent was obtained.

Of the 49 MS patients, 33 had no history of ON, while 16 had a history of ON in one and/or both eyes. Within the scope of the study, 158 eye examinations were performed in a total of 79 cases. Forty-nine cases (98 eyes) diagnosed with MS and included in the study were divided into three groups according to the presence of an ON attack history: healthy eyes (control group), eyes without a history of ON (non-ON group), and eyes with a history of ON (ON group).

The disease duration, Expanded Disability Status Scale (EDSS) scores, and visual acuity and color vision examination findings of the patients with MS were recorded. Visual acuity was evaluated using the Snellen pocket eye chart, with the participants being asked to look at the chart three times and with glasses on for those wearing glasses. The visual acuity of the cases was classified as normal if the test value was 20/20, mild vision loss if 20/50, moderate vision loss if 20/70, and severe vision loss if 20/100 or above. Color vision was assessed using the Ishihara plate, and the number of digits that the participants were able to read was recorded as the result. Accordingly, 1-4 errors were evaluated as mild loss, 4-8 as moderate loss, and 8-12 as severe loss. The clinical disability status of the patients with MS patients was evaluated using the EDSS.

The remaining tests applied to the patients and control groups are given below.

VEP: The pattern VEP technique was used. Care was taken to ensure that no mydriatic drop was administered within the last 72 hours before VEP.

OCT: The Fourier-domain OCT method was chosen to perform the evaluation in more sections.

RNFL thickness analysis: The 'optic nerve head map', 'macular map' and 'ganglion cell complex scan' protocols were applied. In accordance with the protocol, circular scanning was performed in a 360-degree area centered on the optic disc with a diameter of 3.45 mm around the disc. For the analysis of the RNFL thickness, the mean nerve fiber thickness and that of the superior and inferior quadrants were automatically calculated in micrometers (µm) in all eyes. The optic nerve head map analysis was used to calculate the rim area, concave area, disc area, average c/d ratio, horizontal c/d ratio, and vertical c/d ratio. The mean foveal and macular thicknesses in all quadrants were calculated using the macular map analysis. Lastly, the mean, superior and inferior GCC thicknesses were measured using the GCC scan analysis.

Statistical Analysis

In this study, the statistical analysis of the data obtained from the 98 eyes of 49 patients with MS and 60 eyes of 30 healthy individuals was performed using the Statistical Package for the Social Sciences (SPSS) for Windows, v. 21.0. Descriptive statistics (number, percentage, mean, and standard deviation) were used when evaluating the data. The t-test was used to compare the differences in quantitative data between two groups, one-way analysis of variance for the comparison of more than two groups, and the Scheffe test was conducted to determine the groups causing the statistically significant difference. The correlation analysis was applied to determine the relationship between the research parameters. The correlation coefficient was interpreted to indicate a weak correlation if r = 0.000-0.240, a moderate correlation between if r = 0.250-0.490, a strong correlation if r = 0.500-0.740, and a very strong correlation if r = 0.750-1.000. The findings were evaluated at the 95% confidence interval and 5% significance level.

RESULTS

Of the total of 158 eyes included in the study, 68 were in the ON group, 30 were in the non-ON group, and 60 were in the control group. The mean age and gender ratio of the patient and control groups, and the mean disease duration and EDSS score of the patient group are presented in (Table 1).

In the ON group, visual acuity was evaluated as normal in 17 (56.6%) patients, mild vision loss in 5 (16.7%) patients, moderate vision loss in 6 (20.0%), and severe vision loss in 2 (6.7%). Of those without a history of ON, 56 (82.3%) had normal visual acuity findings, while mild vision loss was detected in 7 (10.3%) and moderate vision loss in 5 (7.4%). In the control group, all the eyes (n = 60; 100.0%) had visual acuity values within normal limits.

Table 1: Age and gender ratio of the patient and control groups and disease duration and mean EDSS score of the patients

	MS (n = 49)	Control (n = 30)
Mean age	32.78 ± 7.35	25.97 ± 3.56
Gender ratio (F:M)	33/16	13/17
Mean disease duration		
-ON group	5.88 ± 3.74	
-Non-ON group	6.36 ± 3.63	
Mean EDSS score		
-ON group	0.69 ± 1.54	
-Non-ON group	0.85 ± 1.42	

MS: Multiple Sclerosis, ON: Optic Neuritis, EDSS: Expanded Disability Status Scale, F: Female, M: Male

In the ON group, color vision was normal in 25 (83.4%) patients, and mild color vision loss was present in 1 (3.3%) patient, moderate in 3 (10.0%) patients, and severe in 1 (3.3%) patient. Among the patients without a history of ON, 60 (88.2%) had normal color vision, while mild and moderate vision loss was detected in 4 patients each (5.9% each). In the control group, all the eyes (n = 60; 100.0%) had normal color vision values. There was a strong positive correlation between visual acuity and color vision in the group with a history of ON and a moderate positive correlation in the group without a history of ON ($r = 0.698$; $p = 0.0001 < 0.05$ and $r = 0.446$; $p = 0.0001 < 0.05$, respectively). A moderate correlation was determined between VEP p100 latency and color vision in the group with and without a history of ON ($r = 0.373$; $p = 0.002 < 0.05$ and $r = 0.373$;$p = 0.002 < 0.05$, respectively)

OCT Findings

1- RNFL thickness

The RNFL layer of the patients with MS was thinner than that of the control group, and the difference was more significant for the eyes with a history of ON ($p = 0.0001$) (Table 2).

