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ORIGINAL ARTICLE

# Correlation of corpus callosum index and optic coherence tomography findings in multiple sclerosis with or without optic nerve involvement

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## Abstract

**Purpose:** To evaluate the correlation of spectral domain optical coherence tomography (SD-OCT) parameters including peripapiller retinal nerve fiber length (RNFL) and ganglion cell layer (GCL) analysis with corpus callosum volumes, which were determined by corpus callosum index (CCI) radiologically in multiple sclerosis (MS) patients.

**Methods:** Forty MS patients, with or without optic neuritis in history, were involved in the study on which RNFL and GCL analysis by SD-OCT were performed. Anterior, middle, posterior, and overall CCI were calculated for all subjects on 1.5 T magnetic resonance imaging scans, on conventional best mid-sagittal T1W image.

**Results:** Seventeen patients had unilateral optic neuritis in history (42.5%) and had significantly lower CCIs compared to cases without optic nerve involvement ($p<0.05$ for each); lower RNFL measurements and lower GCL values in involved eyes compared to uninvolved side ($p=0.03$ and $p<0.001$, respectively). Overall CCI was lower in patients with more attacks in history and in elder MS patients ($p=0.011$ and $p=0.06$, respectively). Overall CCI was also lower in cases with lower mean RNFL and mean GCL measurements possessing a high positive correlation coefficient ($p=0.047$, $p=0.002$; $r=0.316$, $p=0.478$, respectively).

**Conclusion:** This study demonstrated that involvement of optic nerve in MS patients is with lower anterior, middle, posterior, and overall CCI values in addition to lower mean RNFL and GCL values of OCT. The positive correlation of CCIs with OCT parameters shows that the neuroaxonal degeneration in MS simultaneously affects the retina and the brain.

**Keywords:** Corpus callosum index; ganglion cell layer analysis; multiple sclerosis; optic coherence tomography; retinal nerve fiber length.

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Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system which is known to affect young population with 20–40 years of age. It's main etiopathology is based on demyelination and neuronal degeneration leading to axonal loss.[1] It has been reported that postmortem analysis of MS patients indicated 94–99% optic nerve lesions in these subjects, even though no evident optic neuritis in history.[2,3]

Unmyelinated axons of retinal ganglion cells (GC) constitute retinal nerve fiber layer (RNFL), which can be objectively measured by spectral domain optical coherence tomography (SD-OCT) – a high-resolution, non-X-ray retinal imaging technology.[4] OCT gained its popularity in neuro-ophthalmology for its effective use in neurodegenerative diseases. This non-invasive technique yields high-resolution images of retinal morphology.[5] It uses near-infrared light and can analyze the integrity of GC and their axons, which are myelinated after they leave the eye at the level of lamina cribrosa.[6]

It has been known that acute stage of optic neuritis is with a manifest increase in RNFL thickness in up to 82% of cases, measured by OCT due to the axonal stasis and secondary edema of the optic nerve head.[7,8] RNFL values are decreased at the chronic stages of optic nerve involvement, indicating atrophy of the optic nerve axons.[7,8]

RNFL is reported to be thinner in MS patients, which shows a correlation with disease activity and white matter lesion volume in magnetic resonance imaging (MRI).[4] Recent studies concluded that the decrease in RNFL thickness is regarded to be correlated to neurodegeneration, cerebral atrophy, and progressive disease in MS patients.[5,9]

Improved image resolution in SD-OCT also enables to measure the GC-inner plexiform layer (IPL) (GC layer [GCL]) in the macular area which is another recently popular OCT marker for detecting and monitoring the neuronal degeneration.[10] GCL analysis together with the IPL is called GCIPL complex and is analyzed by different segmentation algorithms in different OCT devices of variable manufacturers.[11] GCL thickness measurements are important in acute stages for the evaluation of the disease prognosis since RNFL is evidently increased by optic nerve head edema in acute phase but GCL analysis is not altered by axonal stasis and could potentially provide prognostic evaluation in neurodegeneration during the follow-up.[11]

MRI is the gold standard in MS which absolutely has the main role for the diagnosis and monitoring of treatment response. The whole brain, the white and gray matter volumes – together with the volume of brain lesions are some of the traditional quantitative MRI parameters used in MS patients.[12] However, the need of specially designed post-processing methods and dependence on three-dimensional MRI sequences for their application limits their use in common practice.[13]

