RESEARCH PAPER

Optic nerve changes in multiple sclerosis patients attending outpatient clinic of October 6 University

Ahmed Hesham Moneer [1], Rabie Mohamed Hassanien [2], Mohammed El-Mahdy Badra[3]

[1] Lecturer of Ophthalmology- Faculty of Medicine – October 6 University, Egypt

[2] Professor of Ophthalmology- Faculty of Medicine - Minia University, Minia, Egypt

[3] M.B. B.CH, Ophthalmology-Faculty of Medicine – 6 October University, Egypt

[*]**Corresponding author:** Mohammed El-Mahdy badra

E-mail: mohamedmahdi050@gmail.com

Abstract

Background: Multiple sclerosis (MS) is a chronic inflammatory autoimmune disorder characterized by demyelination and axonal degeneration within the central nervous system. OCT and OCTA provide noninvasive methods for evaluating structural and vascular alterations in the optic nerve and retina, and they are increasingly utilized as biomarkers for monitoring disease progression in MS.

Aim: To evaluate optic nerve changes in MS individuals via OCT and OCTA.

Patients and methods: This is a cross – sectional study on MS individuals to evaluate optic nerve changes via OCT and OCT angiography. The study was executed at October 6 university hospitals (Ophthalmology Department) over 6 months.

Results: Mean age was 31.9 ± 7.0 years; MS duration 3.38 ± 2.0 years. RNFL thickness averaged 98.5 ± 14.9 µm, with significant thinning in superior/inferior quadrants. GCC showed stronger positive correlations with EDSS scores (r=0.421, p=0.002) than RNFL. Angio disc density averaged 48.0 ± 4.6%, with no significant EDSS correlations. Reduced vessel density indicated early hypoperfusion.

Conclusion: OCT and OCTA reveal RNFL/GCC thinning and microvascular changes in MS, with GCC as a sensitive neurodegeneration biomarker. These metrics aid early detection and monitoring.

Key words: Multiple Sclerosis, OCT Angiography, Optic nerve, EDSS.

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disorder characterized by demyelination and axonal degeneration within the central nervous system (CNS), with considerable variation in prevalence and incidence across different geographic regions (1).

Various diagnostic tools and imaging modalities have been developed to evaluate the structural and functional integrity of the optic nerve, providing clinically relevant information in patients with MS (2). Retinal optical coherence tomography (OCT) is a noninvasive and well-tolerated imaging technique that enables reproducible, high-resolution visualization and quantitative assessment of retinal structures (3). Because the retina represents an extension of CNS tissue that is directly accessible to optical imaging, OCT was introduced into clinical neuroimmunology approximately two decades ago and has since become a sensitive tool for assessing optic nerve and retinal pathology in MS (4).

Advancements in high-resolution spectral-domain OCT have enabled the detection and longitudinal monitoring of subtle retinal and optic nerve alterations in vivo. Evidence indicates that significant loss of retinal ganglion cells (RGCs) and thinning of the retinal nerve fiber layer (RNFL) occur in patients with MS following episodes of optic neuritis (ON) (5). MS-associated ON leads to axonal damage within the optic nerve, resulting in thinning of both the RNFL and the combined ganglion cell–inner plexiform layer (GCIPL) (6). In addition, cross-sectional studies have demonstrated significant thinning of neuronal and axonal retinal layers even in eyes without a history of ON among patients with MS (7).

OCT angiography (OCTA) is a relatively recent, noninvasive imaging modality that provides high-resolution visualization of retinal microvasculature. This technique acquires sequential scans at the same retinal location to detect blood flow dynamics (8). By

eliminating signals from stationary tissues, the remaining signal reflects the intrinsic movement of blood cells within retinal vessels, enabling visualization of both arterial and venous circulation across the scanned area (9).

