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RESEARCH

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Unveiling the retinal secrets of neuromyelitis optica spectrum disorder

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Abstract

Background Vascular alterations are now recognized as important contributors to the pathophysiology of neuromyelitis optica spectrum disorder (NMOSD). This study aimed to use optical coherence tomography (OCT) and OCT-angiography (OCTA) to assess alterations in the retinal structure and microvasculature in patients with NMOSD, so we can understand pathophysiology of NMOSD, implicating this on disease activity, visual outcome and management on the future.

Methods A case–control study was conducted on 40 NMOSD patients with (NMOSD + ON) and without (NMOSD – ON) history of optic neuritis and 36 healthy subjects. The following data were assessed in NMOSD patients: clinical history, EDSS, and visual function testing. Both groups underwent spectral domain (SD)-OCT and OCTA.

Results In this study, NMOSD + ON patients had a statistically significant reduction in all SD-OCT parameters compared to healthy control. Regarding OCTA, there was a significant reduction in radial peripapillary capillary density (RPCD) in NMOSD + ON (*P*-value < 0.001) and some sectors of NMOSD–ON compared to healthy control. NMOSD + ON patients had significant differences in RPCD compared to those without (*P*-value < 0.001).

Conclusions Here we show that the advance of this study is that retinal microvascular alterations have been noticed in NMOSD–ON eyes, indicating that subclinical primary retinal vasculopathy and disease activity may occur in NMOSD before onset of ON and retinal atrophy. This may have implications on early detection of disease activity, early interference in management and prognostic tool to visual outcome in following the patients.

Keywords NMOSD, OCT, OCTA, Retinal structure and vascular alterations, Disease activity, Visual outcome, RPCD

Background

Neuromyelitis optica spectrum disorders (NMOSD) are idiopathic inflammatory autoimmune disorder of the central nervous system primarily relapsing in nature [1, 2]. The prevalence of NMOSD in various studies ranges from 0.5 to 10 per 100,000 [3]. Optic neuritis (ON) attacks occurred in 45% of NMOSD patients at disease onset, and 64.1% of patients experienced ON at least once throughout the disease entire course [4, 5].

Ophthalmological examination may be useful to help clinicians diagnose NMOSD since NMO-related optic neuritis directly impacts visual ability [6, 7]. Optical coherence tomography is a non-invasive method that makes it easy to analyze retinal structures effectively [8–10].

In, the past few years, many studies have suggested that retinal nerve fiber layer (RNFL) and macular thickness analysis using OCT are very useful for the detection of axonal loss and treatment effects monitoring in MS and NMOSD [6, 11, 12].

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Apart from examining distinct retinal layers, the geometric and topological characteristics of the retinal microvasculature may provide significant insights for the early diagnosis of (NMOSD) [13]. Significant reductions in microvasculature and structural thickness are observed to be linked to impaired visual acuity. Furthermore, the weakening of the retinal structure rises when ON attacks recur, although it is unrelated to how long the condition lasts [14–16].

According to reports, ON associated with NMOSD can result in substantial thinning of the retinal nerve fiber layer (RNFL), which indicates diffuse axonal injury, large optic nerve lesion longer than that of MS, and severe visual impairment after just one ON episode. Unfortunately, nothing is currently known about how the retinal vascular network is altered in NMOSD [17, 18].

In NMOSD, the retinal microvasculature is a frequent and early target of inflammatory assault. Changes in the retinal micro vascular network of NMOSD are thought to be a sign of the initiation and progression of retinopathy [17].

According to earlier research, NMOSD eyes with and without optic neuritis had considerably lower densities in the RPC (radial peripapillary capillary density) than did healthy controls [16].

Along with proven immune-mediated mechanisms, vascular changes are increasingly accepted as important contributors in the pathophysiology of neuroinflammatory disorders, especially in multiple sclerosis and NMOSD. The retinal vascular imaging could provide insight into the pathophysiology of NMOSD because the anatomical connections exist between the cerebral and retinal vasculatures and share similar characteristics [17].

The relatively new technology of optical coherence tomography angiography (OCTA) images the retinal and choroidal vasculature using a non-intrusive, depth-resolved technique. OCTA offers an alternative quantitative assessment of retinal impairment by measuring vascular density instead of structural atrophy. Additionally, it might act as a substitute marker for vascular pathology in the central nervous system [19].

OCT can be used to quantity the thickness of the retinal nerve fiber layer (RNFL) besides the ganglion cell and inner plexiform layer (GCIPL). Studies using OCT have determined severe thinning of the RNFL and GCIPL in NMOSD eyes with history of ON, denoting retinal axonal and neuronal loss [20].

These data suggest that OCT-A might be a cost-effective tool to study subclinical disease activity and astrocyte loss in individuals with NMOSD.

The principal outcome of earlier studies was that NMOSD eyes with or without a history of ON had significantly reduced peripapillary and parafoveal vascular density. The results show convincing proof that vascular alterations take place in NMOSD eyes even before ON develops, indicating subclinical primary retinal vasculopathy, supporting the astrocyte-associated vascular alteration [17].

Thus, the purpose of this study was to detect alterations in the retinal structure (measured by SD-OCT) and microvasculature network (measured by OCTA) in patients with NMOSD with or without a history of ON and to correlate between retinal vascular abnormalities and retinal structure in NMOSD patients to each other and correlate them with clinical variables.

Methods

This study is a case control study performed on 40 aquaporin-positive NMOSD patients, aged 15–55 years, who were diagnosed using the 2015 international consensus diagnostic criteria for neuromyelitis optica spectrum disorder [21] and either had an optic neuritis history (NMOSD + ON) or did not (NMOSD-ON), as determined by the clinical diagnostic criteria for optic neuritis [22]. From February 1, 2021, until August 1, 2022, patients were continuously recruited from the multiple sclerosis clinic at local hospital. Another 36 age and sex-matched healthy individuals were enrolled as controls at the same time.

Exclusion criteria included NMOSD patients with a history of ON or any other relapse within the last 3 months, NMOSD patients were receiving intravenous or oral steroids within three months, patients with ophthalmic diseases, such as glaucoma or cataract, or another neurological disease such as cerebrovascular disease, patients with neurological syndromes mimicking NMOSD as sarcoidosis, chronic infection or SLE. Any patient or control with prior ocular surgery that can have an impact on the visual outcomes or the macular morphology or with refractory error within + 3.00 to − 6.00 and also those who received drugs with identified effect on the vision such as isoniazid, ethambutol, sildenafil or any other drugs might affect vision [17].

As regards methodology details, both the patient and control groups' demographic information was gathered. Visual function testing was carried out for patients and controls. The best corrected visual acuity (BCVA) of both eyes was measured on the same day as OCT and OCT-A examination for each eye individually using the Snellen chart. Visual acuity was measured by logMAR [23], fundus examination with optic disc evaluation, and intraocular pressure measurement were performed.

NMOSD patients were evaluated regarding clinical data, disease course, annualized relapse rate (ARR), full neurological examination, disease-modifying

therapy (DMT), and the Expanded Disability Status Scale (EDSS) [24].

Investigations needed for diagnosis of NMOSD such as MRI brain and cervical spine with an injection of gadolinium contrast, and aquaporin four testing (serum samples were tested for AQP 4 IgG utilizing cell-based assay) were gathered.

The following procedures; optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA) were performed on patients and control groups alike.

