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Evaluation of retinal nerve fiber layer thickness and optic nerve functions in fellow eye of neuromyelitis optica with unilateral optic neuritis

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Abstract:

Purpose: Peripapillary retinal nerve fibre layer (RNFL) thickness might be useful in monitoring ongoing subclinical structural damage especially in eyes with no history of optic neuritis (ON) in neuromyelitis optica (NMO).

Objective: To evaluate the peripapillary RNFL thickness and optic nerve functions in fellow eye of NMO with unilateral optic neuritis.

Materials and Methods: A comparative cross-sectional study was conducted in 2 tertiary hospitals from August 2017 to May 2019. RNFL thickness and optic nerve functions were evaluated. Statistical analysis was performed using Statistical Package for Social Science version 24.

Results: A total of 26 NMO patients and 26 controls were involved in this study. The median age (IQR) of NMO patients was 32.5 (12) years old. The RNFL thickness was significantly reduced in NMO patients with non-ON eyes as compared to control group. Best corrected visual acuity between the 2 groups were comparable (0.20 vs 0.00, $p=0.071$). Contrast sensitivity was also reduced in NMO patients (non-ON eyes) at all 5 spatial frequencies. In NMO group, 34.6% have normal colour vision. The mean deviation (MD) of Humphrey visual field (HVF) was higher in NMO group ($p<0.001$). There was a moderate correlation between RNFL thickness and contrast sensitivity. Weak correlation was found between the RNFL thickness with visual acuity and mean deviation of visual field test.

Conclusion: Our study showed that the fellow eye of NMO patients with unilateral ON revealed a significant reduction in RNFL thickness and all the optic nerve functions have subtle early changes that signify a subclinical retinal damage.

Keywords:

Neuromyelitis optica, optic nerve functions, retinal nerve fiber layer thickness

Introduction

Neuromyelitis optica (NMO) is a chronic inflammatory disorder involving the brain and spinal cord which commonly manifest as optic neuritis (ON) and transverse myelitis. The retinal nerve fiber layer (RNFL) damage is found to be more severely affected in NMO as compared to multiple sclerosis (MS).^[1]

A study conducted revealed that patients with MS experience morphological changes of the optic nerve after ON correlates with visual dysfunction.^[2] In non-ON eyes of MS patients with good vision, the optic nerve dysfunction might still present.^[2] On the other hand, in NMO, there are only few published articles evaluating the visual dysfunction and anatomical parameters in eyes with no history of ON.^[3,4] As such, in our study, we decided to evaluate the changes in peripapillary RNFL thickness and conduct

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a complete assessment of optic nerve functions in fellow eye of NMO with unilateral ON in comparison to healthy controls. Moreover, no related studies were conducted in the Asian population including Malaysia.

Methodology

Subjects

This is a comparative cross-sectional study conducted in the neuromedical and ophthalmology clinic of a tertiary center from November 27, 2017, to May 2019. This study adheres to the tenets of the Declaration of Helsinki and was approved by the local ethical boards on November 1, 2017 (USM/JEPeM/17070356).

All participants had given their written informed consent prior to their inclusion in the study. Twenty-six NMO cases were selected. The included patients were diagnosed as neuromyelitis optica spectrum disorder (NMOSD) based on the 2015 international panel for NMO diagnosis criteria,^[5] where it requires at least 1 of 6 core clinical characteristics which are (1) ON, (2) acute myelitis, (3) area postrema syndrome, (4) acute brainstem syndrome, (5) acute diencephalic clinical syndrome, and (6) symptomatic cerebral syndrome together with the detection of AQP4-immunoglobulin (Ig) G. In NMOSD without AQP4-IgG, at least 2 core clinical characteristics must be present where at least one is fulfilling the first three clinical characteristics. Diagnosis is only confirmed after additional magnetic resonance imaging is done as reflected in Table 1. The final confirmation of NMO in the patients was further confirmed by a neurologist. NMO patients with unilateral ON which were diagnosed over a period of 6 months were included in the study. Besides that, the individuals identified must be able to ambulate and undergo examinations in the clinic such as visual acuity testing, slit-lamp examination, contrast sensitivity

testing, visual field testing, color vision testing, and optical coherence tomography (OCT). Healthy controls consist of patient's families and clinic staffs.