Corpus callosum is the connective bundle formed by white matter fibers crossing across the cerebral hemispheres. It is the favorite topic of recent studies since it is proposed to have a role in reflecting the level of brain atrophy in demyelinating diseases – due to its sensitivity in focal loss of white matter.[14] Assessment of CC quantitatively is based on two methods; manually as two-dimensional measurements of the CCI and CC area or with the use of some software programs for volumetric analysis such as the CC volume.[9,15] Calculating the CCI is regarded by far the most practical method in current literature.[13] The corpus callosum index (CCI) regarded as a new radiological marker in neurodegenerative disorders and is thought to correlate to the level of brain atrophy in MS.[13] It even shows a high correlation with the lesion load and cognitive dysfunction in these patients.[13]

Our study was designed to evaluate the correlation of SD-OCT parameters including RNFL and GCL in MS patients with corpus callosum volumes, which were determined by CCI radiologically, and mainly aiming to investigate the effect of optic nerve involvement on this correlation.

## Materials and Methods

The study was approved by the local ethics committe at Ufuk University Faculty of Medicine on May 16, 2018 (no: 20180516/7) and was in accordance with the ethical standards stated in the 1964 Declaration of Helsinki. Informed consent was obtained from all participants.

Forty MS patients having at least 5 years of disease duration were enrolled in the study. MS diagnosis was made according to the 2010 revised McDonald criteria,[16] and all patients were recruited from the outpatient clinics of our neurology and ophthalmology departments. Patients aged between 18 and 50 years and Expanded Disability Status Scale (EDSS) score between 0 and 5.5 were included in the study. Patients who had an MS attack in the past 30 days and patients who were uncooperative to ophthalmological evaluation were excluded from the study. Data including the duration of follow-up (follow-up time since diagnosis) and number of attacks during follow-up were detected from patient records.

Ophthalmological evaluation included detection of best-corrected visual acuity, slit lamp biomicroscopy, intra-

ocular pressure measurement, fundus examination, examination of refractive errors, and visual field examination by Humphrey perimeter.

OCT scan was performed using a Cirrus HD 400 spectral OCT platform (Carl Zeiss Meditec, Model 400, Dublin, USA, Version 8.1.0.117). Only high-quality images (signal strength ≥7) were selected for the study. The peripapillary retinal nerve fiber length (RNFL) thickness was measured by an optic disc cube scan protocol (200 × 200 pixels) in a 6×6 $mm^2$ area centered on the optic disc. The macular cube scan 512 × 128 protocol was used to evaluate 6×6 $mm^2$ area centered on the fovea in terms of GC complex layer (GCL) analysis. The algorithm of the GCL analysis protocol is based on the identification of the macular GC-IPL, from the outer boundary of the RNFL to the outer limit of the IPL.

The average RNFL thickness (and those of the four quadrants; superior, nasal, inferior, and temporal), the thicknesses of the six wedge-shaped sectors of the GCL were automatically calculated and reported. Scans with misalignment, segmentation failure or decentration of the measurement circle, artifacts induced by eye movement during scan, and dropout or missing parts on deviation maps were excluded from the analysis. OCT scans with signal strength equal to or more than 7 (out of 10) were included in the study.

The brain MRI studies were performed on the same week with clinical examinations and OCT scans, using a 1.5 Tesla GE Signa HD×T scanner with a 16-channel head coil. Anatomical images were acquired with the following parameters: T1-weighted sagittal sequence; TE/TR = 23.74/2889.4 ms; flip angle = 90; matrix size = 288×192; FOV = 256 mm; slice thickness = 5 mm; slice gap = 0 mm; and 46 slices. For lesion assessment, T2-weighted images were acquired with the following parameters: FLAIR sequence; TE/TR = 144.3/8800 ms; flip angle = 90; matrix size = 320×224; FOV = 240 mm; slice thickness = 5 mm; slice gap = 0 mm; and 30 slices. Other T1- and T2-weighted images also obtained in axial and coronal planes. Intravenous gadolinium was used when it was necessary. When contrast media were injected, three-dimensional BRAVO sequences with TE/TR = 450/8.95 ms; flip angle = 12; matrix size = 256×256; FOV = 240 mm; slice thickness = 1 mm; slice gap = 0 mm; and 320 slices were created.

