ORIGINAL RESEARCH PAPER

Volume-8 | Issue-4 | April-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ASSESSMENT OF RETINAL NERVE FIBER LAYER THICKNESS BY OPTICAL COHERENCE TOMOGRAPHY IN PATIENTS WITH MULTIPLE SCLEROSIS. A SINGLE INSTITUTION STUDY.

Ophthalmology

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ABSTRACT

BACKGROUND: Axonal loss is thought to occur early in the course of multiple sclerosis (MS). It is supposed to be associated with, and predictive of, neurologic deficits progressing to permanent disability. Optical coherence tomography (OCT) is used to measure axonal loss in the retinal nerve fibre layer (RNFL).

MATERIAL AND METHODS: An observational study was conducted on 20 patients of MS . All subjects underwent neurological examination (EDSS scoring) and OCT on two visits minimum 2 months apart.

RESULTS: Total of 40 eyes of 20 patients were subdivided into 14 eyes having optic neuritis (MS – ON group) and 26 eyes without optic neuritis. As the duration of disease increased, RNFL was found to be significantly thinned in all parameters except in the temporal quadrant. Average RNFL thickness were found to have negative correlation (r = -0.440) with disease duration. Negative correlation (r=-0.637) was also found between EDSS score change and average RNFL thickness change. The eyes having optic neuritis showed statistically significant RNFL thinning as compared to the eyes without optic neuritis.

CONCLUSIONS: The RNFL thickness is not only significantly thinner in those with history of optic neuritis, but it is also affected remarkably even in absence of prior optic neuritis; suggesting subclinical ongoing axonal loss in patients with MS

KEYWORDS

Optical coherence tomography; Retinal nerve fibre layer thickness; multiple sclerosis.

INTRODUCTION

Multiple sclerosis (MS) is primarily considered a demyelinating disease, but axonal loss is of critical importance since this pathologic change appears to correlate with a patient's ultimate disability[1]. Axonal loss is thought to occur early in the disease course and is thought to be to be associated with, neurologic deficits and is predictive of progression to permanent disability. MRI correlates with demyelination related disease severity but it does not identify axonal loss directly and so has poor correlation with neurological disability. Optical coherence tomography (OCT) is capable of imaging histologically identifiable layers of the retina in real time with highly refined resolution, accuracy and reproducibility. Its sensitivity allows direct visualization and measurement of retinal nerve fiber layer thickness (RNFLT) and macular volume with micron-scale resolution[2].

As optic neuritis (ON) is often the pivotal event in establishing the diagnosis in patients with MS, RNFLT is of particular interest. Optic disc pallor, loss of contrast sensitivity, visual field defects, and delayed latency of visual-evoked potentials (VEPs) to assess optic nerve dysfunction, may occur subclinically in many other patients[3]. Nearly 20% of all patients with MS present initially with ON, and overall 30–70% of MS patients develop ON during disease course[4,5]. Preliminary studies have found a loss of RNFL thickness in ON, likely due to axons that are destroyed in optic nerve[6,7]. Axonal loss in the RNFL, as measured by OCT, can potentially become a model to study axonal loss throughout the central nervous system in patients with MS. In this particular study, we intend to correlate RFNL thickness as measured by OCT with EDSS score as a clinical tool for neurological disability in patients of MS in Indian context.

MATERIAL AND METHODS

This was an observational study, conducted in the Department of Ophthalmology , SMHS, Srinagar in collaboration with Department of Neurology, in a tertiary care hospital in Kashmir. For tests of association using bivariate correlations, we assumed a moderate inverse correlation between RFNL thickness and EDSS scores. To detect a moderate correlation ® =.30), a sample of 40 analyzable subjects (=eyes, patient no. =20) would provide 80% power, to discover that the correlation is significantly different from there being no correlation (i.e. that the correlation would be zero) at the alpha error of 0.05 (one tailed). For this purpose, 20 admitted as well as outdoor adult patients, belonging to either sex, fulfilling McDonald's 2010 criteria for MS diagnosis, regardless of MS subtype, previous history of optic neuritis and status of treatment by immunomodulators; were enrolled as cases. Subjects with i) Opacities in the ocular media, such as cataracts, corneal haze, vitreous hemorrhage, or inflammatory reaction, ii) Optic nerve abnormalities, glaucoma, retinal disease, and optic disc or peripapillary retinal edema, were excluded. A written informed consent was obtained from all the subjects being enrolled for the study after due approval of the hospital ethics committee.

