

Study of retinal nerve fiber layer analysis using optical coherence tomography in different demyelinating diseases and its correlation with the severity of visual impairment

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Purpose: This purpose of this study was to find the association between severity of visual impairment and retinal nerve fiber layer (RNFL) thickness loss in different demyelinating diseases using optical coherence tomography (OCT) and, simultaneously, assess the fellow eye for subclinical RNFL thickness loss. **Methods:** This cross-sectional, observational study included 60 eyes of 30 patients above the age of 20 years with diagnosed cases of multiple sclerosis (MS), neuromyelitis optica (NMO), and clinically isolated syndrome (CIS) who had history of (h/o) optic neuritis (ON) attack were included. Participants included in the study group underwent best-corrected visual acuity (BCVA) measurement, color perception, swinging flashlight test, slit-lamp examination, and dilated fundus examination (DFE). RNFL thickness was measured using spectral domain OCT (SD-OCT) (Optovue RTVue-V6.11 A Fourier). Intergroup analysis of RNFL thickness was done using a Chi-square test ($P < 0.05$ was considered significant). Spearman's rank correlation coefficient (Spearman's ρ) was used for association ($\rho < 0.963$ was considered significant). **Results:** RNFL thickness was significantly reduced in patients with NMO than MS, while all patients of CIS had the highest RNFL thickening ($P = 0.00048$). Lower visual function scores correlated with reduced average overall RNFL thickness, and this association was statistically significant in affected ($R = 0.942$) and fellow eyes ($R = 0.963$). **Conclusion:** The severity of visual impairment significantly correlated with the severity of axonal loss in affected as well as the fellow eye. NMO is associated with more widespread axonal injury in the affected optic nerve. Hence, RNFL thickness is an indicator of the progression of visual impairment in demyelinating diseases and OCT can help distinguish the etiology and, therefore, may be useful as a surrogate marker of axonal involvement in demyelinating diseases.

Key words: Multiple sclerosis, neuromyelitis optica, optic neuritis, optical coherence tomography, retinal nerve fiber layer

The retinal nerve fiber layer (RNFL) is composed predominantly of unmyelinated axons of retinal ganglion cells, which become myelinated within the optic nerve to form a white matter tract and convey the visual information from the retina to the lateral geniculate nucleus.^[1] Therefore, measurements of the RNFL should give relatively direct measures of the number of axons present.

Axonal loss has been recognized in the RNFL in the early stages of demyelinating diseases, such as multiple sclerosis (MS) and neuromyelitis optica (NMO).^[2,3] MS is a demyelinating disease having a relapsing–remitting type of inflammation, and although sparing of axons is typical, indirect evidence suggests that axonal loss is the major cause of irreversible neurological disability.^[4] Nearly half of the MS patients develop optic neuritis (ON) and it is the heralding event in 15–20% of the patients.^[5] Even without a history of (h/o) ON, the RNFL by optical coherence tomography (OCT) in MS is typically thinner than in normal controls.^[2] NMO is

another type of Demyelinating disease that has a predilection for the optic nerve and spinal cord characterized by often severe, recurrent episodes of optic neuritis and transverse myelitis. The disease course can be devastating and distinct from MS.^[3] Clinically isolated syndrome (CIS) is often the first manifestation of MS, and it typically affects the optic nerve, brain, and spinal cord.

CIS is a term that describes a first clinical episode that last for at least 24h and occur in the absence of fever or infection, with no clinical features of encephalopathy^[6] with concern for demyelination in the setting of an episode but not enough evidence to meet criteria for MS.

OCT has enabled the measurement of peripapillary RNFL loss with micron-level resolution and excellent reproducibility.

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It uses low-coherence interferometry (LCI) to generate noninvasive, *in vivo*, high-resolution (<10 μm), cross-sectional images of the RNFL by measuring backscatter of the infrared light.^[7]

Methods

It was a cross-sectional observational study that included 60 eyes of 30 patients above 20 years of age with diagnosed cases of MS, NMO, and CIS who had h/o attack of ON from June 2016 to December 2017. Patients having severe cognitive dysfunction and unwilling to give consent were excluded.