The CCIs for all patients were calculated independently by two radiologists (GKA and BS). Mid-sagittal T1-weighted magnetic resonance images were used for the method. The greatest anteroposterior axis of the CC was marked with a straight line and its craniocaudal axis at its midpoint was also marked with another straight line perpendicular to the first. Points named as a, a', b, b', and c, c' were noted. The anterior (aa'), medium (cc'), and posterior (bb') segments of the CC were measured and their proportion to the greatest anteroposterior diameter of the CC (ab) was calculated according to the pre-described formula by Figueira et al., determining the overall CCI in our study. [13] We also calculated three additional CCI types (anterior CCI, middle CCI, and posterior CCI) in addition to the pre-described CCI to check out which segment of CCI is effected more in neurodegenerative process of MS. Figure 1 describes calculation of CCI types calculated in our study. Correlation analysis was performed between OCT and CCI values.

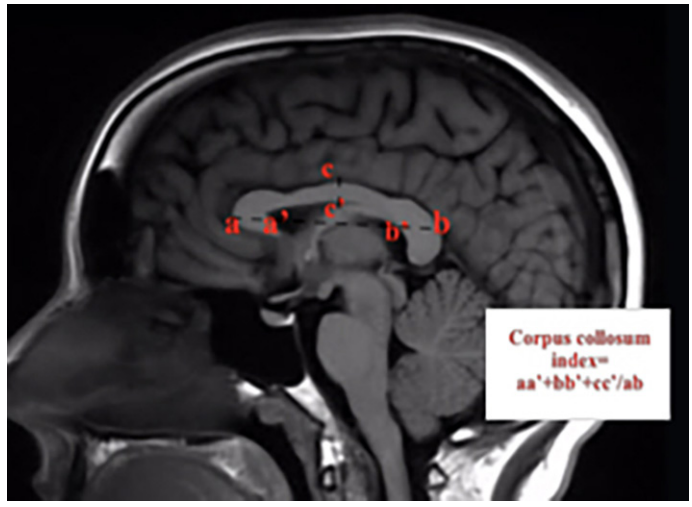


**Fig. 1.** Calculation of corpus callosum index types used in our study.
aa': Anterior CC, bb': Posterior CC, cc': Middle CC, ab: Total CC
aa'+bb'+cc'/ ab =Corpus callosum index (Overall)
aa'/ab= Anterior corpus callosum index
bb'/ab= Posterior corpus callosum index
cc'/ab= Middle corpus callosum index.

## Statistical Analysis

Data analyses were performed using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). The normality of distribution of continuous variables was determined by Kolmogorov–Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean±SD for normal distributions and median (minimum-maximum value) for skewed distributions.

Differences of statistical analysis among normally distributed variables between two independent groups were compared by Student's t-test. Mann–Whitney U-test was applied for comparisons of the not normally distributed data.

Univariate linear regression, univariate logistic regression, and multivariate linear regression were performed to analyze the association of risk factors thought to be related with disease groups. The degrees of relation between variables were analyzed with Pearson correlation or Spearman correlation analysis. P<0.05 was accepted as level of significance in all statistical analysis tests.

## Results

Forty MS patients (28 females-12 males) were included in the study. Mean age of the patients was 39±10.81 (22–67) years. Mean follow-up time was 5.05±2.93 (2–14) years and mean number of attacks was 3 (minimum 1-maximum 6).

Overall CCI was lower in patients with more attacks in history and in elder MS patients (p=0.011 and p=0.06, respectively). Duration of the disease was not found to have a significant correlation with CCIs in MS patients (p>0.01) (Table 1 and Fig. 2).

Increase in age and number of attacks were significantly correlated to lower average RNLF in OCT of all MS patients (p=0.002 and p=0.034, respectively), and elder age of the patients was significantly associated with lower average GCL values (p<0.001) (Table 2). Female or male gender did not have any significant difference on OCT measures or CCIs of MS patients (p>0.05).

Overall CCI was lower in cases with lower average RNFL and average GCL measurements among all eyes of MS patients with high correlation coefficients (p=0.047, p=0.002; r=0.316, p=0.478, respectively) (Table 3, Figs. 3 and 4).