2- GCC thickness

The mean, superior and inferior GCC layers of the patients with MS were thinner than those of the control group, and the difference was more significant for the eyes with a history of ON ($p = 0.0001$) (Table 2).

3- Macular thickness

When the macular thickness measurements were compared, there was a significant difference between the controls and the eyes with and without a history of ON attacks in all quadrants ($p = 0.0001$) except for the superior outer macula ($p = 0.073$) (Table 3).

Table 3: Comparison of the macular thickness measurements between the groups

	ON group (n = 30)	Non-ON group (n = 68)	Control group (n = 60)	p
Temporal inner macula (µm)	273.800 ± 17.010	288.740 ± 18.932	304.120 ± 11.215	**0.0001**
Superior inner macula (µm)	288.200 ± 16.240	304.970 ± 26.541	318.130 ± 12.802	**0.0001**
Nasal inner macula (µm)	283.600 ± 16.332	300.870 ± 21.291	315.350 ± 14.744	**0.0001**
Inferior inner macula (µm)	285.300 ± 14.907	297.910 ± 20.398	313.400 ± 16.425	**0.0001**
Temporal outer macula (µm)	257.230 ± 14.880	267.970 ± 18.383	278.570 ± 13.086	**0.0001**
Superior outer macula (µm)	264.500 ± 14.545	281.490 ± 55.705	282.830 ± 11.469	**0.073**
Nasal outer macula (µm)	276.830 ± 14.944	289.790 ± 17.914	304.200 ± 14.251	**0.0001**
Interior outer macula (µm)	260.600 ± 14.462	268.880 ± 15.332	282.070 ± 12.809	**0.0001**

ON: Optic Neuritis, µm: micrometers

4- Foveal thickness

The mean foveal thickness measurement was 227.400 ± 14.675 for the ON group, 231.760 ± 19.123 for the non-ON group, and 240.600 ± 15.822 for the control group. Foveal thinning was detected in both MS groups regardless of the presence of an ON history, and this was statistically significant compared to the control group ($p = 0.001$). When the ON and non-ON group were compared, foveal thinning was more common in the former.

5- Horizontal and vertical c/d ratios

There was an increase in the horizontal and vertical c/d ratios in the patients with a history of ON compared to the control group and patients without a history of ON, but it was not at a statistically significant level ($p > 0.005$). Correlation analyses revealed a strong positive correlation between mean GCC thickness and mean RNFL thickness in patients with and without a history of ON ($r=0.693$ $p<0.001$, $r=0.764$, $p<0.001$, respectively). A moderate correlation was observed between foveal thickness and mean GCC thickness in eyes without a history of ON ($r = 0.356$; $p = 0.003$). Except for the superior outer macular thickness, the macular thicknesses in all the remaining quadrants were correlated with the mean, superior and inferior GCC thicknesses. In addition, the macular thicknesses in all quadrants were correlated with all foveal thickness, except for the superior outer macula.

VEP Findings

When the VEP P100 latency measurement was compared between the groups, it was prolonged in both the eyes with and without ON (116.400 ± 13.003 and 114.676 ± 13.617, respectively) compared to the control eyes (102.117 ± 7.796) ($p = 0.0001$). The VEP amplitude measurements were similar between the three groups ($p=0,293$). In the correlation analysis, a thinner RNFL was correlated with a lower VEP amplitude in the ON group ($r = 0.444$; $p = 0.014$). In the non-ON group, the VEP P100 latency was prolonged as the mean RNFL thickness decreased ($r = 0.615$; $p = 0.0001$). In the ON group, the VEP amplitude decreased as the mean GCC thickness decreased ($r = 0.415$; $p = 0.023$).

In the present study, a statistically significant relationship was determined between the mean GCC thickness and the EDSS score ($r = -0.434$; $p = 0.012 < 0.05$).

DISCUSSION

Consistent with the literature, the present study supports the presence of optic nerve and retinal damage in MS patients with or without a history of ON (12). It is considered that axonal damage can be better evaluated by increasing the number of parameters measured with the OCT technique.

The deterioration in visual acuity and color vision was more common in MS patients than in controls, being even more frequent in eyes with a history of ON. The fact that visual functions were impaired in the eyes of MS patients without a history of ON suggested that it is a subclinical disease. A study in a large cohort of patients in 2022 revealed that 79% of patients reported vision issues, with evidence of optic nerve damage in 99% of these patients and 61% of those without visual impairment. The same study demonstrated that optic nerve damage was similar to white matter lesions (13). In the MS group, the prolongation of VEP p100 latency was correlated with color vision impairment. The correlation between visual acuity and color vision in both eyes with and without a history of ON indicated the importance of evaluating color vision together with visual acuity in clinical practice.