All patients underwent standard ocular examination protocol, which included best-corrected visual acuity (BCVA) measurement by Snellen VA chart, color perception by Ishihara pseudoisochromatic plates (PIP), swinging flashlight test (for relative afferent pupillary defect (RAPD) evaluation), slit-lamp examination, and dilated fundus examination (DFE). RNFL thickness was measured using spectral domain (SD-OCT) (Optovue RTVue-V6.11 A Fourier).

Visual acuity

The VA of all cases was measured with a retroilluminated Snellen 20-ft wallchart and recorded as the 4m logarithm of the minimum angle of resolution (logMAR acuity). Refraction was done followed by the BCVA measurement. Refractive errors were corrected using wide-angle lenses when needed. In our study, out of the 30 patients only 2 patients of relapsing–remitting MS (RRMS) stage had a h/o moderate myopia (2–4 D), 6 patients (2 of NMO, 1 of CIS, and 3 of MS) had h/o presbyopia while remaining patients had no h/o spectacle use prior to attack of ON.

OCT examination

All OCT imaging was obtained by a single observer. RNFL images were acquired by taking three circular 3.4 mm diameter scans, centered on the optic disc, the mean of which was used to express RNFL thickness. The thicknesses of the quadrants of the RNFL were automatically calculated by the OCT device software as the distance between the first reflection at the vitreoretinal interface and anterior boundary of the second reflective layer corresponding to the retinal pigment epithelium and choriocapillaris. The average values of three different measurements per quadrant (superior, inferior, nasal, and temporal) were calculated. The overall data obtained in all quadrants (12 values averaged) were identified as the RNFL overall.

The sectors were defined in a clockwise order for the right eye (RE) and counterclockwise for the left eye (LE). Following ranges were assigned for overall RNFL thickness (μm) measured by OCT:

1. >115 μm
2. 95–114 μm
3. 65–94 μm
4. 35–64 μm
5. <35 μm .

Following the last attack of ON, the mean duration at which OCT was performed was within 3 months in RRMS, 2 years in secondary progressive MS (SPMS), and 8 months in NMO patients. While in CIS patients, the examination was done within 1–5 days of diagnosis.

Results

Thirty subjects completed the study (6 NMO, 6 CIS, and 18 MS) in 18 months duration. Among the 18 diagnosed cases of MS included in the study, 12 were of relapsing–remitting MS (RRMS) while 6 were of SPMS. Only 2 cases of MS had a h/o bilateral attack of ON. There were no significant differences among the three groups for mean age (25–45 years) and gender predilection (female predominance) [Tables 1a and b].

Out of a total of 30 patients, 12 patients were not able to perform a color vision test because of the gross diminution of vision. However, in the remaining cases of the patients who were able to read the Ishihara chart, only 2 (6.66%) cases showed a red–green deficiency. The pupillary reaction was observed to be sluggishly ill sustained in six eyes and absent in four eyes (afferent pupillary defect [APD]), while 22 eyes were found to have relative APD (RAPD). Fundus examination revealed six eyes with optic disc pallor, 22 eyes with blurred and hyperemic disc margins, while only 4 eyes had optic atrophy.

After a clinical episode of ON, the overall unadjusted mean RNFL for those with NMO was significantly lower than those with MS, while all the patients with CIS had the highest RNFL thickening. [Figs. 1 and 2 demonstrating RNFL thickness of both eyes in a patient affected with NMO]. Estimated means by repeated measures yielded mean RNFL thickness of 45.5 μm for NMO, 66.15 μm for MS, and 111.5 μm for CIS patients [Table 2] Examining the quadrants individually showed that the temporal quadrant is predominantly and severely affected. In fellow eyes also there were 56.25% cases showing RNFL thinning predominantly in temporal quadrant. On the simultaneous assessment of fellow eyes, it was found that mean RNFL thinning (75.18 μm) in MS patients is significantly greater than in the fellow eyes of NMO patients (87.50 μm) [Table 3].