An optic nerve head flow index (ONH-FI), derived from OCTA, is used to quantify vascular density and blood flow velocity within the capillary network, as well as the caliber of larger retinal vessels (10). Compared with conventional fluorescein angiography, this parameter offers the advantage of assessing deeper perfusion of the optic nerve head, while also providing broader coverage than laser Doppler techniques (11).

Accordingly, our designed to determine optic nerve changes in patients with MS via OCT and OCTA.

Patients and methods

This is a cross – sectional study on MS patients to evaluate optic nerve changes via OCT and OCT angiography. The study was executed at October 6 university hospitals (Ophthalmology Department) over 6 months.

Inclusion criteria: Age (18 to 45 years), corrected visual acuity 20/200 in at least one eye and diagnosis of MS confirmed within 5 years.

Exclusion criteria: Participants were excluded if they had had intravenous or oral corticosteroids within the preceding 30 days, experienced an MS relapse within the previous 60 days, or had an intraocular pressure exceeding 21 mmHg. Additional exclusion criteria included inability to maintain visual fixation, refractive errors greater than +3 or −4 diopters documented during an ophthalmologic examination within the past year, the presence of any condition affecting the optic nerve, or the use of medications known to influence optic nerve function

Sample Size:

Prior data indicate that Structural and vessel density significantly correlated with each other in the HC cohort (Spearman's rho =0.477, $p<0.001$), and more so in the MS+ON (rho =0.788, $p<0.001$), and MS−ON cohorts (rho =0.719, $p<0.001$) **(11).**

Then, we needed to study 28 MS eyes (10 ON positive and 18 negative ON), along with 32 control eyes, to allow rejection of the null hypothesis that the diagnostic accuracy "area under ROC" (AROC), for MS and control eyes are equal with probability (power) 80%. The probability of committing a Type I error for this test of the null hypothesis was set at 0.05.

Methods

All participants were subjected to the following:

Complete history taking: Age, sex, comorbidities (hypertension, hyperlipidemia, diabetes, coronary artery disease, peripheral vascular disease, obesity and smoking history), and MS disease type and duration, and **ophthalmology examinations:** We used the RTVue XR Avanti device (ReVue software, Optovue Inc, Fremont, California, USA). Participants were dilated eye pupil using cyclophrine eye drops. Imagine was done from 9am – 1am. Slit lamp examination, fundus examination, best corrected visual acuity and IOP (intra-ocular pressure) were done.

OCT "Structural Index" tests: OCT set for average RNFL thickness measurement, OCT set for average ganglion cell complex (GCC) thickness measurement, OCT set for average peri-papillary nerve fiber layer thickness, OCT set for average macular GCC thickness and OCT sub foveal choridal thickness.

OCTA of macula and peri-papillary region with documentation of: Vessel density, an OCTA- measured parameter, was known as the ratio of the vascular area to the total measured area.

Studied outcomes: The diagnostic accuracy of OCT Structural Indices (nerve fiber layer, GCC, macular GCC) regarding diagnosis and prediction of ON in MS cases. The diagnostic accuracy of OCTA of Vessel Density, regarding diagnosis and prediction of ON in MS.

Ethical Considerations

A documented consent was gathered from each participant prior to enrollment in the study, and the clinical examinations monitored principles of Declaration of Helsinki.

Statistical Analysis

Data were gathered, coded, and subsequently entered into a spreadsheet using Microsoft Excel 2016 for Windows (Microsoft Office 2016, Microsoft Corporation, USA). Statistical analysis was performed using the IBM Statistical Package for the Social Sciences (SPSS), version 21 (IBM Corp., USA).

Continuous data was shown as mean ± standard deviation and categorical data as numbers and percentage. Data was presented as tables and graphs, t-test was used to compare between two groups' quantitative data shown as mean and standard deviation. For comparisons in between more than 2 groups, analysis of variance (ANOVA) was applied. Chi-squared or Fisher's Exact tests was applied to compare between the qualitative data shown as number and percentage. Correlation (Spearman

and/or Pearson) was applied to identify relations between data. Results was considered statistically significant at a p-value of less than or equal 0.05.