RNFL thickness measurement is the most commonly used OCT parameter in MS patients (14). Similar to the literature, it was thinner in MS patients in the present study (15). RNFL includes unmyelinated axons, and its thinning is considered to indicate axonal damage (16). It has been known since the first study by Parisi et al. in 1999 that it is also thinned in eyes without ON (12). Consequently, Trip et al. suggested that this finding might be due to axonal damage in the optic nerve (17).

The mean, superior, and inferior GCC layer thickness was determined to be thinner in MS patients than in controls, being even more so in those with a history of ON. In a study comparing newly diagnosed MS patients without ON and healthy controls, there was no significant difference in RNFL measurements; however, a decrease in GCC layer thickness was observed in MS patients (18). Moreover, this study, which concluded that the EDSS score increased as the mean GCC thickness decreased, might indicate that OCT can also be used in disability follow-up. As a matter of fact, the finding of a statistically significant correlation between EDSS and GCC thinning in a similar study published in 2021 supports the results of the present study (19). Although a strong relationship was determined between the mean GCC thickness and the mean RNFL thickness in both patients with and without a history of ON, considering the literature data, it is suggested that the GCC layer measurement is more advantageous.

The fact that macular thickness measurements (except for the superior outer macular) and foveal thickness were also observed to be thinner in MS patients, being more in ON eyes, and their correlation with each other was similar to the findings in the literature (20,21) The macula is a relatively more consistent structure between individuals, and the measurement of the macula may reflect the integrity of retinal ganglion cells (20,22). Evaluation of macular information, together with other OCT parameters, would contribute to the use of OCT as a retinal biomarker in MS patients (23). The correlation of all quadrant thicknesses of the macula (except for the superior outer macular thickness) with mean, superior, and inferior RNFL thickness and mean, superior and inferior GCC thickness might be an indicator showing that the use of different parameters of OCT together may be more reliable in demonstrating axonal damage. Furthermore, a moderate relationship was determined between foveal thickness and mean GCC thickness in eyes without a history of ON, suggesting that foveal measurement may also be valuable during diagnosis and follow-up.

The present study revealed an increase in the c/d horizontal and vertical ratios in patients with a history of ON compared to those without a history of ON and the control group, but it was not statistically significant. In some studies, mean c/d and vertical c/d ratios were significantly higher in MS patients than in controls. Although it was stated that this OCT parameter could be a measure for neuroprotection monitoring (18), this study results suggest that it may not be as sensitive as RNFL, GCC, macula, and fovea thickness detected in OCT.

In eyes with a history of ON, mean RNFL and mean GCC thinness were moderately correlated with low VEP amplitude. In addition, RNFL thinness was correlated with VEP p100 latency prolongation in eyes without ON. Axonal loss in MS is known to be a major factor in the development of disability, and the degree of axonal loss at disease onset may be critical in the long term in reflecting disease prognosis (24). Thus, the detection of axonal loss is very beneficial in the follow-up and management of the disease. The prolongation of VEP P100 latency is more crucial in diagnosis. Low amplitude is known to contribute to the evaluation of axonal damage. VEP also has a role in treatment monitoring. On the other hand, OCT provides the opportunity to directly visualize the axons of the central nervous system in vivo. Measurement of RNFL thickness has been correlated with the degree of permanent visual dysfunction following ON and associated with axonal loss (15). While VEP parameters are mostly used to indicate clinical and subclinical ON attacks in MS patients (25,26), OCT parameters are prominent in the diagnosis and follow-up of ON (8,17,27) It is crucial to use VEP and OCT tests separately in clinical practice.

The limitations of the present study were its cross-sectional nature and the inclusion of RRMS patients only. Performing prospectively by including all types of MS and examining the correlation with the addition of magnetic resonance imaging could also give an idea about the use of OCT in disease progression.

CONCLUSION

In conclusion, the fact that deterioration in these values was detected in eyes without ON suggests that it would be beneficial to use OCT not only in MS patients with ON but also in the diagnosis, follow-up, and treatment monitoring of all types of patients.

OCT is recommended for use as a biomarker in MS patients, but it still has some limitations. Thinning of the RNFL and GCC is not specific to MS and may demonstrate individual differences. Further studies on this subject and discovering additional findings will contribute to the literature and clinical practice. As the number of parameters evaluated in OCT is increased, its distinctive feature will increase. With the developing technology, devices that give more detailed data keep OCT studies up to date.

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Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Thesis

This study was prepared by rearrangement of the specialty thesis by Emine Cengiz with date 2014, entitled as “Optical coherence tomography (OCT) and visual evoked potentials (VEP) findings on multiple sclerosis patients”.

Ethical Declaration

Ethical permission was obtained from the Gaziantep University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date 24 February 2014 and number 79, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: EKC, AA, YEF, CÖ, GBÇ, Design: EKC, AA, YEF, CÖ, GBÇ, Supervising: EKC, AA, YEF, Financing and equipment: EKC, AA, CÖ, YEF, GBÇ, Data collection and entry: EKC, AA, YEF, CÖ, GBÇ, Analysis and interpretation: EKC, AA, YEF, CÖ, GBÇ, Literature search: EKC, AA, YEF, GBÇ

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