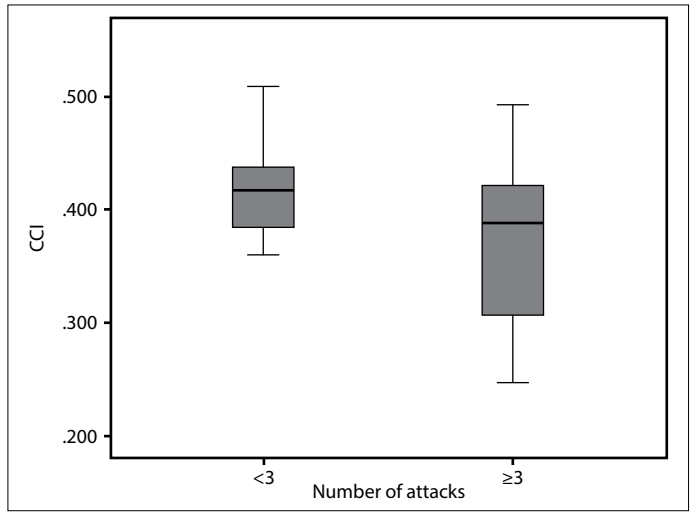


**Fig. 2.** Effect of number of attacks on overall CCI measures (p=0.011). CCI: Corpus callosum index.

Seventeen patients had optic neuritis in history (42.5%), and all were unilaterally affected. They had significantly lower overall CCI than MS patients without optic neuritis in history (p=0.004). Anterior, middle, and posterior CCI values are also found to be significantly lower in MS cases with optic nerve involvement compared to cases without optic nerve involvement (p<0.05 for each) (Table 4).

Cases with optic neuritis in history had lower RNFL measurements and lower GCL values in involved eyes compared to uninvolved side (p=0.03 and p<0.001, respectively) (Table 5).

The interobserver reliability of this method is found to be high since no significant variations were found between

**Table 1.** Effects of clinical and demographical properties of MS patients on measures of CC

| Measures of corpus callosum | | Age of patient (years) | Number of attacks | Duration of disease (years) |
|---|---|---|---|---|
| Anterior CC | r | –0.457 | –0.350 | –0.159 |
| | p | 0.003 | 0.027 | 0.326 |
| Middle CC | r | –0.467 | –0.283 | –0.224 |
| | p | 0.002 | 0.077 | 0.164 |
| Posterior CC | r | –0.259 | –0.189 | –0.260 |
| | p | 0.107 | 0.243 | 0.106 |
| Total CC | r | –0.045 | 0.187 | –0.122 |
| | p | 0.784 | 0.249 | 0.454 |
| CCI | r | –0.424 | –0.400 | –0.208 |
| | p | 0.006 | 0.011 | 0.198 |
| Anterior CCI | r | –0.407 | –0.424 | –0.113 |
| | p | 0.009 | 0.006 | 0.489 |
| Middle CCI | r | –0.455 | –0.295 | –0.195 |
| | p | 0.003 | 0.064 | 0.227 |
| Posterior CCI | r | –0.254 | –0.332 | –0.225 |
| | p | 0.113 | 0.037 | 0.162 |

r: Pearson's correlation coefficient. Statistically significant p and r values are in bold. CC: Corpus callosum; CCI: Corpus callosum index.

**Table 2.** Effects of demographical and clinical properties of multiple sclerosis patients on measures of OCT

| Measures of OCT* | | Age | Number of attacks | Duration of disease |
|---|---|---|---|---|
| A-RNFL | r | –0.481 | –0.336 | –0.101 |
| | p | 0.002 | 0.034 | 0.534 |
| T-RNFL | r | –0.270 | –0.050 | 0.162 |
| | p | 0.092 | 0.762 | 0.319 |
| N-RNFL | r | –0.382 | –0.169 | –0.017 |
| | p | 0.015 | 0.296 | 0.915 |
| S-RNFL | r | –0.471 | –0.402 | –0.359 |
| | p | 0.002 | 0.010 | 0.023 |
| I-RNFL | r | –0.375 | –0.249 | –0.098 |
| | p | 0.017 | 0.121 | 0.547 |
| A-GCL | r | –0.880 | –0.285 | –0.069 |
| | p | <0.001 | 0.074 | 0.674 |

*OCT values for each patient are detected by the mean of OCT measures from both eyes. r: Pearson's correlation coefficient, statistically significant p and r values are in bold. OCT: Optic coherence tomography; RNFL: Retinal nerve fiber length; GCL: Ganglion cell layer. A: Average; T: Temporal; N: Nasal; I: Inferior; S: Superior.