The exclusion criteria for both the groups are concurrent neurodegenerative diseases (Parkinson's disease and Alzheimer's disease), previous history of ocular trauma, history of intraocular surgery, optic neuropathies such as glaucoma hereditary, infectious, ischemic, compressive, or toxic optic neuropathy, underlying retinopathy or maculopathy due to hereditary or acquired conditions, and refractive error of more than +3.00 or more than -3.00 diopters and impaired media opacity including corneal scar, significant cataract, and vitreous hemorrhage that affect the quality of OCT image.

Universal sampling was also conducted on NMO patients by Hospital Sultanah Bahiyah (HSB) and Hospital Universiti Sains Malaysia (HUSM) neuromedical and ophthalmology clinic.

Data collection and analysis

The demographic data (age, race, and gender), duration of illness, previous ocular surgery or treatment, and systemic comorbid were obtained through history taking and medical records. Those who fulfilled the selection criteria were explained the nature of the study and written consent were obtained. All patients underwent a comprehensive ophthalmological examination that included best-corrected visual acuity (BCVA), slit-lamp examination, dilated fundus examination, and applanation tonometry. The visual acuity with appropriate refraction was measured using a Snellen chart and was recorded as logarithm of minimum angle of resolution acuity. Peripapillary RNFL thickness measurement was acquired with Heidelberg spectralis spectral-domain OCT (Heidelberg Engineering).

Table 1: Comparison of the demographic data in fellow eye of neuromyelitis optica with unilateral optic neuritis and control groups

Variable	NMO (non-ON eyes) (n=26), n (%)	Control (n=26), n (%)	P
Age (years), median (IQR)	32.5 (12)	28.5 (8)	0.062 ^a
Gender			
Male	7 (26.9)	10 (38.5)	0.375 ^b
Female	19 (73.1)	16 (61.5)	
Race			
Malay	25 (96.2)	22 (84.6)	0.350 ^c
Chinese	1 (3.8)	4 (15.4)	
Duration of illness, median (IQR), years	5 (4)	NA	NA
Laterality of the eye			
Right	13 (50.0)	26 (100)	<0.001 ^b
Left	13 (50.0)	0 (0)	
AQP4-IgG			
Positive	21 (80.8)	NA	NA
Negative	5 (19.2)		

^aMann-Whitney U-test, ^bChi-square test, ^cFisher's exact test. NMO=Neuromyelitis optica, NA=Not available, ON=Optic neuritis, IQR=Interquartile range

The peripapillary RNFL thickness was determined using the device's standard protocol from a circular scan around the optic nerve head. Peripapillary RNFL thickness values were divided into four quadrants. The superior and inferior quadrants were further divided into nasal and temporal sectors. The software automatically compares an average RNFL thickness with a normative database.

Visual field analysis using Humphrey perimetry 30-2 full-threshold SITA algorithm (Zeiss Meditec, Dublin, California, USA) was employed. Mean deviation (MD) measured in decibels was recorded too. Visual field test results were used if the false-positive, false-negative, and fixation loss scores measured <33%.

Functional acuity contrast test (FACT) was also used to evaluate contrast sensitivity. All individuals were tested under monocular vision at five different spatial frequencies (1.5, 3, 6, 12, and 18 cycles per degree [CPD]). The contrast sensitivity was then recorded as the lowest contrast level achieved by a patient for each spatial frequency. Each contrast value for each spatial frequency was transferred into a logarithmic scale according to standardized values. Color vision was also assessed using Farnsworth panel D-15. Types of color defect (protan, deutan, or tritan) were recorded.

All statistical analyses were calculated using the Statistical Package for Social Sciences version 24 (IBM, Armonk, New York, USA). For data with

normal distribution, differences between evaluations of peripapillary RNFL thickness in fellow eye in NMO with unilateral ON and healthy controls were compared using independent *t*-test, whereas, for nonnormally distributed data, Mann-Whitney U-test was used. Pearson's Chi-square test was also used for a comparison in categorical data, with the assumption of <20% has expected count <5, whereas if the assumption of >20% has expected count <5, Fisher's exact test was used. The linear correlation between the structural and functional parameters was determined using nonparametric Spearman rho correlation coefficient, as all the data were skewed. The strength of the correlation was obtained using the guide for the absolute value of *r*.