Patient information was documented in a proforma including presenting complaints, present, past, personal and family history, with details of duration of disease. All patients underwent a detailed physical and neurological examination on two visits 2 months apart. For EDSS scoring, we used the Kurtzke's Functional Systems and Expanded Disability Status Scale. All subjects underwent OCT of both eyes regardless of history of previous optic neuritis and RFNL thickness was measured with characterization in all four quadrants of retina centered at ONH, in department of Ophthalmology; using ZEISS CIRRUS HD-OCT. Data in both visits 2 months apart was compared to find the type of correlation between the two over time; in patients of MS with and without ON. Statistical analysis was performed by the SPSS program for Windows, version 17.0 .Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. Data were checked for normality before statistical analysis using Shaipro Wilk test. Normally distributed continuous variables were compared using ANOVA. Multiple comparison test was used to assess the differences between the individual groups using Bonferroni correction. Categorical variables were analyzed using the chi square test. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

RESULTS

As per our mandate, 20 cases of multiple sclerosis were enrolled. They were studied on two occasions two months apart. The patients were in the age group ranging from 19 to 50 years. The mean age in 'MS – ON' group was 33.4 years (SD of 8.23) and in 'MS – NON' group was 29.9 years (SD of 10.5). There was no significant statistical difference between the groups. Female predominance was observed in both the groups.

The major variables to be compared between 'MS – ON' and 'MS –NON' groups included RNFL thickness in different sectors, namely nasal, temporal, superior and inferior as well as average RNFL thickness. The former group was again subdivided into ON – eyes and their fellow non – ON eyes. A total of 40 eyes of 20 patients were subdivided into 14 eyes having ON (of the group 'MS – ON') and 26

eyes without ON. The latter group also included 6 fellow non – ON eyes of the group 'MS – ON'.

The mean disease duration in our study was 3.04 years (SD= 3.305) with median of 1.75 years (range 0.2 – 12). The distribution of subjects by disease duration is given in table 1. The RNFL was found to be significantly thinned in all parameters except in temporal quadrant, as the duration of disease increases, especially in the second visit, suggesting ongoing RNFL thinning between 2 visits as shown in table 1.

Table 1:Duration of disease and quadrant wise RNFLT thickness

RNFL thickness			Duration of MS			P value
			0 -3 year (n=12)	4-6 year (n=4)	>6 year (n=4)	
Nasal	0 months	Mean	76.64	72.25	61.58	< 0.001
		SD	17.46	19.44	15.26	
	2months	Mean	69.44	63	48.17	0.094
		SD	14.83	13.93	17.4	
Temporal	0 months	Mean	56.47	52.58	48.08	0.158
		SD	8.66	15.98	14.28	
	2months	Mean	50.25	44.5	45.25	0.019
		SD	7.13	14.66	13.91	
Superior	0 months	Mean	111.25	106.67	97.67	<0.001
		SD	16.15	10.92	8.36	
	2months	Mean	105.61	92.67	89.67	0.011
		SD	15.43	10.32	7.19	
Inferior	0 months	Mean	116.94	116.92	103.17	<0.001
		SD	11.48	20.78	10.28	
	2months	Mean	109.31	102.5	94.17	0.004
		SD	10.22	17.8	8.31	
Average	0 months	Mean	90.33	87.1	77.62	< 0.001
		SD	10.67	12.84	9.23	
	2months	Mean	83.65	75.67	69.31	
		SD	9.32	9.26	7.66	

Average and inferior RNFL thickness were found to have moderate negative correlation (r = -0.450, -0.395 respectively) with disease duration (p <0.001 and 0.007 respectively)

The eyes having ON showed statistically significant RNFL thinning in all variables at both the visits as compared to the non – ON *fellow eyes* of patients with 'MS with ON'; the eyes of 'MS without ON' and normative data for the respective RNFL value; except the $RNFL_{Superior}$ at 0 months and $RNFL_{Inferior}$ at 2 months, which were also reduced, but were not found to be statistically significant as show in table 2**.** Even the eyes not having ON also showed thinning in RNFL thickness as compared to the normative data, suggesting subclinical axonal loss even in absence of history of ON in patients with MS.