The Optovue RTVueTM system (Optovue Inc., Fremont, CA, USA) was used for spectral domain OCT. The peripapillary RNFL technique and the macular map protocol, which allows for fast macular scanning for GCC measurements, were both applied to the examined eye (each patient examined for single eye). At the Ophthalmology Department of Cairo University Hospital, a single experienced ophthalmologist conducted each examination.

We obtained OCT angiography images with the same OCT device, optic disc OCTA scan in which radial peripapillary capillary vascular density (RPCD) was measured in 4.5 × 4.5 scan around optic disc boundary, and including whole image scan, inside disc scan, and peripapillary scan: that further divided into multiple sectors, superior hemisphere, inferior hemisphere, nasal superior, nasal inferior, inferior nasal, inferior temporal, temporo superior, superior temporal and superior nasal.

There are other studies that discussed this study topic regarding OCT, OCTA in NMOSD patients with similar methods and approaches [16, 17, 19, 25–27].

Regarding statistical methods, data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). For quantitative variables, mean and standard deviation were used to summarize the data, and for categorical variables, frequencies (the number of cases) and relative frequencies (percentages) were used. Analysis of variance (ANOVA) with multiple comparisons post hoc test was used to compare groups for normally distributed quantitative variables. Comparatively, non-parametric Kruskal–Wallis test and Mann–Whitney test were used for non-normally distributed quantitative variables [28]. An analysis using the Chi-square (χ^2) test was done to compare categorical data. Exact test was used instead when the expected frequency is less than 5 [29]. The Spearman correlation coefficient was used to determine correlations between quantitative variables [30]. Logistic regression was done to detect independent predictors of ON [31]. *P*-values less than 0.05 were considered as statistically significant.

Results

Regarding the demographics and clinical characteristics of NMOSD patients and controls, this study was performed on 40 aquaporin-4-positive NMOSD patients; 30 had a history of ON (NMOSD + ON), 10 had no ON (NMOSD-ON), and 36 were age and sex-matched controls. The demographic characteristics of the NMOSD patients and healthy controls are shown in (Table 1).

The mean age of onset of patients in our population is 27.6 ± 9.8 SD years, with a mean duration of illness of 66.4 ± 50.3 months. Seventy-five percent of the patients had a history of ON, either unilateral or bilateral. The mean annualized relapse rate (ARR) is 1 ± 0.55 SD, while the mean EDSS of the patients is 3.96 ± 1.62 SD. The patients' clinical characteristics, investigations, and treatment are shown in Table 2.

There was a statistically significant difference between patients with a history of ON and healthy control regarding visual acuity (*P*-value ≤ 0.001). In contrast to IOP, which shows no difference.

As regards OCT, patients with a history of ON had significantly lower retinal nerve fiber layer, ganglion cell complex parameters (Fig. 1a, b), and significantly higher global loss volume (GLV) and focal loss volume (FLV) than the control group (*P*-value < 0.001 in the whole scan). There were no statistically significant differences for these parameters between patients without a history of ON and healthy control (Table 3, Fig. 2a, b).

As regards OCTA, patients with a history of ON had a significantly lower radial peripapillary capillary vessel density (RPCD) in comparison to controls (*P*-value < 0.001 in all sectors) (Fig. 3a, b). Also, some sectors (peripapillary, superior hemisphere, nasal superior, temporo inferior, temporo superior, and superior nasal) were significantly lower in patients without a history of ON in comparison to controls (*P*-value = 0.04, 0.033, 0.037, 0.025, 0.39, 0.36, respectively) (Table 4, Fig. 4a, b,).

Regarding the impact of ON on the characteristics of NMOSD patients, NMOSD patients with ON had significantly lower RNFL, GCC thickness parameters, and

Table 1 Demographic characteristics of NMOSD patients and healthy controls

Items		Patient group (*n* = 40)	Control group (*n* = 36)
Age (years)	Range	15–50	26–40
	Mean ± SD	33.23 ± 10.55	31.97 ± 3.09
Sex (*n*, %)	Female	39 (97.5)	30 (83.3)
	Male	1 (2.5)	6 (16.7)

NMOSD: neuromyelitis optica spectrum disorder, n: number, SD: standard deviation

Table 2 Clinical characteristics, imaging and aquaporin-4 status among our NMOSD patients

Items		Patient group (n = 40)
Age of onset of the disease (years)	Mean ± SD	27.6 ± 9.8
Duration of illness (months)	Mean ± SD	66.4 ± 50.3
Total number of relapses	Mean ± SD	4.63 ± 3.39
History of ON (*n*, %)	With	30 (75%)
Unilateral or bilateral ON history	Unilateral	11(27.5%)
	Bilateral	19 (47.5%)
Number of ON attacks	Mean ± SD	1.92 ± 2.14
EDSS at time of questionnaire (mean ± SD)		3.96 ± 1.62
EDSS	< 4	18 (45%)
	4–6.5	21 (52.5%)
	> 6.5	1 (2.5%)
Annual relapse rate	Mean ± SD	1 ± 0.55
DMT (*n*, %)	No treatment	6 (15%)
	Rituximab	27 (67.5%)
	Azathioprine	3 (7.5%)
	Azathioprine and steroid	4 (10%)
Spinal MRI (cervical spine, dorsal spine) (*n*, %)	Normal ≥ Three segments < Three segments	6 (15%) 30 (75%) 4 (10%)
MRI brain (*n*, %)	Normal	24(60%)
	Abnormal	16 (40%)

NMOSD: neuromyelitis optica spectrum disorder, n: number, SD: standard deviation, %: percentage, ON: optic neuritis, EDSS: Expanded Disability Status Scale, DMT: disease-modifying therapy

significantly higher global and focal loss volumes (GLV, FLV) compared to those without ON (*P*-value < 0.001 in all segments) (Table 5). These differences denote severe structural atrophy in the retina between NMOSD + ON patients compared to NMOSD–ON patients; whereas, both groups of patients are age and sex-matched (*P*-value = 0.346, 1, respectively), and there were no statistically significant differences between them regarding age of onset, the number of relapses, disease duration, EDSS, annual relapse rate (ARR), brain, cervical imaging and DMT.

There were statistically significant differences between NMOSD patients with and without ON in all scans of RPCD (*P*-value < 0.001 in all sectors) (Table 6). These significant differences denote severe affection in the vascular density in NMOSD + ON compared to NMOSD – ON.

In NMOSD patients with ON, there was a statistically significant negative correlation between all SD-OCT (RNFL, GCC) parameters and visual acuity affection (*P*-value < 0.001 in all grid sectors), except for GLV and FLV, there was positive correlation (*P*-value < 0.001). This denotes that the structural atrophy and retinal layer volume loss strongly affect visual acuity.

A statistically significant negative correlation existed between RPCD parameters in all grid sectors and visual acuity affection (*P*-value < 0.001 in all sectors). Also, most sectors of RPCD with number of ON attacks. There were a statistically significant positive correlation between SD-OCT parameters (RNFL, GCC) and radial peripapillary capillary density (RPCD) detected by OCTA in all sectors (*P*-value < 0.001 in whole image) except for GLV and FLV there were significant negative correlation (*P*-value < 0.001) (Fig. 5a, b).