Table 1a: Summary of MS, NMO, and CIS cases

Variables	MS	NMO	CIS
Number	18	6	6
Age (Years; mean [range])	25-45	26-48	25-40
Sex (F/M)	13/5	4/2	4/2
VA-affected eye (mean of logMAR)	1.075	1.334	0.466
RNFL-affected eyes, (μm ; mean)	66.15	45.5	111.5
RNFL fellow eyes (μm ; mean)	75.18	87.50	116.66

Table 1b: Age distribution of total cases

Age Groups	No. of Cases			Percentage
	MS	NMO	CIS	
15-24	1	-	-	3.33%
25-34	7	4	4	50.0%
35-44	8	1	1	33.33%
45-50	1	-	1	6.66%
>50	1	1	-	6.66%
Total		30		100%

MS=Multiple sclerosis, NMO=Neuromyelitis optica, CIS=Clinically isolated syndrome, VA=Visual acuity, LogMAR=Logarithm of the minimum angle of resolution, RNFL=Retinal nerve fiber layer

Table 2: Mean RNFL thickness in fellow eyes and “its comparison between subgroups”

Overall RNFL thickness (µm)	MS	Percentage	NMO	Percentage	CIS	Percentage
>115	0	0	0	0	3	50
95-114	0	0	0	0	3	50
65-94	13	65	1	16.66	0	0
35-64	7	33	3	50	0	0
<35	0	0	2	33.34	0	0
	MS	Percentage	NMO	Percentage	CIS	Percentage
Mean RNFL Thickness	66.15	-	45.5	-	111.5	-
Total No. of Cases	20	-	6	-	6	-

RNFL=Retinal nerve fiber layer, MS=Multiple sclerosis, NMO=Neuromyelitis optica, CIS=Clinically isolated syndrome

Table 3: Mean RNFL thickness in affected eyes and “its comparison between subgroups”

Overall RNFL Thickness (µm)	MS	Percentage	NMO	Percentage	CIS	Percentage
>115	3	18.75	0	0	5	83.33
95-114	4	25	3	50	1	16.64
65-94	8	50	1	16.66	0	0
35-64	1	6.25	2	33.34	0	0
<35	0	0	0	0	0	0
	MS	Percentage	NMO	Percentage	CIS	Percentage
Mean RNFL Thickness	75.18	-	87.50	-	116.66	-
Total No. of Cases	16	-	6	-	6	-

Chi-square value is 19.30, P value is 0.013 (<0.05). RNFL=Retinal nerve fiber layer, MS=Multiple sclerosis, NMO=Neuromyelitis optica, CIS=Clinically isolated syndrome

Table 4: Correlation between RNFL thickness loss and VA in Affected eye

VA	No. of affected eyes	Mean of overall RNFL thickness (µm)	Percentage
NOPL	2	56.32	6.25
HM/PL	4	57.75	12.5
CF	9	66.50	28.12
6/60-6/36	7	58.12	21.87
6/24-6/18	7	78.11	21.87
6/12-6/9	3	90.46	9.37
Total	32		100

VA=Visual acuity, RNFL=Retinal nerve fiber layer, NOPL=No perception of light, HM/PL=Hand movements/Perception of light, CF=Counting

Associations were tested between the RNFL changes and visual functions for the subgroups using the Spearman’s rank correlation coefficient (Spearman’s ρ), and it was found that the severity of Visual impairment very well correlated with the severity of RNFL thinning and was statistically significant in affected ($R = 0.942$; $P = 0.00048$) [Fig. 3 and Table 4] as well as fellow eyes ($R = 0.963$; $P = 0.0048$) [Fig. 4 and Table 5].