Results

Demographic data

Twenty-six patients with NMO (no history of ON) and 26 healthy controls were included in the study. The median (interquartile range [IQR]) age of the NMO patients was 32.5 (12) years and the median (IQR) age of the healthy controls was 28.5 (8) years. Age (*P* = 0.062), gender (*P* = 0.375), and race (*P* = 0.350) did not show statistically significant difference between NMO patients and healthy controls. The median time from the diagnosis of NMO was 5 years. Female was predominant in the NMO group (73.1%, *n* = 19). Majority of the individuals in both the groups were Malay (90.4%, *n* = 47). In the NMO

Table 2: Comparison of retinal nerve fiber layer thickness in fellow eye of neuromyelitis optica with unilateral optic neuritis and control groups

RNFL	NMO (non-ON eyes)	Control	Mean difference (95% CI)	<i>P</i>
Superior temporal, mean (SD), μm	132.19 (10.96)	150.50 (15.58)	18.31 (10.80, 25.81)	<0.001 ^a
Superior nasal, mean (SD), μm	110.65 (21.14)	122.46 (18.81)	11.81 (0.66, 22.95)	0.038 ^a
Nasal, mean (SD), μm	72.35 (7.19)	77.81 (10.79)	5.462 (0.35, 10.57)	0.037 ^a
Inferior nasal, mean (SD), μm	106.96 (17.66)	115.38 (23.07)	8.423 (-3.02, 19.87)	0.146 ^a
Inferior temporal, median (IQR), μm	143.50 (14.00)	157.00 (15.00)	-	<0.001 ^b
Temporal, mean (SD), μm	72.54 (9.15)	78.15 (9.67)	5.62 (0.371, 10.86)	0.036 ^a
Central, mean (SD), μm	98.19 (9.30)	107.00 (6.82)	8.81 (4.266, 13.35)	<0.001 ^a

^aIndependent *t*-test, ^bMann-Whitney U-test. RNFL=Retinal nerve fiber layer, SD=Standard deviation, ON=Optic neuritis, IQR=Interquartile range, NMO=Neuromyelitis optica, CI: Confidence interval

Table 3: Comparison of retinal nerve fiber layer thickness in fellow eye of neuromyelitis optica with unilateral optic neuritis between seropositive and seronegative neuromyelitis optica groups

RNFL	Seropositive NMO (non-ON eyes) (<i>n</i> =21)	Seronegative NMO (non-ON eyes) (<i>n</i> =5)	Mean difference (95% CI)	<i>P</i>
Superior temporal, mean (SD), μm	132.33 (10.11)	131.6 (15.47)	0.733 (-12.22, 10.75)	0.90 ^a
Superior nasal, median (IQR), μm	104.00 (22.00)	110.00 (41.00)	-	0.47 ^b
Nasal, mean (SD), μm	71.57 (6.95)	75.60 (8.05)	4.03 (-3.31, 11.37)	0.27 ^a
Inferior nasal, mean (SD), μm	105.38 (19.31)	113.60 (3.91)	8.22 (-9.96, 26.40)	0.36 ^a
Inferior temporal, median (IQR), μm	141.00 (17.00)	146.00 (15.00)	-	0.26 ^b
Temporal, mean (SD), μm	73.24 (9.41)	69.60 (8.20)	-3.64 (-13.10, 5.82)	0.44 ^a
Central, median (IQR), μm	96.00 (9.00)	109.00 (25.00)	-	0.67 ^b

^aIndependent *t*-test, ^bMann-Whitney U-test. RNFL=Retinal nerve fiber layer, SD=Standard deviation, ON=Optic neuritis, IQR=Interquartile range, NMO=Neuromyelitis optica, CI=Confidence interval

group, 80.8% ($n = 21$) were seropositive for AQP4-IgG and 19.2% ($n = 5$) were seronegative. In the recruited NMO patients, 50% of eyes without history of ON were right eyes. In the control group, only right eye results were included in the study. Distribution of age, gender, race, duration of illness, laterality of eye, and serology status for AQP4-IgG is shown in Table 1.

Retinal nerve fiber layer thickness

The overall and different quadrant results of RNFL thickness of NMO and control groups are reflected in Table 2. In the non-ON eyes of NMO patients, the RNFL thickness was thinner in all quadrants as compared to the control group. The differences were statistically significant in all quadrants except inferior nasal quadrant ($P = 0.146$).