Correlation between SD-OCT parameters and RPCD parameters in NMOSD-ON patients showed that in NMOSD patients without ON, there was a statistically significant positive correlation between some SD-OCT parameters and RPCD parameters in a few sectors (peripapillary, superior hemisphere, inferior hemisphere, temporo superior, and superior temporal) (Table 7).

Multivariate regression analysis was done to detect the subclinical affection of optic nerve in the NMOSD-ON group among all SD-OCT and OCTA parameters. The independent predictor was peripapillary vessel density, especially the nasal inferior sector (*P*-value = 0.017, OR = 0.647, 95% CI 0.453–0.925).

To summarize our results in this study NMOSD + ON patients had a statistically significant reduction in all SD-OCT parameters compared to healthy control but not in NMOSD–ON (*P*-value < 0.001). Regarding OCTA there was a significant reduction in radial peripapillary capillary

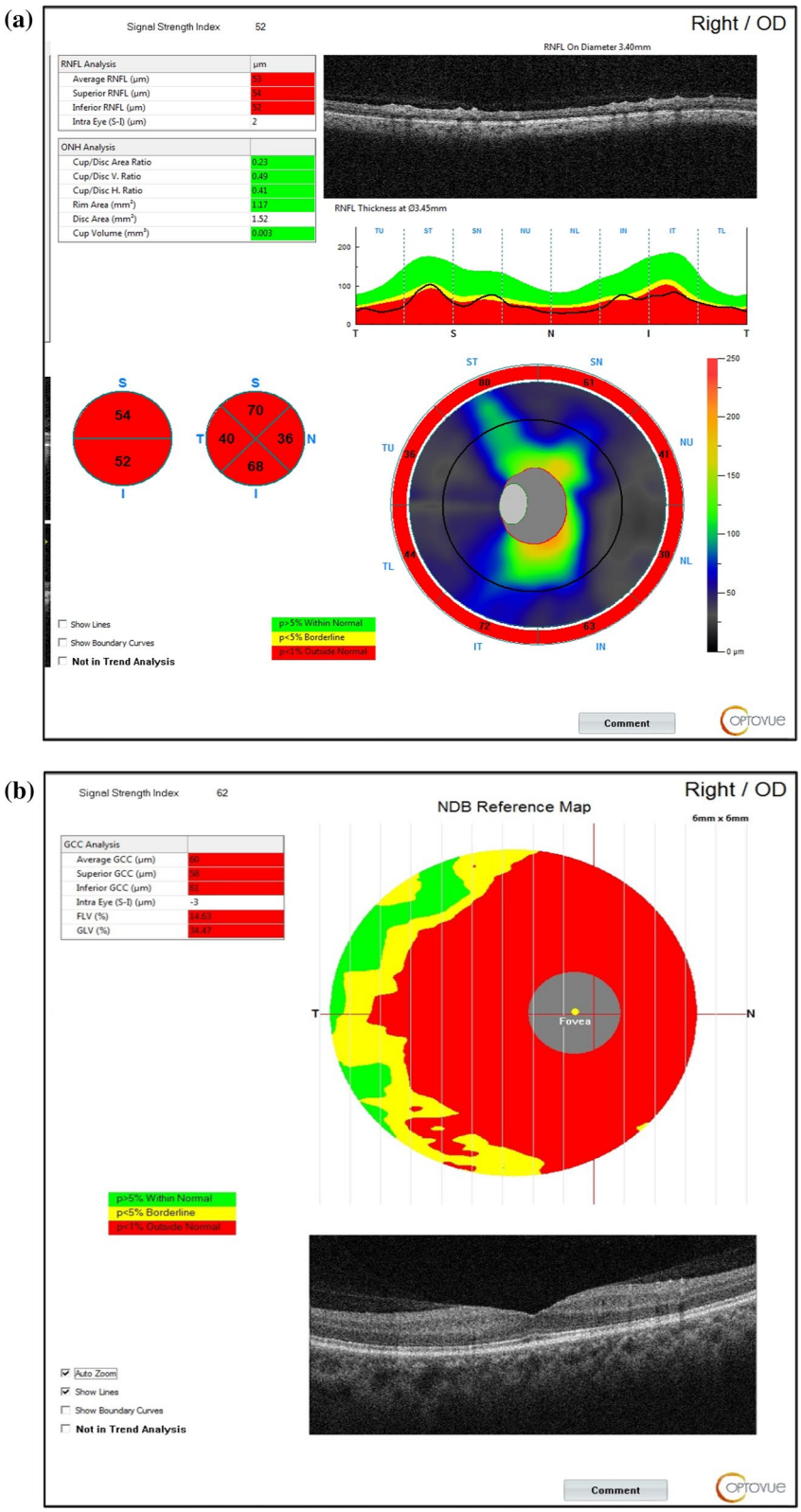


Fig. 1 **a**, **b** SD OCT imaging for RNFL

Table 3 Spectral domain OCT parameters among study groups

SD-OCT parameters	NMOSD + ON (mean ± SD)	NMOSD -ON (mean ± SD)	Healthy controls (mean ± SD)	NMOSD + ON versus Controls (p value)	NMOSD -ON versus controls (p value)
Average RNFL (μm)	69.43 ± 20.3	100.50 ± 9.42	103.03 ± 7.77	< 0.001*	1.000
Superior RNFL (μm)	70.67 ± 21.21	101.80 ± 8.64	105.42 ± 8.65	< 0.001*	1.000
Inferior RNFL (μm)	68.17 ± 20.94	99.60 ± 11.34	101.33 ± 7.69	< 0.001*	1.000
Average GCC (μm)	73.57 ± 16.46	97.70 ± 7.70	101.11 ± 7.62	< 0.001*	1.000
Superior GCC (μm)	72.13 ± 16.13	97.00 ± 8.10	97.92 ± 16.91	< 0.001*	1.000
Inferior GCC (μm)	71.27 ± 18.25	97.90 ± 7.69	101.25 ± 7.23	< 0.001*	1.000
FLV (%)	8.73 ± 5.28	1.32 ± 1.84	0.60 ± 0.36	< 0.001*	1.000
GLV (%)	23.07 ± 14.24	3.07 ± 3.37	1.79 ± 1.55	< 0.001*	1.000

NMOSD: neuromyelitis optica spectrum disorder**,** NMOSD + ON: patients with history of ON, NMOSD – ON: without history of ON, SD: standard deviation, SD-OCT: spectral domain optical coherence tomography, RNFL: retinal nerve fiber layer, GCC: ganglion cell complex, FLV: focal loss volume, GLV: global loss volume

*$p < 0.05$ is significant, < 0.01 is highly significant, < 0.001 is extremely significant

density (RPCD) in NMOSD + ON (*P*-value < 0.001 in all sectors) and some sectors of NMOSD–ON compared to healthy control. NMOSD + ON patients had significant differences in RPCD compared to those without (*P*-value < 0.001). In NMOSD + ON patients, significantly positive correlation existed between all OCT and OCTA parameters (*P*-value < 0.001) and a negative correlation of both with visual acuity (*P*-value < 0.001).

Discussion

Neuromyelitis optica spectrum disorder (NMOSD) is an uncommon but severe inflammatory demyelinating condition that relapses and is presenting with catastrophic optic neuritis (ON). Vision impairment results from the optic neuritis in NMOSD, which damages the optic nerve and retina's neuroaxonal structure [32].