Discussion

Our study demonstrated that ON occurred unilaterally in these diseases with only two cases showing reduced color vision. The demographic details revealed female preponderance with the mean age being 25–45 years. The pupillary reaction was observed to be sluggishly ill-sustained in 6 eyes and absent in four eyes (afferent pupillary defect [APD]), while 22 eyes

Table 5: Correlation between the mean of overall RNFL thickness and VA in the fellow eye

VA	No. of fellow eyes	Mean of Overall RNFL thickness	Percentage
NOPL	0	0	0
HMPL	0	0	0
CF	0	0	0
6/60-6/36	5	64.40	17.85
6/24-6/18	6	68.32	21.43
6/12-6/9	9	95.57	32.15
6/6	8	112.44	28.57
Total	28		100

VA=Visual acuity, RNFL=Retinal nerve fiber layer, NOPL=No perception of light, HM/PL=Hand movement/Perception of Light, CF=Counting finger

were found to have relative APD (RAPD), these findings corroborated with the study of Miller *et al.* (1978).^[8] The finding of significant RNFL thinning in MS patients following an attack of ON corroborates with an earlier study carried out by Costello *et al.*,^[9] who observed similar findings in the clinically affected eyes. This study further demonstrated that following a remote episode of ON, NMO was associated with more severe axon loss than MS, while the patients with CIS showed little or no variation in RNFL thickness. Ratchford *et al.*,^[10] in their study, confirmed the occurrence of greater loss of RNFL thickness in NMO than in MS patients, whereas Noval *et al.*^[11] found that all patients of CIS had normal overall RNFL thickness. Our study also found that the temporal