The RNFL thickness in the non-ON eyes of seropositive NMO patients was slightly thinner in all quadrants as compared to seronegative NMO group except at superior temporal quadrant where the RNFL thickness was comparable. However, the differences are not statistically significant [Table 3].

Best-corrected visual acuity/contrast sensitivities/color vision

As shown in Table 4, NMO patients with eyes without ON have a slightly lower BCVA as compared to the controls (0.20 vs. 0.00, $P = 0.071$). However, the finding was not statically significant [Table 4]. Besides that, contrast sensitivity was also affected in NMO patients in all five spatial frequencies of FACT chart (1.5, 3, 6, 12, and 18 CPD with $P = 0.014$, $P = 0.001$, $P = 0.002$, $P = 0.051$, and $P = 0.366$, respectively) [Table 5]. In NMO patients, 34.6% had normal color vision. For those with abnormal color vision, no specific types of color defect were found. The results are shown in Table 6.

Table 4: Comparison of best-corrected visual acuity in fellow eye of neuromyelitis optica with unilateral optic neuritis and control groups

BCVA	NMO (non-ON eyes)	Control	Z	P ^a
LogMAR, median (IQR)	0.20 (0.20)	0.00 (0.20)	-1.808	0.071

^aMann-Whitney U-test. ON=Optic neuritis, IQR=Interquartile range, NMO=Neuromyelitis optica, BCVA=Best-corrected visual acuity

Table 5: Comparison of contrast sensitivity in fellow eye of neuromyelitis optica with unilateral optic neuritis and control groups

Contrast sensitivity, spatial frequency	NMO (non-ON eyes)	Control	Z	P ^a
1.5, median (IQR), log	1.56 (0.34)	1.70 (0.07)	-2.449	0.014
3, median (IQR), log	1.68 (0.23)	1.90 (0.18)	-3.213	0.001
6, median (IQR), log	1.73 (0.37)	1.95 (0.30)	-3.031	0.002
12, median (IQR), log	1.34 (0.74)	1.63 (0.30)	-1.949	0.051
18, median (IQR), log	1.08 (0.91)	1.16 (0.47)	-0.904	0.366

^aMann-Whitney U-test. ON=Optic neuritis, IQR=Interquartile range, NMO=Neuromyelitis optica

Visual field

From the data given in Table 7, we observe that the median of MD of Humphrey visual field (HVF) in the fellow eye of NMO patients with unilateral ON was -3.16 dB, whereas it was -0.99 dB in the control group. The results of the visual field assessment are shown in Table 7. A significant difference was found between the NMO and control groups ($P < 0.001$). In assessing the pattern of visual field defect, the types of localized visual field loss are shown in Table 7.

Correlation of optic nerve functions and retinal nerve fiber layer thickness in fellow eye of neuromyelitis optica with unilateral optic neuritis

The contrast sensitivity that measured at different spatial frequencies correlates with the RNFL thickness in different quadrants and the findings are reflected in Table 8. The findings revealed a statistically significant moderate correlation between RNFL thickness at inferior temporal and contrast sensitivity at 1.5 CPD ($r = 0.516$, $P = 0.007$), inferior temporal and contrast sensitivity at 3 CPD ($r = 0.423$, $P = 0.031$), and superior nasal and contrast sensitivity at 18 CPD ($r = 0.462$, $P = 0.017$). Inferior nasal quadrant thickness was moderately correlated with all spatial frequencies of contrast sensitivity except at 1.5 CPD which had a weak correlation (3 CPD, $r = 0.437$; 6 CPD, $r = 0.398$; 12 CPD, $r = 0.446$; and 18 CPD, $r = 0.478$). These moderate correlations were statistically significant (3 CPD, $P = 0.025$; 6 CPD, $P = 0.044$; 12 CPD, $P = 0.022$; and 18 CPD, $P = 0.013$). The correlation between visual acuity and MD of HVF with RNFL thickness ranged from very weak to weak. The inferior nasal quadrant thickness was significantly correlated with visual acuity.