Vascular alterations are becoming more widely acknowledged as significant aspects in the pathogenesis of neuroinflammatory diseases, particularly neuromyelitis optica spectrum disorder (NMOSD), in addition to established immune-mediated processes [19].

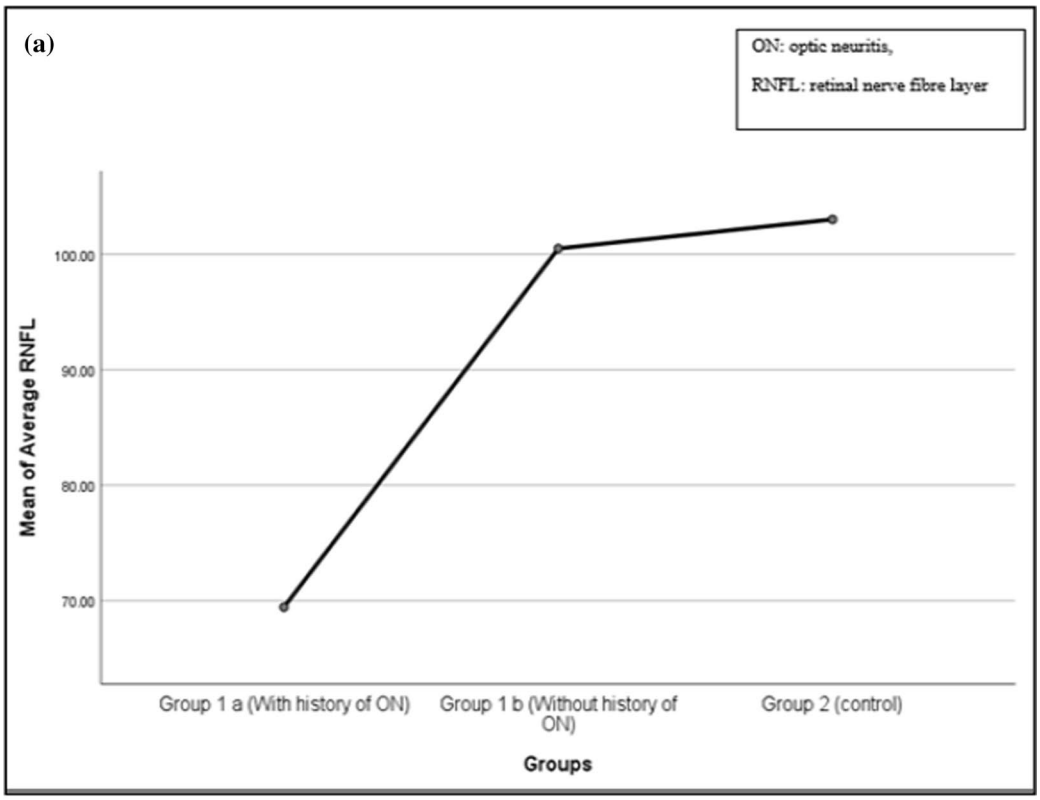
Optical coherence tomography angiography (OCTA), a relatively new technology, provides depth-resolved, non-invasive pictures of the retinal and choroidal vasculature. OCTA measures vascular density rather than structural atrophy, offering a different quantitative indicator of retinal affection [19].

In this study, we aimed to assess the retinal vascular abnormalities through OCT angiography in NMOSD patients with or without a history of ON compared to each other and with healthy controls and investigate their correlations with neuroaxonal structural damage evaluated with spectral domain OCT (SD-OCT), as well as visual acuity (VA) and other clinical outcomes.

Our results in this study found that NMOSD + ON patients had a statistically significant reduction in all SD-OCT parameters compared to healthy control but not in NMOSD–ON. With regard to OCTA, there was a significant reduction in radial peripapillary capillary density (RPCD) in NMOSD + ON in all sectors and some sectors of NMOSD–ON compared to healthy control. NMOSD + ON patients had significant differences in RPCD compared to those without history of ON. In NMOSD + ON patients, significantly positive correlation existed between all OCT and OCTA parameters and a negative correlation of both with visual acuity. Retinal microvascular changes were present in NMOSD–ON eyes indicating that subclinical primary retinal vasculopathy may occur in NMOSD prior to ON and RNFL atrophy.

These results goes with results of other studies as we will discuss in details and they give us an image about understanding the pathophysiology of NMOSD, and how it is changed from being only inflammatory disease to another pathology related to retinal vascular alterations which is also related to aquaporin-4 antibodies. these results will help us in early detecting cases with retinal affection even before development of ON attacks and structural damage allowing close monitoring to those patients and also as prognostic marker and also can be monitoring biomarker by serial follow-up retinal imaging by OCTA and detecting the changes and finally all this will reflected on disease management regarding early intervention with suitable DMTs, escalation during follow-up or finally for future medications that targeting this pathophysiology of the disease but this needs more research in this context.

The retinal microvasculature is an early and frequent target of inflammatory attacks in NMOSD. Changes in