**Table 3.** Correlation of OCT measures with CCI values in multiple sclerosis patients

| Measures of CC (mm) | | Average RNFL* | Average GCL* |
|---|---|---|---|
| Anterior CC | r | 0.235 | 0.390 |
| | p | 0.145 | 0.013 |
| Middle CC | r | 0.273 | 0.529 |
| | p | 0.088 | <0.001 |
| Posterior CC | r | 0.332 | 0.309 |
| | p | 0.036 | 0.052 |
| Total | r | 0.042 | -0.022 |
| | p | 0.796 | 0.893 |
| CCI | r | 0.316 | 0.478 |
| | p | 0.047 | 0.002 |
| Anterior CCI | r | 0.206 | 0.372 |
| | p | 0.202 | 0.018 |
| Middle CCI | r | 0.261 | 0.515 |
| | p | 0.103 | 0.001 |
| Posterior CCI | r | 0.333 | 0.324 |
| | p | 0.036 | 0.041 |

*OCT values for each patient are detected by the mean of OCT measures from both eyes. r: Pearson's correlation coefficient. Statistically significant p and r values are in bold. OCT: Optic coherence tomography; RNFL: Retinal nerve fiber length; GCL: Ganglion cell layer; CC: Corpus callosum; CCI: Corpus callosum index.

the CCI calculations of the two radiologists involved in our study ($p<0.05$).

## Discussion

GCL and retinal nerve fiber analysis by OCT are recently used parameters to detect the level of neurodegeneration in many neurological disorders such as MS, Alzheimer's disease, or Parkinson's disease based on degenerative background.[17]

In our study, increase in age and number of attacks were found to be significantly correlated to lower average RNLF in OCT of all MS patients. In addition, elder age of the patients was significantly found to be associated with lower average GCL values. MS cases with optic neuritis in history revealed lower RNFL measurements and lower GCL values in involved eyes compared to uninvolved side. Decrease in RNFL and GC complex analysis values in MS patients even without any optic nerve involvement during the disease was subject of many previous studies and was thought to

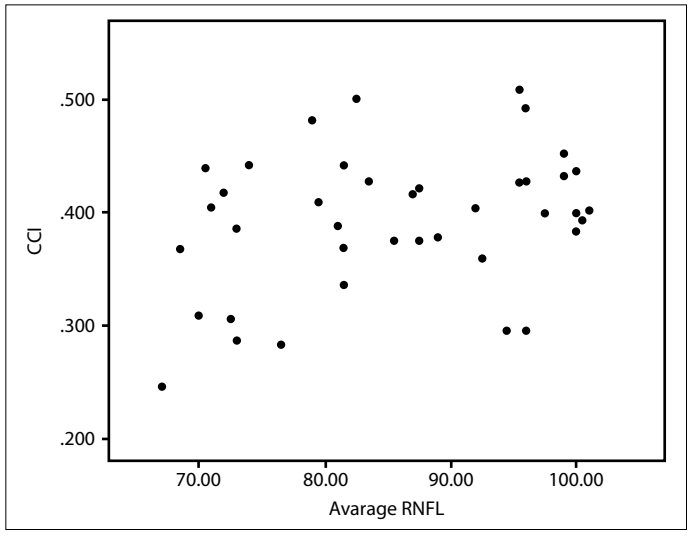


**Fig. 3.** Correlation analysis of overall CCI and average RNFL values in all MS cases (Scatter plot analysis) (r=0.316, p=0.047). CCI: Corpus callosum ındex; RNFL: Retinal nerve fiber length; MS: Multiple sclerosis.