Results

Table (1) Demographic characteristics of investigated cases

	N	%
Age (years) Median (min-max)	31.921±7.0 (19-49)	
Marital status		
Single	14	28.0
Married	34	68.0
Divorced	2	4.0

Table 1 shows the clinic-demographic characteristics of the investigated cases. The mean age was 31.9 ± 7.0 years (range: 19–49). Regarding marital status, 68% were married, 28% were single, and 4% were divorced.

Table (2): MS duration and treatment among investigated cases

	N	%
MS duration (years) Median (min-max)	3.38(0.25-14.0)	
MS treatment		
No	4	8.0
Rebif	12	24.0
Marovarex	2	4.0
Mabthera	4	8.0
Interferon	6	12.0
Gilenyia	22	44.0

Table 2 shows that the mean duration of MS was 3.38 ± 2.0 years (range: 1.5–14 years). Regarding treatment, the most frequently used drug was Gilenya (44%), followed by Rebif (24%), Interferon (12%), Marovarex and Mabthera (8% each), while 8% of patients were not on treatment.

Table (3): EDSS characters among investigated cases

	N=50	%
EDSS Mean ±SD (Min-Max)	5.0±0.89 (4-7)	
Visual		
0	38	76.0
1	2	4.0
2	10	20.0
Cerebral		
0	24	48.0
1	24	48.0
2	2	4.0
Cerebellar		
0	14	28.0
1	14	28.0
2	22	44.0
Pyramidal		
0	10	20.0
1	10	20.0
2	30	60.0
Brain stem		
0	46	92.0
1	4	8.0
Sensory		
2	48	96.0
3	2	4.0
Bowel and bladder	50	100.0
0		

Table (3) shows that the mean EDSS score was 5.0 ± 0.89 (range: 4–7). Visual involvement was the most frequent (76%), followed by cerebral (48%), cerebellar (28%), and pyramidal (20%) manifestations. Brain stem involvement was present in 8%, while bowel and bladder dysfunction were observed in all cases (100%).

Table (4): RNFL mean values among investigated cases

RNFL	N=50	%
Average	98.54±14.97	60-126
Superior	121.66±21.22	72-164
Inferior	126.60±25.19	72-188
Nasal	78.86±14.94	45-122
Temporal	71.02±14.62	41-106
rim area	1.55±0.46	0.68-2.29

Table 4 shows that the mean average RNFL thickness was 98.5 ± 14.9 µm (range: 60–126). The superior quadrant showed the highest mean thickness (121.6 ± 21.2 µm), followed by the inferior (126.6 ± 25.2 µm), nasal (78.9 ± 14.9 µm), and temporal (71.0 ± 14.6 µm) quadrants. The mean rim area was 1.55 ± 0.46 mm² (range: 0.68–2.29).

Table (5): Angio disc among investigated cases

Angio disc	N=50	
	Mean±SD	Min-Max
Average	48.07±4.55	32.3-54.5
Superior	49.96±6.75	31-62
Inferior	51.22±6.09	30-61
Nasal	46.38±6.01	26-55
Temporal	52.3±6.76	33-62

Table 5 shows that the mean average angio disc density was 48.0 ± 4.6% (range: 32.3–54.5). The highest values were recorded temporally (52.3 ± 6.7%) and inferiorly (51.2 ± 6.1%), while the lowest were nasally (46.4 ± 6.0%).