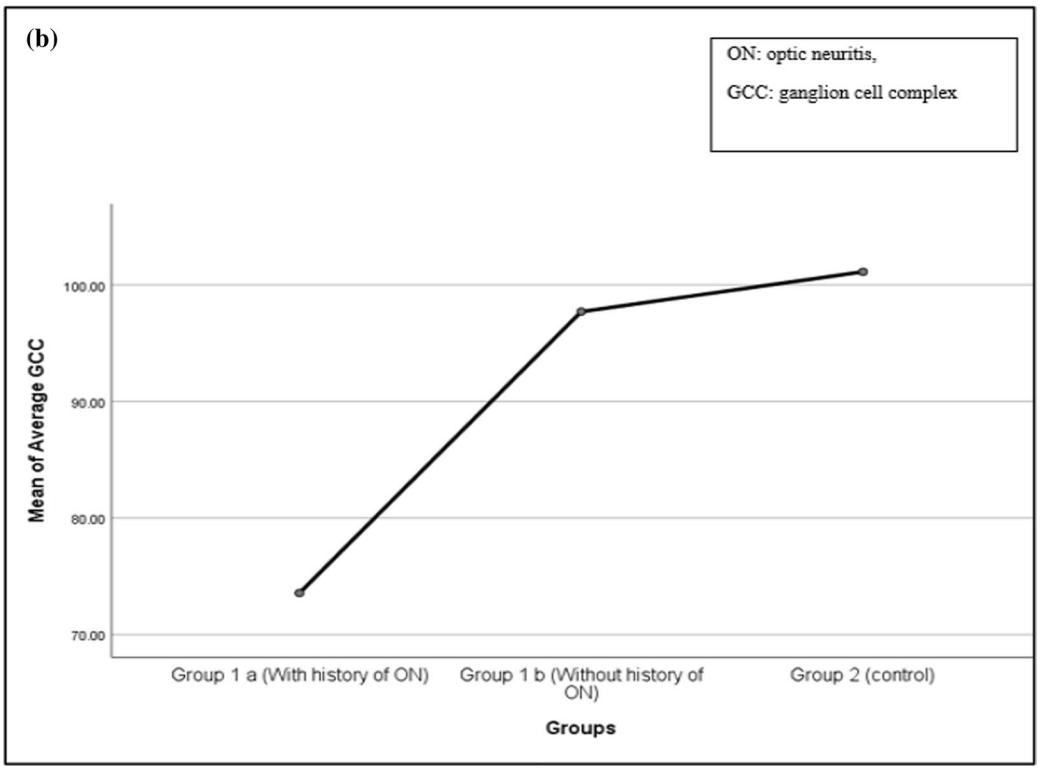


Fig. 2 **a**, **b** Spectral domain OCT parameters among study groups

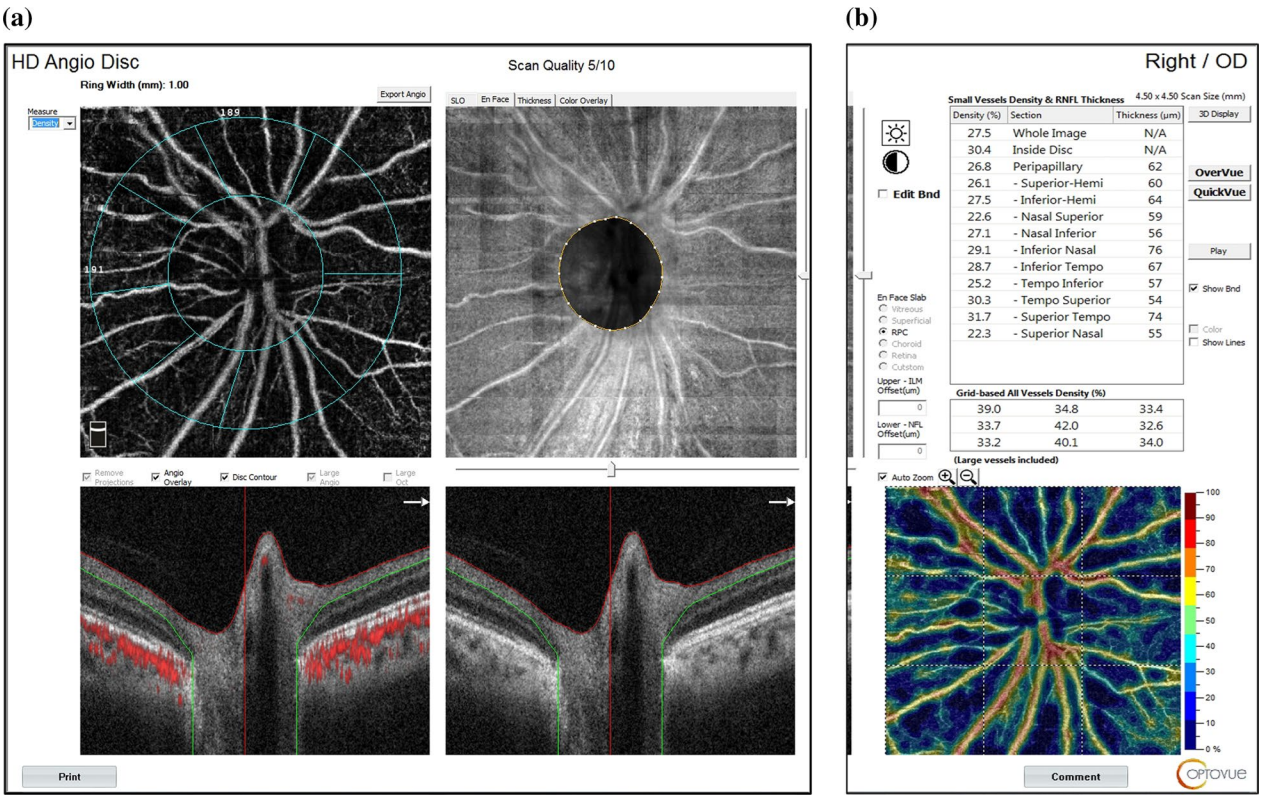


Fig. 3 **a**, **b** Peripapillary OCTA images

Table 4 RPCD among the three study groups

OCT-A grid sector (Radial peripapillary capillary density)	NMOSD + ON (mean ± SD)	NMOSD -ON (mean ± SD	Healthy controls (mean ± SD)	NMOSD + ON versus controls (p value)	NMOSD -ON versus controls (*p* value)
Whole image	38.78 ± 8.21	51.04 ± 1.56	53.14 ± 3.74	< 0.001*	0.943
Inside disc	46.62 ± 7.7	52.17 ± 3.08	53.78 ± 5.18	< 0.001*	1.000
Peripapillary	38.55 ± 10.38	52.35 ± 1.95	57.13 ± 2.75	< 0.001*	0.04*
Superior hemisphere	37.98 ± 11.05	52.12 ± 2.13	57.75 ± 2.9	< 0.001*	0.033*
Inferior hemisphere	39.06 ± 10.08	53.50 ± 2.41	54.93 ± 3.18	< 0.001*	1.00
Nasal superior	35.27 ± 10.94	51.1 ± 3.11	55.93 ± 3.98	< 0.001*	0.037*
Nasal inferior	36.51 ± 8.52	49.66 ± 4.17	51.77 ± 4.91	< 0.001*	1.00
Inferior nasal	38.97 ± 13.37	54.14 ± 3.22	54.55 ± 4.19	< 0.001*	1.00
Inferior temporal	42.6 ± 15	60.09 ± 3.79	59.42 ± 3.07	< 0.001*	1.00
Temporo inferior	39.04 ± 9.29	51.38 ± 3.43	56.97 ± 3.64	< 0.001*	0.025*
Temporo superior	42.07 ± 9.76	54.7 ± 3.04	59.89 ± 2.94	< 0.001*	0.039*
Superior temporal	40.02 ± 14.43	56.86 ± 2.04	58.65 ± 3.36	< 0.001*	1.00
Superior nasal	35.74 ± 12.92	51.15 ± 4.88	57.52 ± 4.47	< 0.001*	0.036*

NMOSD + ON: patients with history of ON, NMOSD – ON: without history of ON, SD: standard deviation, OCTA: optical coherence tomography angiography

*$p < 0.05$ is significant, < 0.01 is highly significant, < 0.001 is extremely significant

the retinal microvasculature in NMOSD patients are thought to be a sign of retinopathy onset and development [17]. Previous investigations support the concept that NMOSD is a primary astrocytopathy. In the retina, there exist AQP4 expressing astrocytic cells called 'Müller cells', which may be directly targeted by AQP4-ab