Discussion

Prevalence

In general, NMO has a poor prognosis and low prevalence. Two studies were conducted to measure the prevalence rate, age range, and gender most commonly affected by the NMO. Data collected from the two nation-wide studies and the current study that we undertook were compared to a similar study conducted in Japan. There seems to be a striking similarity between the two countries in terms of prevalence rate, age range, and gender. In the first nationwide study, the crude prevalence rate of NMO

was 1.94 per 100,000.^[6] In a similar study that was carried out in Penang, the prevalence of NMOSD was 1.85 per 100,000 population.^[7] Correspondingly, the prevalence rate in Japan was 2 per 100,000 population.^[8] In addition, the onset age ranged from 32.6 to 45.7 years old.^[9] Similarly, the local studies conducted revealed that the median (IQR) age of NMO patients was 32.5 (12) years old. Females are predominant in NMO.^[10,11] This is comparable to the our study where 73.1% of NMO patients were female. The two studies only differ in terms of ethnicity. Majority of our study participants were Malays (90.4%). This is because this study was conducted in Kedah and Kelantan where the Malay population is predominant in both the states. In 2014, Viswanathan and Wah conducted a study showed that 67.7% of the Malaysians who were diagnosed with idiopathic inflammatory demyelinating disease were AQP4-IgG seropositive.^[12] However, in our study, 80.8% ($n = 21$) of the NMO patients were seropositive for AQP4-IgG.

Table 6: Comparison of color vision in fellow eye of neuromyelitis optica with unilateral optic neuritis and control groups

Color vision (D15)	NMO (non-ON eyes)	Control	P
Normal	9 (34.6)	26 (100)	<0.001 ^a
Abnormal	17 (65.4)	0	

^aChi-square test. ON=Optic neuritis, NMO=Neuromyelitis optica

Table 7: Comparison of visual field in fellow eye of neuromyelitis optica with unilateral optic neuritis and control groups

HVF	NMO (non-ON eyes) (%)	Control (%)	P
MD, median (IQR)	-3.16 (2.91)	-0.99 (1.91)	<0.001 ^a
Normal	12 (46.2)	26 (100)	<0.001 ^b
Abnormal	14 (53.8)	0	
One quadrant	5 (19.2)	0	
Hemianopia	1 (3.8)	0	
Central/centrocecal	2 (7.7)	0	
Arcuate	2 (7.7)	0	
Enlarged blind spot	3 (11.5)	0	
Periphery	1 (3.8)	0	

^aMann-Whitney U-test, ^bChi-square test. ON=Optic neuritis, NMO=Neuromyelitis optica, IQR=Interquartile range, HVF=Humphrey visual field, MD=Mean deviation

Table 8: Correlation of optic nerve functions and retinal nerve fiber layer thickness in fellow eye of neuromyelitis optica with unilateral optic neuritis

Quadrants of RNFL	Central (r, P)	Superior temporal (r, P)	Superior nasal (r, P)	Nasal (r, P)	Inferior nasal (r, P)	Inferior temporal (r, P)	Temporal (r, P)
BCVA (Log MAR)	-0.159, 0.438	-0.154, 0.452	-0.163, 0.425	-0.350, 0.080	-0.398, 0.044	-0.271, 0.180	-0.033, 0.874
Contrast sensitivity							
1.5	0.273, 0.177	0.239, 0.240	-0.063, 0.761	0.293, 0.146	0.331, 0.099	0.516, 0.007	0.278, 0.169
3	0.339, 0.090	0.296, 0.142	0.231, 0.257	0.308, 0.126	0.437, 0.025	0.423, 0.031	0.291, 0.149
6	0.317, 0.115	0.299, 0.138	0.206, 0.313	0.385, 0.052	0.398, 0.044	0.310, 0.123	0.333, 0.096
12	0.235, 0.248	0.185, 0.365	0.342, 0.087	0.382, 0.054	0.446, 0.022	0.119, 0.561	0.144, 0.482
18	0.286, 0.157	0.184, 0.369	0.462, 0.017	0.288, 0.154	0.478, 0.013	0.071, 0.729	0.184, 0.367
HVF (MD)	0.096, 0.641	0.007, 0.972	0.266, 0.189	0.092, 0.656	0.355, 0.075	0.094, 0.647	0.054, 0.192

r, Spearman's rho. RNFL=Retinal nerve fiber layer, BCVA=Best-corrected visual acuity, Log MAR=Logarithm of minimum angle of resolution, HVF=Humphrey visual field, MD=Mean deviation