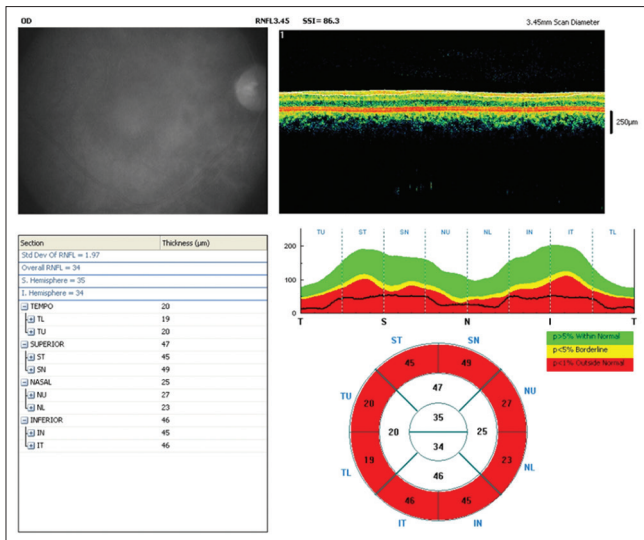


Figure 1: Demonstrating OCT of the RE of patient affected with NMO

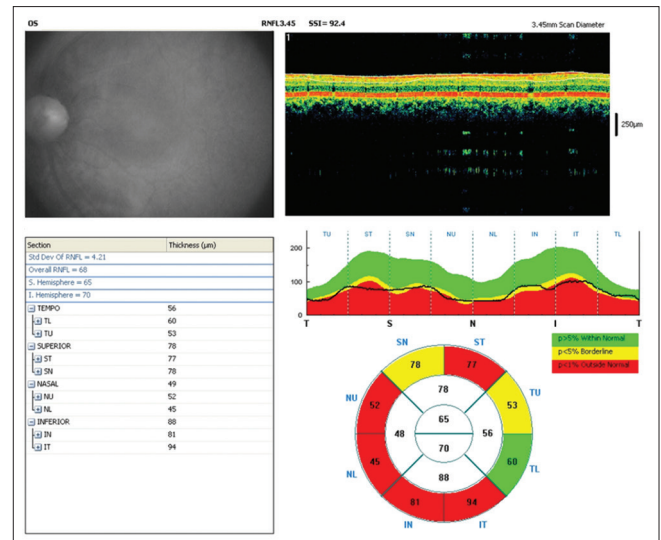


Figure 2: Demonstrating OCT of LE of patient affected with NMO

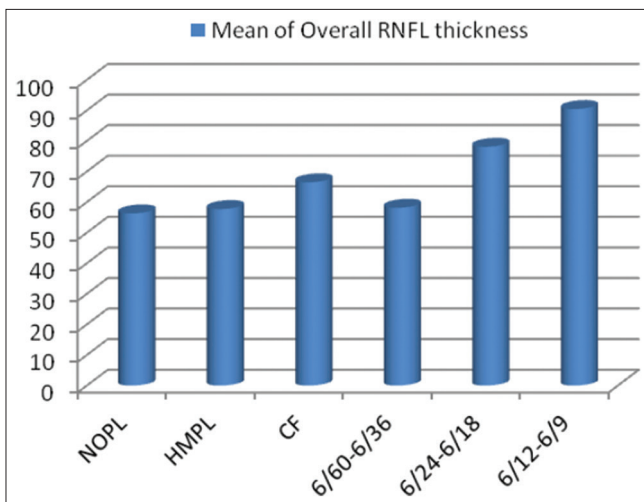


Figure 3: Demonstrating graph showing the correlation between visual impairment and RNFL thickness in the affected eye

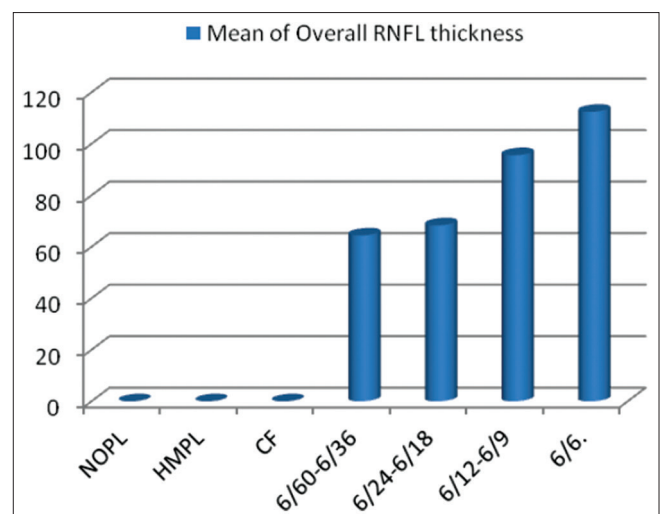


Figure 4: Demonstrating graph showing the correlation between visual impairment and RNFL thickness in the fellow eye

quadrants were affected to a greater magnitude, whereas the other quadrants were not demonstrably different indicative of affliction of the papillomacular bundle, which correlated with the study carried out by Parisi *et al.* (1999).^[12]

It is seen in our study that there is a value of overall RNFL thickness of <65 µm below which there is severe visual impairment (<logMAR 1.0 or worse) and a value of <35 µm from where complete visual recovery is hardly possible, which is in favor with the study done by Naismith *et al.*^[3] and Nakamura *et al.*,^[13] who agreed on the fact that there is a critical value of RNFL thickness below which further decrease of the RNFL lead to incomplete visual recovery, This critical value has been set at 71.41 µm. Below 50–52 µm, vision drops to ≤20/100.^[3] Hence, the severity of Visual impairment very well correlated with the severity of RNFL thinning, and it was statistically significant in affected ($R = 0.942$; $P = 0.00048$), as well as fellow eyes ($R = 0.963$; $P = 0.0048$). It was also found that the mean RNFL thinning (75.18 µm) in fellow eyes of MS patients is significantly greater than in the fellow eyes of NMO

patients (87.50 µm), suggesting that there is a more common occurrence of subclinical axonal loss in MS than in NMO. This is correlated with the study by Naismith *et al.*^[3] and Bennett *et al.*,^[14] who found the mean RNFL thickness loss of fellow eyes in MS was greater than the fellow NMO eyes. The data herein lend credence to the concept that OCT can be used to identify axon destruction in the optic nerve using RNFL thickness as a surrogate marker for axon loss.

Conclusion

OCT has provided a basis for correlating structural aspects of the anterior visual pathway, axonal loss with visual function in MS and NMO, assess subclinical axonal loss in patients with normal VA in the fellow eye, and even predict visual recovery in these patients by assessing the extent of the neuroaxonal injury.

Hence, evaluating the axonal damage and the severity of visual impairment by measuring RNFL thickness loss using

OCT is extremely useful in assessing the progression of visual loss in demyelinating diseases.

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Conflicts of interest

There are no conflicts of interest.

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