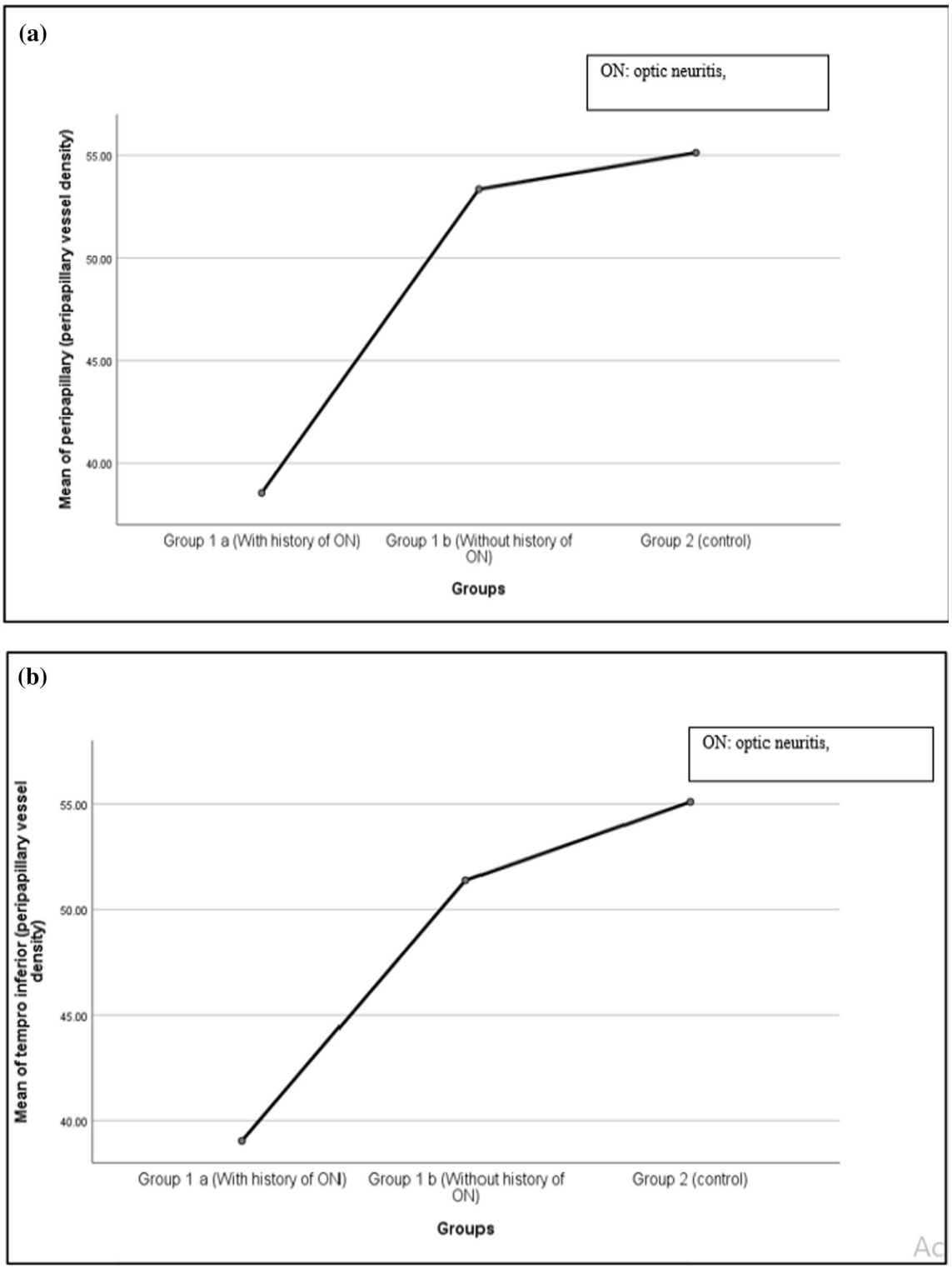


Fig. 4 **a**, **b** Radial peripapillary capillary density among the three study groups

Table 5 SD OCT parameters among the two groups of patients

SD- OCT parameters	NMOSD + ON Mean ± SD	NMOSD –ON Mean ± SD	(P value)
Average RNFL	69.43 ± 20.83	100.50 ± 9.42	< 0.001*
Superior RNFL	70.67 ± 21.21	101.80 ± 8.64	< 0.001*
Inferior RNFL	68.17 ± 20.94	99.60 ± 11.34	< 0.001*
Average GCC	73.57 ± 16.46	97.70 ± 7.70	< 0.001*
Superior GCC	72.13 ± 16.13	97.00 ± 8.10	< 0.001*
Inferior GCC	71.27 ± 18.25	97.90 ± 7.69	< 0.001*
FLV	8.73 ± 5.28	1.32 ± 1.84	< 0.001*
GLV	23.07 ± 14.24	3.07 ± 3.37	< 0.001*

NMOSD + ON: patients with history of ON, NMOSD – ON: without history of ON, SD: standard deviation, SD-OCT: spectral domain optical coherence tomography, RNFL: retinal nerve fiber layer, GCC: ganglion cell complex, FLV: focal loss volume, GLV: global loss volume

*$p < 0.05$ is significant, < 0.01 is highly significant, < 0.001 is extremely significant

Table 6 RPCD parameters among the two patients groups

Radial peripapillary capillary density	NMOSD + ON Mean ± SD	NMOSD – ON Mean ± SD	(*P* value)
Whole image	38.78 ± 8.21	51.04 ± 1.56	< 0.001*
Inside disc	46.62 ± 7.70	52.17 ± 3.08	0.047*
Peripapillary	38.55 ± 10.38	52.35 ± 1.95	< 0.001*
Superior hemisphere	37.98 ± 11.05	52.12 ± 2.13	< 0.001*
Inferior hemisphere	39.06 ± 10.08	53.50 ± 2.41	< 0.001*
Nasal superior	35.27 ± 10.94	51.10 ± 3.11	< 0.001*
Nasal inferior	36.51 ± 8.52	49.66 ± 4.17	< 0.001*
Inferior nasal	38.97 ± 13.37	54.14 ± 3.22	< 0.001*
Inferior temporal	42.60 ± 15.00	60.09 ± 3.79	< 0.001*
Temporo inferior	39.04 ± 9.29	51.38 ± 4.43	< 0.001*
Temporo superior	42.07 ± 9.76	54.70 ± 3.43	< 0.001*
Superior temporal	40.02 ± 14.43	56.86 ± 2.04	< 0.001*
Superior nasal	35.74 ± 12.92	51.15 ± 4.88	< 0.001*

NMOSD + ON: patients with history of ON, NMOSD –ON: without history of ON, SD: standard deviation, OCTA: optical coherence tomography angiography

*$p < 0.05$ is significant, < 0.01 is highly significant, < 0.001 is extremely significant

and become a probable cause of primary retinopathy in NMOSD [33].

This study confirmed the presence of significant alterations in the retinal structure and microvasculature network in NMOSD patients with a history of ON, as compared to controls and patients without ON, all RNFL and GCC values were significantly lower in patients with ON, with a significant increase in focal and global loss volume (FLV, GLV) this implying severe structural and axonal degeneration but no significant difference in these parameters between patients without history of ON and healthy control. Similarly, RNFL and GCC thickness parameters were thinner in NMOSD + ON compared to healthy controls and NMOSD − ON and same results obtained by previous studies [16, 17, 33, 34] regarding SD-OCT parameters in NMOSD + ON and NMOSD–ON.

Also, in the NMOSD + ON group, a significant correlation was found between all SD-OCT parameters when correlated with visual acuity affection, denoting that the structural atrophy and volume loss of retinal layers strongly affect visual acuity. These findings agree with another study of Kwapong and colleagues [16] who found a significantly reduced structural thickness and microvasculature, as well as the association between these changes and impaired visual acuity.

This study demonstrated that there was no significant correlation between SD OCT parameters (RNFL, GCC thickness) and number of optic neuritis attacks in NMOSD + ON group.

Oertel and colleagues in 2021 found that first optic neuritis attack is usually severe than subsequent attacks, they explained these finding by longer time until reaching to effective anti-inflammatory therapy and the typical choice of less effective therapies (like steroids instead of plasma exchange) at the first attack compared with the following attacks. And the net results is more damage in first attack and reduced neuroaxonal content.