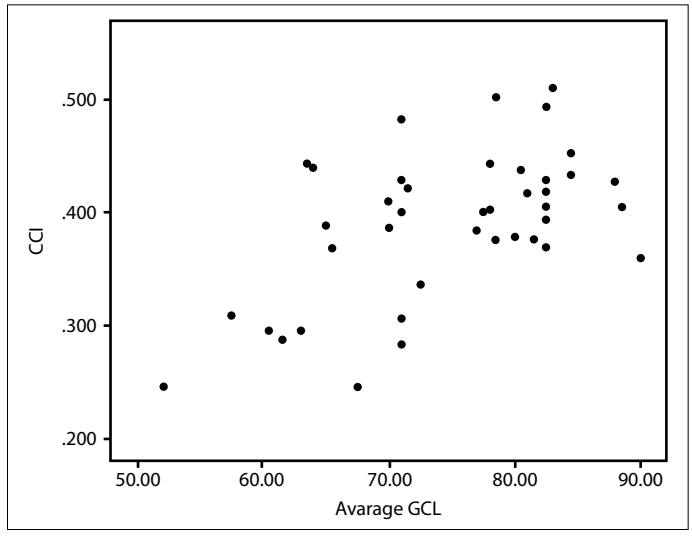


**Fig. 4.** Correlation analysis of overall CCI and average GCL values in all MS cases (Scatter plot analysis) (r=0.478, p=0.002). CCI: Corpus callosum index; GCL: Ganglion cell layer; MS: Multiple sclerosis.

**Table 4.** Corpus callosum measures in study groups

| Corpus callosum measures | Optic neuritis (+) MS patients (n=17) | Optic neuritis (–) MS patients (n=23) | p-value |
|---|---|---|---|
| Anterior CC (mm) | 0.98±0.18 | 1.14±0.16 | 0.005 |
| Middle CC (mm) | 0.48 (0.46) | 0.65 (0.46) | 0.154 |
| Posterior CC (mm) | 1.01±0.20 | 1.14±0.13 | 0.034 |
| Total CC (mm) | 6.89±0.41 | 6.93±0.43 | 0.779 |
| CCI | 0.36±0.07 | 0.42±0.04 | 0.004 |
| Anterior CCI | 0.14±0.03 | 0.17±0.03 | 0.013 |
| Middle CCI | 0.07±0.02 | 0.09±0.02 | 0.003 |
| Posterior CCI | 0.15±0.03 | 0.16±0.02 | 0.035 |

Continuous variables are expressed as either * the mean±standard deviation or βthe median (range). Continuous variables were compared with a Student's t-test or the Mann–Whitney U-test. Statistically significant P-values are in bold. CC: Corpus callosum; CCI: Corpus callosum index; MS: Multiple sclerosis.

**Table 5.** OCT measures in multiple sclerosis cases with optic neuritis in history

| OCT measures | Group 1 Optic neuritis + | | p-value |
|---|---|---|---|
| | Involved eyes (n=17) | Uninvolved eyes (n=17) | |
| Mean RNFL | 75.88±12.54 | 81.76±9.40 | 0.030 |
| T-RNFL | 51.88±11.13 | 52.65±13.80 | 0.770 |
| N-RNFL | 62.53±6.62 | 63.41±9.19 | 0.751 |
| S-RNFL | 101.59±21.53 | 105.00 (50) | 0.134 |
| I-RNFL | 98.00 (60) | 97.00 (49) | 0.753 |
| Mean GCL | 63.00±6.51 | 70.59±4.64 | <0.001 |

Continuous variables are expressed as either *the mean±standard deviation or βthe median (range). Continuous variables were compared with a Student's t-test or the Mann–Whitney U-test. Statistically significant P-values are in bold. OCT: Optic coherence tomography; RNFL: Retinal nerve fiber length; GCL: Ganglion cell layer; T: Temporal; N: Nasal; I: Inferior; S: Superior.

reflect the subclinical disease activity, concurrent demyelination of optic nerve axons, and/or retrograde degeneration of the optic nerve in MS patients.[18] In the meta-analysis by Britze et al., the thickness of GCL was found to be significantly reduced in MS subjects both with and without previous ON compared to healthy controls.[19] This thinning was reported to be associated with visual function and EDSS score of the patients. Reductions in GCL measurements appear before RNFL thinning and are a strong predictor of visual dysfunction over 6 months.[9,19] Since GCL and RNFL analyses were reported in many studies to highly correlate with visual functions and disability in MS, the importance of diagnostic use of OCT is better understood.[19]