Table 2: History of optic neuritis and RNFL thickness

RNFL thickness	Normative data (Mean + SD)	MS with ON				MS without ON (Patients=10, eyes/n=20)		P_0 months	P_2 months
		ON eye (n=14)		Non-ON fellow eye (n=6)					
		0 months	2 months	0 months	2 months	0 months	2 months		
$RNFL_N$	80.9 +18.1	65.09 +18.65	54.48 +14.71	81.11 +14.39	69.89 +21.49	75.6 +17.33	68.7 +14.79	0.038	0.006
$RNFL_T$	69.0 + 12.7	49.05 +9.27	43.57 +8	66.11 +18.5	60.78 +15.62	53.87 +8.4	47.47 +7.35	0.001	<0.001
$RNFL_S$	124.2 + 17.9	101.1 +18.3	94.48 +16.96	111.67 +9.16	104.67 +10.59	110.97 +11.93	102.13 +13.78	0.04	0.112
$RNFL_I$	126.1 + 17.8	109.05 +15.65	99.1 +12.8	120.67 +16.47	111.44 +14.7	115.83 +12.12	107.03 +11.47	0.087	0.024
$RNFL_A$	107.7 + 9.9	81.05 +11.72	72.9 +9.36	94.89 +10.17	86.69 +9.75	89.06 +10.47	81.33 +9.6	0.004	0.001

At both the visits, eyes with ON showed significant thinning as compared to other two subgroups.

The mean baseline EDSS score at 0 months and 2 months were 3.45(SD 1.89) and 3.47(SD 2.25) respectively. The baseline EDSS score was found to be negatively correlated (moderate degree, r = -0.348) with baseline average RNFL thickness, with p-value of 0.006. So, those having higher EDSS score at baseline were noted to have thinner baseline average RNFL thickness. The moderate degree of negative correlation (r=-0.657) was also found between EDSS score change and average RNFL thickness change at second visit, which was statistically highly significant (p <0.001). This suggests that the more the clinical worsening in disease course (increasing EDSS score), the more is the average RNFL

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DISCUSSION

This pilot study intended to look at the RNFLT as measured by OCT; suggesting a role of OCT as a biomarker for axonal loss in MS patients. The age range of patients included 19 to 50 years, with the mean age in 'MS – ON' group of 33.4 years (SD=8.23) and in 'MS – NON' group of 29.9 years (SD=10.5). There was no significant statistical difference between the groups. Female predominance (in both the main groups) was found in this study, which was supported by other similar studies carried out in patients with multiple sclerosis which also showed female predominance .[9-12] The mean disease duration in our study was 3.04 years (SD= 3.305) with median of 1.75 years (range 0.2 – 12).

The baseline RNFLT was found to be significantly thinned in all parameters (though not statistically significant in temporal quadrant) in those with longer disease duration, and the reduction in RNFLT was even more at second visit in this group (p < 0.001). Thus, RNFL thinning was found to be progressively increasing with increasing disease duration. Average and inferior RNFL thickness were found to have moderate degree of negative with disease duration. In studies by Spain et al[10], and Pueyo et al[11], the average RNFLT correlated significantly with MS disease duration which matched with our study. This study also supported the strongest correlation of the inferior quadrant RNFLT with disease duration than any other sector, as reflected in our study also. Similar correlation were also found by Sepulker et al (r = -0.301, p = 0.003) and Gencer et al. [12,13]