In agreement with previous studies [16, 17, 26], this study confirmed the presence of substantial alterations in the retinal microvasculature network in patients with NMOSD with or without a history of ON. This study revealed a significant reduction in vascular density in RPCD (whole image and all peripapillary grid sectors) in NMOSD + ON in comparison to healthy control. Also, there was a significant reduction in some RPCD sectors in NMOSD–ON compared to healthy controls.

Concurrently, this study revealed a significant difference in RPCD between NMOSD + ON and NMOSD–ON. Despite that, OCTA finding in NMOSD–ON compared to healthy control was not associated with any changes in SD-OCT parameters, which implies that vascular alterations occurred in NMOSD eyes even before the onset of ON and the occurrence of structural damage in the retina, denoting subclinical primary retinal vasculopathy.

Regarding the explanation of reduced retinal vascular density in NMOSD patients, according to Chen and colleagues [26], a pathological study of NMOSD patients revealed that the vascular walls of the optic nerve were penetrated by inflammatory cells. Damaged astrocyte and vascular endothelial cells that induced by inflammation likely directly reduces vascular perfusion and could facilitate neurodegeneration. Müller cells are responsible for water homeostasis, energy metabolism, and neurotransmitter recycling, and maintaining the function of

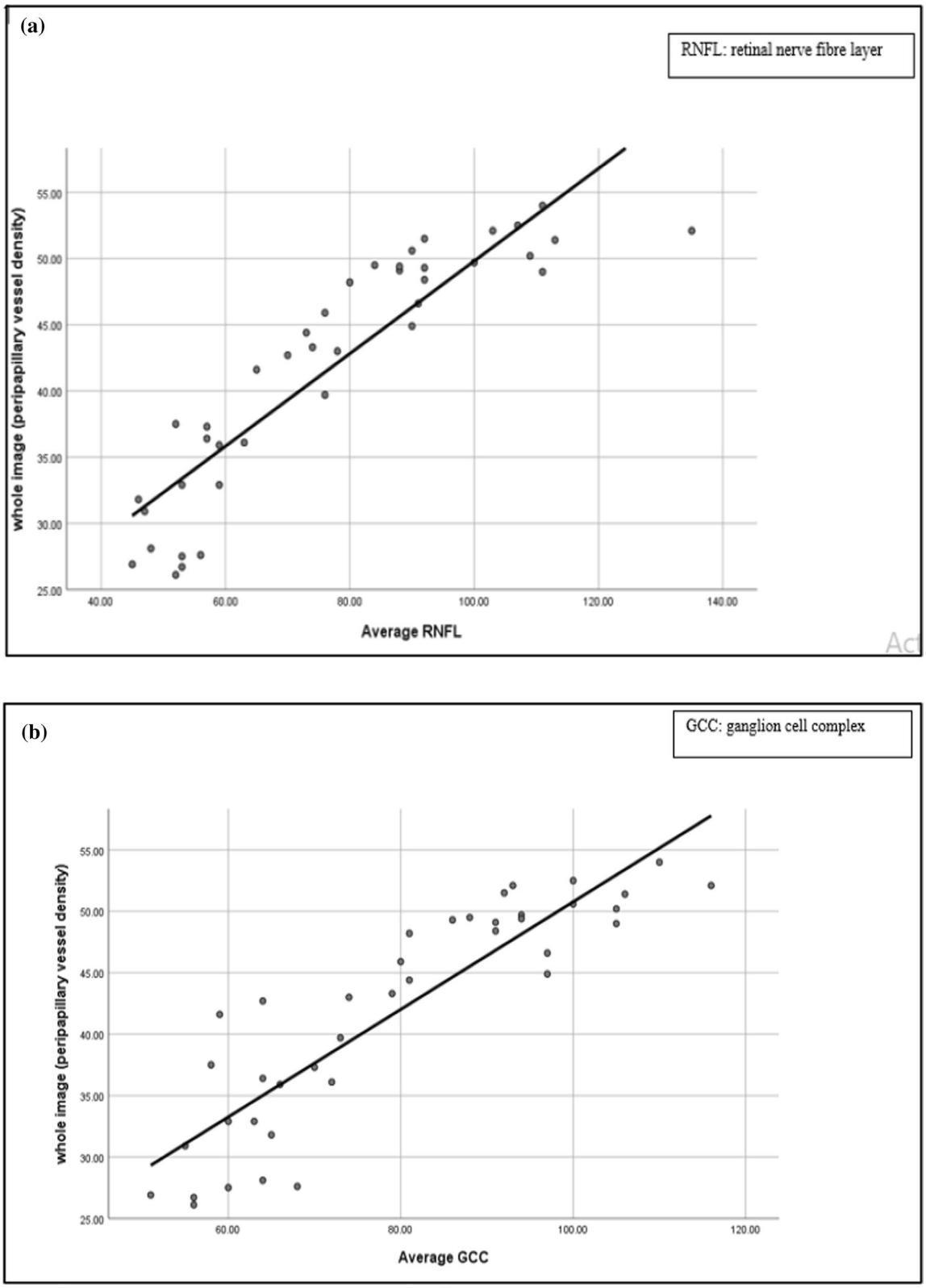


Fig. 5 **a**, **b** Correlation between radial peripapillary capillary density and (RNFL, GCC) in NMOSD + ON

Table 7 Correlations between SD-OCT parameters and RPCD parameters in NMOSD – ON

NMOSD -ON RPCD/SD OCT	Average RNFL	Superior RNFL	Inferior RNFL	Average GCC	Superior GCC	Inferior GCC	FLV	GLV
Whole image								
r	0.584	0.427	0.576	0.565	0.515	0.456	– 0.673	– 0.552
P value	0.077	0.219	0.082	0.089	0.128	0.185	0.033*	0.098
Inside disc								
r	0.113	– 0.006	0.036	– 0.107	– 0.109	– 0.088	– 0.426	0.043
P value	0.756	0.987	0.920	0.769	0.763	0.808	0.220	0.907
Peripapillary								
r	0.687	0.573	0.709	0.650	0.600	0.578	– 0.576	– 0.636
P value	0.028*	0.083	0.022*	0.042*	0.067	0.080	0.082	0.048*
Superior hemisphere								
r	0.665	0.587	0.681	0.741	0.699	0.610	– 0.498	– 0.705
P value	0.036*	0.074	0.030*	0.014*	0.024*	0.061	0.143	0.023*
Inferior hemisphere								
r	0.511	0.305	0.636	0.571	0.564	0.608	– 0.709	– 0.588
P value	0.132	0.392	0.048*	0.084	0.090	0.062	0.022*	0.074
Nasal superior								
r	0.614	0.585	0.588	0.547	0.479	0.365	– 0.442	– 0.552
P value	0.059	0.075	0.074	0.102	0.162	0.300	0.200	0.098
Nasal inferior								
r	0.426	0.201	0.527	0.517	0.527	0.517	– 0.733	– 0.527
P value	0.220	0.577	0.117	0.126	0.117	0.126	0.016*	0.117
Inferior nasal								
r	0.244	0.269	0.365	0.412	0.359	0.537	– 0.286	– 0.413
P value	0.497	0.452	0.300	0.237	0.309	0.110	0.424	0.235
Inferior temporal								
r	– 0.255	– 0.299	– 0.103	– 0.128	– 0.079	0.043	0.067	0.127
P value	0.476	0.402	0.777	0.725	0.829	0.907	0.855	0.726
Temporo inferior								
r	0.486	0.573	0.430	0.413	0.345	0.365	– 0.345	– 0.345
P value	0.154	0.083	0.214	0.235	0.328	0.300	0.328	0.328
Temporo superior								
r	0.320	0.549	0.362	0.646	0.644	0.665	– 0.080	– 0.595
P value	0.367	0.100	0.304	0.044*	0.044*	0.036*	0.827	0.070
Superior temporal								
r	0.390	0.324	0.474	0.747	0.796	0.665	– 0.182	– 0.632
P value	0.265	0.361	0.166	0.013*	0.006*	0.036*	0.614	0.050*
Superior nasal								
r	0.085	– 0.104	– 0.055	0.164	– 0.176	– 0.16-	– 0.248	0.188
P value	0.815	0.776	0.881	0.650	0.627	0.650	0.489	0.603