Table (6): correlation between RNFL and MS duration, neurological EDSS score among investigated cases

		MS duration
RNFL (average)	r	-.193
	p value	.180
RNFL(SUPRIOR)	r	.079
	p value	.585
RNFL(INFERIOR)	r	-.195
	p value	.174
RNFL(NASAL)	r	-.187
	p value	.192
RNFL(TEMPORAL)	r	-.061
	p value	.673
RNFL(Rim area)	r	.135
	p value	.351
		Neurological (EDSS)
RNFL (average)	r	**.300**
	p value	**.034***
RNFL(SUPRIOR)	r	.174
	p value	.227
RNFL(INFERIOR)	r	.240
	p value	.094
RNFL(NASAL)	r	**.449**
	p value	**.001***
RNFL(TEMPORAL)	r	.189
	p value	.189
RNFL (Rim area)	r	.049
	p value	.734

r: Spearman correlation coefficient *statistically significant

Table (6) shows that there was no statistically significant correlation between MS duration and RNFL parameters including average, superior, inferior, nasal, temporal quadrants, and rim area (all $p > 0.05$). Correlation between RNFL and neurological EDSS score among investigated cases. There was a significant positive correlation among EDSS score and both average RNFL thickness ($r = 0.300$, $p = 0.034$) and nasal RNFL thickness ($r = 0.449$, $p = 0.001$). No significant correlations were documented among EDSS score and superior, inferior, temporal RNFL quadrants, or rim area (all $p > 0.05$).

Table (7): relation between GCC and MS duration, Neurological (EDSS)

		MS duration
GCC (AVERAGE)	r	-.140
	p value	.333
GCC (Superior hemi)	r	-.162
	p value	.261
GCC (Inferior hemi)	r	-.154
	p value	.287
GCC (FLV%)	r	.143
	p value	.322
GCC (GLV%)	r	.197
	p value	.170
		Neurological (EDSS)
GCC (AVERAGE)	r	**.421**
	p value	**.002***
GCC (Superior hemi)	r	.256
	p value	.073
GCC (Inferior hemi)	r	**.445**
	p value	**.001***
GCC (FLV%)	r	-.115
	p value	.427
GCC (GLV%)	r	-.092
	p value	.526

r: Spearman correlation coefficient *statistically significant

Table 7 shows that no significant correlation was documented among MS duration and GCC parameters, including average thickness, superior hemi, inferior hemi, FLV%, and GLV% (all p > 0.05). There was a significant positive correlation among EDSS score and both average GCC thickness (r = 0.421, p = 0.002) and inferior hemi GCC thickness (r = 0.445, p = 0.001). No significant correlations were found with superior hemi, FLV%, or GLV% (all p > 0.05).

Table (8): relation between Angio disc findings and MS duration, Neurological (EDSS).

		MS duration
Angio. Disc (Average)	r	.089
	p value	.539
Angio. Disc (Superior)	r	.275
	p value	.053
Angio. Disc (inferior)	r	-.100
	p value	.489
Angio. Disc (nasal)	r	.062
	p value	.669
Angio. Disc (temporal)	r	.083
	p value	.566
		Neurological (EDSS)
Angio. Disc (Average)	r	.149
	p value	.302
Angio. Disc (Superior)	r	.060
	p value	.680
Angio. Disc (inferior)	r	.162
	p value	.262
Angio. Disc (nasal)	r	.040
	p value	.780
Angio. Disc (temporal)	r	.125
	p value	.389

r: Spearman correlation coefficient *statistically significant

Table 8 shows that no significant correlations were observed between MS duration and angio disc parameters as average, superior, inferior, nasal, and temporal sectors (all p > 0.05). No significant correlation was documented among EDSS score and angio disc parameters (average, superior, inferior, nasal, temporal) (all p > 0.05).

Case presentation

Case 1:

Female patient,25 years old, single, was diagnosed MS from 8 years ago, on GILENYIA treatment, Previous attack of ON from 6 months, BCVA 6/18,Fundus ex was normal, Neurological (EDSS) Total 4.5,

OCT-Angio was done.