Clinical manifestation

The attacks of ON in NMO are commonly unilateral (80%) than bilateral (20%).^[13] Our study only considers patients with unilateral ON and the unaffected eyes that have been selected. This is done to help clinicians to determine the presence of subclinical destruction of the optic nerve in the fellow eyes without a history of ON in NMO patients. The results of the study shows that the onset of ON and myelitis usually occurs sequentially rather than simultaneously.^[14] The interval separating disease-defining attacks of ON and myelitis can be quite wide. It ranges from years to decades. Ocular pain with profound and persistent visual loss is a hallmark of ON in NMO.^[15]

Demographic data

In our study, the median age of healthy controls was 28.5 years (8). It was slightly lower as compared to NMO group, 32.5 (12). Although the difference was not statistically significant ($P = 0.062$), it may still affect the difference in RNFL thickness, contrast sensitivity, and visual field.

Retinal nerve fiber layer thickness

In this study, we evaluate peripapillary RNFL thickness and assessed the correlation between the morphological changes and optic nerve functions of NMO patients without a history of ON. Three to six months after ON is the optimal period to detect RNFL thinning and to predict visual recovery. As such, initiation of regenerative strategies specifically aimed at restoring optic nerve functions should be carried out within 6 months of the acute ON event.^[16] It is important to take note that retinal damage is attack related and does not occur progressively.^[1,17] OCT shows a more severe retinal damage after ON episodes in NMO than in relapsing-remitting MS. Identification of substantial RNFL loss (>15–20 μm) after ON should prompt clinicians to consider the patients as having a NMO spectrum condition.^[4,18] Besides that, Ratchford *et al.* found that in patients with no history of ON, the RNFL thickness was mildly thinner in NMO group (97.9 μm)

in comparison to the control group (102.4 μm). However, it was not statistically significant. The lack of statistical significance in NMO group with no history of ON could be attributed to the small sample sizes ($n = 8$).^[4] Other studies carried out suggested that subclinical ON in NMO is uncommon. In addition, RNFL thickness in NMO patients without a history of ON was usually normal.^[1,18] In contrast, Merle *et al.* found that in NMO patients with eyes in the absence of history of ON, the average RNFL thickness was thinner as compared to the control group (89.28 \pm 24.73 μm vs. 106.24 \pm 12.46 μm).^[19] A study conducted by Sotirchos *et al.* also concluded that subclinical involvement of anterior visual pathway may occur in NMO patients. They found that in eyes without history of ON in NMO patients, macular RNFL thickness, ganglion cell layer, inner plexiform layer, and outer nuclear layer thinning was detected.^[20] This was supported by Syc *et al.* where thinning of the ganglion cell layer and inner plexiform layer was reported.^[21] In our study, RNFL thickness in NMO patients without a history of ON was thinner in all quadrants and the differences were statistically significant as compared to the control group except inferior nasal quadrant. This can be postulated that an ON attack might cause a small degree of retinal injury to contralateral eye causing a subclinical damage.^[4] Other possibilities include the thinner RNFL in the eye without a history of ON that might be due to an ON independent process where there is a possibility of chronic on-going axonal injury in NMO patients.^[4,19] However, a larger study cohort needed to determine the actual pathogenesis.

Another important factor that might affect the RNFL thickness in NMO patients could be the AQP4-IgG seropositivity. AQP4-IgG seropositivity is often associated with poorer visual outcome and longer length of cord lesions.^[22] However, from the literature search, no related study was found in comparison of the RNFL thickness between the seropositive and seronegative NMO patients. In our study, we found that the RNFL thickness in the non-ON eyes of seropositive NMO patients was slightly thinner in all quadrants as compared to seronegative NMO group except at the superior temporal quadrant. This can be due to the natural history of NMO where the seronegative patients are considered as experiencing a monophasic disease, while seropositivity patients usually have a relapsing disease.^[23] ON attacks in NMO are often occur near the optic chiasm; there is a potential carryover effect could affect the contralateral optic nerve after the unilateral ON.^[24]

Best-corrected visual acuity/contrast sensitivity

Studies conducted have shown that in NMO patients who do not have any history of ON, their BCVAs were

slightly poorer than the control group. However, the difference was not significant. The results of the study on visual functions in NMO patients that we conducted seem to concur with those conducted by French^[3] and Americans.^[4] These studies conclude that visual acuities in non-ON eyes in NMO patients showed no significant differences as compared to the control group. Linking to the study that we had carried out, we also found that NMO patients experienced a reduced contrast sensitivity in all five spatial frequencies despite not having any history of ON in the eye that had been selected. The results were statistically significant at 1.5, 3, and 6 CPD. This differs from the studies conducted by French and Americans where it was reported that there were statistically no significant differences in contrast sensitivity between NMO and control group.^[3,4]