SD-OCT: spectral domain optical coherence tomography, RPCD: radial peripapillary capillary density, RNFL: retinal nerve fiber layer, GCC: ganglion cell complex, FLV: focal loss volume, GLV: global loss volume, r: correlation co-affiant

*$p < 0.05$ is significant, < 0.01 is highly significant, < 0.001 is extremely significant

the blood–brain barrier. High level of aquaporin-4 are expressed by these retinal astrocytic cells. Thus, Müller cells may likely be attacked by AQP4-ab before the occurrence of ON, causing retinal vascular rarefaction in patients with NMOSD [26, 33]. This suggests that NMOSD has subclinical disease activity and might drive relapse-independent disease progression [25].

Consistent with previous studies [16, 17, 35], this study showed a significantly negative correlation between all RPCD parameters and visual acuity impairment in

NMOSD patients with ON. Also, there is a significant negative correlation between number of ON attacks and vessel density in RPCD, proving that the increased frequency of ON worsen the microvascular impairment in NMOSD. This goes with the results of Kwapongand colleagues [35]. In contrast, Huang and colleagues [17] found no significant correlations between vessel density parameters and the number of ON attacks. This may explain why this current study involved more sectors in OCTA than Huang's study (13 sectors in this current study versus seven sectors in his study in RPCD). This study goes in agreement with other studies of Huang and colleagues [17], Kwapongand colleagues[16], who found that in NMOSD + ON patients, the peripapillary vessel densities correlated well with the spectral domain OCT parameters (RNFL, GCC), suggesting that the vascular alterations are related to structural damages involving the retina and both related to poor visual outcome.

This study found a significant positive correlation between some OCT parameters (RNFL, GCC) and RPCD in NMOSD-ON. This goes with Huang and colleagues [17] who found a correlation between RPCD and OCT parameters, indicating that these subclinical changes may be interconnected to a certain degree.

Multivariate logistic regression analysis in this study found that peripapillary capillary density, especially the nasal inferior sector, is the most accurate predictor for detecting subclinical optic nerve affection in the NMOSD–ON group between all OCT and OCTA parameters.

RPCD is only vascular plexus in OCTA correlated with SD OCT parameters in NMOSD – ON group. In comparing NMOSD + ON and NMOSD – ON groups, there was highly significant difference between them in RPCD, which means that involvement of RPCD is marked in NMOSD + ON compared to NMOSD – ON.

These results goes in agreement of Huang and his colleagues 2019 that patients with poorer peripapillary perfusion may present with more severe visual acuity impairment and that peripapillary vessel density may be a surrogate predictor of visual outcomes in NMOSD patients with ON.

From these previous points, we can conclude that RPCD is the earliest vascular plexus to be affected in NMOSD – ON group and also the most severely affected plexus in NMOSD + ON group. The identified biomarkers and observed alterations may contribute to the early diagnosis and monitoring of NMOSD, potentially offering a time window for intervention and prevention of disease progression [36–38].

This study had some limitations. First, a small sample size prevented a more comprehensive comparison study between NMOSD patients subgroups (NMOSD with ON versus NMOSD without ON) as NMOSD-ON group was much lower. A larger sample size is needed to prove the results regarding OCT and OCTA. Second, its cross-sectional design made it impossible to determine the exact sequence of the medical events; we cannot demonstrate whether vascular alterations are secondary to fewer energy requirements from the atrophied retina or a primary process causing generalized ischemia with secondary retina atrophy. Therefore, longitudinal studies are necessary to support this hypothesis about microvascular alterations. Also, the broad age spectrum in this study (15–50) is considered a weak point, as we are comparing extremely different ages in their retinal vascular changes. Age may be a corresponding factor in these changes.

Conclusions

Retinal structure and vascular plexus density are significantly reduced in NMOSD patients than in healthy controls. Retinal microvascular changes were present in NMOSD–ON eyes indicating that subclinical primary retinal vasculopathy may occur in NMOSD before the onset of ON and RNFL atrophy. This will have implications on early detection of disease activity and acting as prognostic and monitoring biomarker for disease progression which in turn implicating on patients management. Decreased microvascular density in NMOSD patients correlated with worsening their visual acuity, thus it can be used as monitoring biomarker for visual function that is more accurate and detecting progression even before clinical affection. Correlation between microvascular impairment and structural damage revealed that retinal microvascular alteration may contribute to neuroaxonal loss in NMOSD patients. Radial peripapillary capillary density (RPCD) is the most accurate predictor to detect subclinical optic nerve affection in the NMOSD–ON group between all OCT and OCTA parameters.

Abbreviations

ANOVA	Analysis of variance
ARR	Annualized relapse rate
AQP4-ab	Aquaporin 4 antibody.
BCVA	Best corrected visual acuity
DMT	Disease-modifying therapy
EDSS	Extended Disability Status Scale
FLV	Focal loss volume
GCC	Ganglion cell complex
GCIPL	Ganglion cell and inner plexiform layer
GLV	Global loss volume
IOP	Intra-ocular pressure
NMOSD	Neuromyelitis optica spectrum disorder
NMOSD + ON	NMOSD patients with history of optic neuritis
NMOSD–ON	NMOSD patients without history of optic neuritis
OCT	Optical coherence tomography
OCTA	Optical coherence tomography angiography
ON	Optic neuritis
RNFL	Retinal nerve fiber layer
RPCD	Radial peripapillary capillary density

SD-OCT	Spectral domain optical coherence tomography
SLE	Systemic lupus erythromatosis
SPSS	Statistical Package for the Social Sciences

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Author contributions
ASA assisted in the interpretation of data and shared in writing, editing, and revision the manuscript and submission. OE provided the idea and design of study and shared in supervision. NME participated in the data gathering and study design. AH helped to outline the manuscript and took part in the study design, analysis, and data interpretation. NE contributed to the analysis of ophthalmological part of the study and helped to draft the manuscript. ESH participated in the study design and gathering of data. HA participated in the collection of data and contributed to the manuscript's drafting. SA contributed to the data interpretation and the manuscript's drafting. All authors read and approved the final manuscript.

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Availability of data and materials
Authors report that the data sets used and/or analyzed during this study are available from the corresponding author upon reasonable request.

Declarations

Ethical approval and consent to participate
This study was performed in agreement with the Declaration of Helsinki. The Cairo University Research Ethical Committee granted this project ethical permission, the committee's date 16/9/2020, and reference number MD-197-2020. Informedwritten consent to participate in this study was obtained from all participants. All figures attached in this manuscript are original and belong to our work, including images of our patients.

Consent for publication
Not applicable.

Competing interests
The authors declare that there is no competing interests.

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