Measurement of CCI is a two-dimensional calculation method for brain atrophy and does not require a special computer program – easily applied in a few seconds on the scans.[15] Recent studies are focused on its clinical effectivity and its correlation with brain volumetric measurements. It is highly used nowadays as a clinical marker of atrophy and lesion load in MS.[13,15]

Overall CCI was found to be lower in patients with more attacks in history and in elder MS patients. Duration of the disease was not found to have a significant correlation with CCIs in MS patients. Among our study subjects, 42.5% had optic neuritis in history and all were unilaterally affected. They had significantly lower overall CCI than MS patients without optic neuritis in history. Anterior, middle, and posterior CCI values are also found to be significantly lower in MS cases with optic nerve involvement compared to cases without optic nerve involvement. The literature contains limited data about the effect of age, duration of the disease, number of attacks, and involvement of optic nerve on CC volumes and CCI values. CC is normally resistant to age-related changes in healthy individuals, but it has been shown that CC atrophy emerges in MS patients overtime.[20] CC volume, CCI values, and regional changes correlate well with disability in MS patients.[21,22] Simon et al. reported that patients with relapsing remitting MS and moderate disability have measurable amounts of cerebral atrophy that progresses yearly and that the course of cerebral atrophy was influenced by prior inflammatory activity of MS evaluated by the presence of gadolinium-enhancing brain lesions as seen on MRI, but the study does not yield exact correlations of disease duration and CC volumes.[23] In a recent study by Cilingir et al., lower CCI values were found in MS cases with longer disease duration.[4]

Overall CCI was calculated to be lower in our study, in cases with lower average RNFL and average GCL measurements among all eyes of MS patients with high correlation coefficients. In fact, there are limited studies in the literature about the association between RNFL and CC measures. The thinning of RNFL in MS is shown to be associated with the atrophy of whole-brain white matter and total deep gray

matter.[24,25] According to a study by Scheel et al., a positive correlation between the volume of the central part of the CC and RNFL thickness was found and reported.[26] Cilingir et al. reported that lower RNFL values in MS patients were associated with lower CCI values. They reported no association between CCI and RNFL measurements in the control group. They also noted that they found this correlation in patients with no history of ON.[4] However, the association between CCI and GCL analysis measurements during the follow-up of MS cases is still a mystery and has no reported data in former studies.

The calculations of CCI measurements in our study were performed by two radiologists, which were detected to have statistically insignificant variations among their measurements. Hence, the described method used to analyze CCIs on MR scans is thought to be reliable. The interobserver and intraobserver reliability of this method is reported to be high in previous studies, too.[4,27]

Our study additionally calculated and used new measures of CCI (anterior, middle, and posterior) which have not been used previously in any other study. Our aim was to investigate if there was a predilection for atrophy in any part of CC during the process of neurodegeneration. No specific type of CCI was found to be selectively effected, pointing out homogeneous degeneration of the area.

Main limitations of our study are the small sample size, it's cross-sectional design, and lack of the long-term follow-up results. The main strength of our study is its novel research of the correlation between already known OCT measures of neurodegeneration and different types of CCIs which have not been used previously in the literature for MS cases.

In the light of our study, we report that involvement of optic nerve in MS patients is with lower anterior, middle, posterior, and overall CCI values. It's high correlation with RNFL and GCL measures of OCT supports its parallel effectivity in the use of monitoring neuroaxonal degeneration in MS. New randomized and larger sized controlled trials on the topic should be carried on in the future.

**Ethics Committee Approval:** The study was approved by the local ethics committe at Ufuk University Faculty of Medicine on May 16, 2018 (no: 20180516/7).

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions:** Concept: P.A.O.; Design: P.A.O., R.S.; Supervision: A.S.; Resource: M.F.K.; Materials: G.K.A., R.S.; Data Collection and/or Processing: P.A.O., M.F.K.; Analysis and/or Interpretation: P.A.O.; Literature Search: P.A.O., M.F.K.; Writing: P.A.O.; Critical Reviews: A.S., R.S.

**Conflict of Interest:** None declared.

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