Visual field defect

NMO generally causes more severe visual field defects which may manifest with bitemporal or homonymous visual field defects.^[25] Altitudinal hemianopia is the most common finding in NMO patients after an ON.^[26] Merle *et al.* also found that 12.1% of the NMO patients experienced an altitudinal visual field defect. This suggests that it might be related to vascular deficit during an ON episode in NMO.^[3,26] In NMO patients with no history of ON, 50% had normal visual field.^[3] This is consistent with our results where 46.2% ($n = 12$) had normal visual field. Surprisingly, the related study found that the another half of their patients had paracentral scotoma (30%) and diffuse abnormalities (20%).^[3] In our study, variable patterns of localized field defect were detected in the eyes without a history of ON. These include one quadrant, hemianopia, centrocecal, arcuate, enlarged blind spot, and peripheral visual field defect.

Correlation of optic nerve functions and retinal nerve fiber layer thickness in fellow eye of neuromyelitis optica with unilateral optic neuritis

A study done by Merle *et al.* found that in eyes with a history of ON in NMO, there is a significant correlation between the average thickness of RNFL with visual acuity and contrast sensitivity. However, no correlation was found between the average thickness of RNFL and color vision.^[19] From the literature review, only very few studies were carried out on the functional and structural parameters in NMO patients in the eyes without ON.^[3,4] However, no correlation tests were performed. This study reports the first results obtained regarding the structural and functional correlations in subclinical optic neuropathies in eyes with no history of ON in NMO patients. We found that there is a moderate correlation between RNFL thickness with visual acuity and contrast sensitivity. However, only weak correlation is found between the MD of HVF and RNFL thickness.

Limitations and recommendations

1. There is lacking long-term evaluation and systemic morbidity assessment. This study is a cross-sectional study where the duration of disease and the natural history of NMO were not been studied. NMO is known to be a chronic inflammatory demyelinating disease with a higher relapsing rate, especially in those with AQP4-IgG seropositive. Kurtzke Scale from an Expanded Disability Status Scale (EDSS) can be used to assess the disease's global handicap. The handicap progression can be related to the disease duration and the severity of visual loss.^[3] Ratchford *et al.* identified a strong correlation between RNFL thickness and EDSS in patients with NMO.^[4] In future studies, the RNFL thickness should be evaluated further in a longer duration to determine the severity and the rate of progressive RNFL loss related to this chronic disease
2. There is no evaluation on visual electrophysiology tests in this study. Visual electrophysiology tests such as visual evoked potential (VEP) and electroretinogram are the tests to evaluate the function of visual pathway from the retina to the occipital cortex. These tests may aid the disease detection and monitoring. Prolonged latency in VEP signifies demyelination, whereas shortening of the latency indicates re-myelination. If the test was performed in the eyes with no history of ON, a subclinical optic nerve involvement can be detected too. However, these tests were not performed in our study as the tests are not available in one of our data collection centers. We suggest the tests to be carried out in future studies so that a complete structural and functional assessment can be obtained
3. There is no retrospective entry regarding the treatment of acute attack of ON or long-term management in prevention of relapses. We suggest that in future, a prospective interventional study can be done to determine the RNFL thickness in pre- and posttreatment for ON. This may help us to identify whether there is a possibility that early and prompt treatment is able to limit the disease activity both in the ON eye as well as non-ON eyes.

Conclusion

In conclusion, our study showed that the fellow eyes of NMO patients with unilateral ON have a significant reduction in RNFL thickness in all quadrants except the inferior nasal quadrant. All the optic nerve function parameters have a subtle early change as compared to the control group. This signifies that a subclinical retinal damage is present even in the eyes with no history of ON. Patients with NMO in the absence of ON had optic nerve dysfunction that correlates with structural changes (RNFL thickness). There is a moderate correlation between RNFL thickness and contrast

sensitivity. Weak correlation was found between the RNFL thickness with visual acuity and MD of visual field test.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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