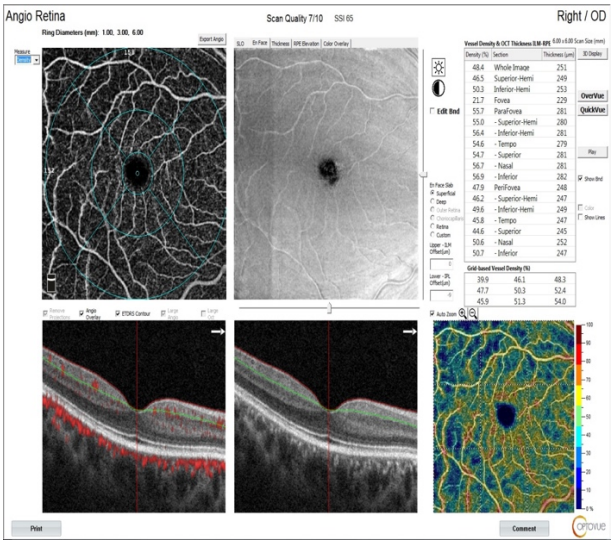

Figure (1): showing macular density, Whole density: 48.4, Superior-hemi: 46.5, Inferior-hemi: 50.3

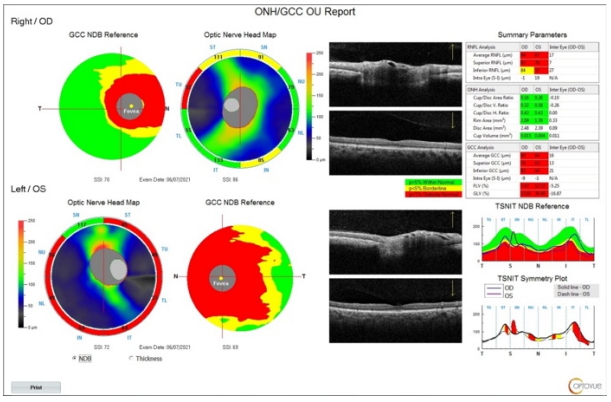

Figure (2): showing GCC, Average: 80, Superior hemi: 76, Inferior hemi: 85, Focal loss volume: 7.47, Global loss volume: 13.61

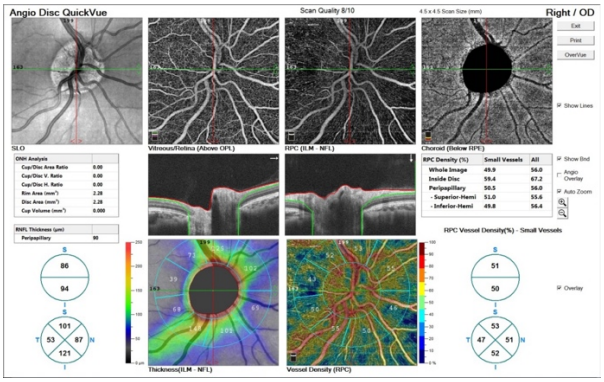

Figure (3): angio disc showing RPC Density averge: 49.9%, superior: 53% inferior: 52%, nasal: 51%, temporal: 47%. RNFL Thickness average: 90, superior: 101, inferior: 121, nasal: 87, temporal: 53, Rim area: 2.28

Discussion

Our study demonstrated that the mean age was 31.9 ± 7.0 years (range: 19–49). Regarding marital status, 68% were married, 28% were single, and 4% were divorced.

Our study demonstrated that the mean duration of MS was 3.38 ± 2.0 years (range: 1.5–14 years). Regarding treatment, the most frequently used drug was Gilenya (44%), followed by Rebif (24%), Interferon (12%), Marovarex and Mabthera (8% each), while 8% of patients were not on treatment.

Our findings showed that that the mean EDSS score was 5.0 ± 0.89 (range: 4–7). Visual involvement was the most frequent (76%), followed by cerebral (48%), cerebellar (28%), and pyramidal (20%) manifestations. Brain stem involvement was present in 8%, while bowel and bladder dysfunction were observed in all cases (100%).

We found that the mean average RNFL thickness was 98.5 ± 14.9 µm (range: 60–126). The superior quadrant showed the highest mean thickness (121.6 ± 21.2 µm), followed by the inferior (126.6 ± 25.2 µm), nasal (78.9 ± 14.9 µm), and temporal (71.0 ± 14.6 µm) quadrants. The mean rim area was 1.55 ± 0.46 mm² (range: 0.68–2.29).

Our study demonstrated that the mean average angio disc density was 48.0 ± 4.6% (range: 32.3–54.5). The highest values were recorded temporally (52.3 ± 6.7%) and inferiorly (51.2 ± 6.1%), while the lowest were nasally (46.4 ± 6.0%).

Our findings showed that both RNFL and GCC thicknesses were reduced in MS patients, with GCC thinning demonstrating a stronger correlation with EDSS and disease duration than RNFL thinning. This indicates that GCC thickness may be a more sensitive biomarker for neuroaxonal loss in MS.

These findings are in line with **Spain et al. (11)**, who reported significant reductions in GCC and RNFL in MS patients, especially in those with extended duration of the disease. Similarly, **García-Martín et al. (12)** documented that GCC thinning occurs earlier and more prominently than RNFL thinning, suggesting that damage to RGCs may precede axonal loss.

Interestingly, in our study, temporal RNFL values were relatively preserved, whereas superior and inferior sectors showed the most significant thinning. This sectoral vulnerability has also been described by **Gabilondo et al. (13)**, who suggested that variations in axonal density and vascular supply across RNFL sectors may explain this pattern.

We recorded a strong negative correlation among GCC thickness and both MS duration and EDSS score, whereas RNFL thinning showed a weaker relationship with clinical disability.

This aligns with data of **Ratchford et al. (14)** and **Saidha et al. (15)**, who documented that GCC thickness is a stronger predictor of neurological disability than RNFL thickness. This could be explained by the fact that GCC primarily reflects neuronal cell body loss, which may better mirror neurodegenerative processes than RNFL, which represents downstream axons that may degenerate later.

Our study demonstrated a significant decrease in radial peripapillary capillary vessel density (RPC VD%) in the superior quadrant, while other regions showed minimal changes. Furthermore, macular superficial capillary plexus vessel density (SCP VD%) was significantly reduced, particularly in the superior and inferior sectors.

These findings suggest that retinal hypoperfusion may occur early in the disease process, independent of overt optic neuritis. **Murphy et al. (16)** similarly reported significant microvascular alterations in MS patients without corresponding structural damage, supporting the hypothesis that vascular dysfunction may precede neurodegeneration.

Several mechanisms could explain these findings: Neuroinflammation-induced microvascular damage: Inflammatory processes in MS may directly affect retinal capillaries, leading to reduced perfusion **(17)**. Secondary vascular regression: Thinning of RNFL and GCC reduces the metabolic demand of retinal neurons, leading to autoregulatory reduction in blood supply. Endothelial dysfunction: Previous studies suggest that primary vascular impairment and blood-retinal barrier disruption may play a role in MS-related hypoperfusion **(18)**.

Clinical Implications

GCC thickness appears to be a more reliable biomarker than RNFL for monitoring neurodegeneration in MS. OCTA changes suggest that vascular alterations may occur early in the disease process, despite the lack of optic neuritis. Integration of structural and microvascular OCT metrics may enhance early detection, risk stratification, and monitoring of MS progression.

Conclusion

In conclusion, OCT demonstrates various structural and microvascular alterations in the retina of patients with MS. The integration of these structural and microvascular parameters may serve as potential biomarkers for the diagnosis of the disease

Recommendation

Structural OCT& OCTA results should be read with caution in MS patients who had previous ON & even those who did not have previous ON. Larger patient cohorts, extended follow-up periods, and multicenter studies are essential to accurately characterize optic nerve damage in individuals with MS as assessed by OCT-A. Additional research is required to validate this emerging imaging modality for the early detection and longitudinal monitoring of MS patients.

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