On comparison of the RNFLT parameters ; the eyes having ON showed statistically significant RNFL thinning in all variables at both the visits as compared to the Non -ON *fellow eyes* and MS without ON eyes. Even the MS without ON eyes also showed thinning in RNFLT as compared to the normative data, suggesting subclinical axonal loss even in absence of history of ON in patients with MS. The maximum RNFL thinning was found in the temporal quadrant at both visits in the eyes with ON as compared to their fellow non-ON eyes in the same patients. This could be because of involvement of the papillomacular bundle (situated on the temporal side of the disc) being affected the most. Pueyo et al[11] also showed the greatest thinning in temporal RNFL values in eyes affected with ON, whereas Puliken et al[14], Costello F et al[15] and Saxena et al[12] in addition also showed this pattern of thinning even in the non-affected eyes of MS patients with a trend towards significance. Difference of $RNFL_A$ between Non –ON *fellow eyes* and MS-NON eyes, consisting eyes without ON, was not statistically significant; however, both the groups had more thinning as compared to normative data. Spain et al with similar study also demonstrated the existence of a categorical difference between subject cohort-based ON history. [10] They reported mean $RNFL_A$ was significantly lower in subjects with a history of ON (79.06 µm, 95% CI 75.31–82.81 µm) compared with in those without (93.49 µm, 95% CI 89.74–97.23 µm; *p* < 0.001). The distinction in baseline RNFLT based on subject ON history may have implications for using OCT as an outcome measure in populations with MS heterogeneous in ON status.

Other studies also showed a lower $RNFL_A$ in the affected eye compared to the unaffected eye in MS patients with ON.[8] Parisi et al[9] examined 14 patients with MS who had one episode of ON. The RNFL thickness was shown to be reduced in ON eyes when compared with unaffected

eyes, and control eyes. In another study, Trip et al found a significant reduction in RNFL thickness in ON eyes when compared to both control eyes and unaffected eyes[6]. But in these studies, unaffected eyes' RNFL of MS patients were also found to be significantly thinner than control eyes[6,8,9]. However, no significant differences in the RNFL thickness were found between ON eyes and unaffected eyes in another study[12]. Fisher's study showed significant thinning of RNFL, 92 micron in MS – NON versus controls 105 micron (P<0.001), suggesting that the unaffected eyes of patients with a history of ON are at a similar risk for axonal loss as the eyes of patients with MS in general.[16] In an Indian study by Singh et al significant RNFL thinning was seen in patients of multiple sclerosis compared to the age and sex matched controls in superior and temporal quadrants of right and in all quadrants in the left eye. Significant RNFL thinning was seen in the patients of multiple sclerosis without prior history of optic neuritis than patients with prior history of optic neuritis which was statistically significant (p = 0.001).[18] Retrograde trans-synaptic degeneration of retinal ganglion cells due to MS lesions within the posterior optic pathways has been proposed to be involved in RNFL loss in the absence of ON.[17]

The mean baseline EDSS score at 0 months and 2 months were 3.45 and 3.47 respectively, with corresponding SD of 1.89 and 2.25. The baseline EDSS score was found to be negatively correlated (r = -0.348, p=0.006) with baseline average RNFLT. This matched exactly with the observation by Sepulcre et al, in which RNFL atrophy was correlated with greater disability (r = -0.348, p = 0.001)[12]. An inverse correlation between RNFL thickness and the EDSS was also reported in other studies by Spain et al ($rs = -0.43$, $p < 0.001$), Fisher et al.[10,16] Thus, those having higher EDSS score at baseline were found to have thinner baseline average RNFLT. The moderate degree of negative correlation (r= -0.657) was also found between EDSS score change and average RNFL thickness change at 2 months, which was statistically highly significant (p <0.001). This suggests that the more the clinical worsening in disease course (as reflected by increasing EDSS score), the more is the average RNFL thinning.

CONCLUSION

Clinical outcomes should continue to be the primary endpoints for MS trials, meanwhile OCT would provide a valuable secondary or tertiary outcome, providing appropriate validation of OCT in relation to clinical and visual outcomes. Still more data is necessary to determine whether RNFL loss measured by OCT directly correlates with CNS axonal loss in patients with MS. Since OCT only examines one small aspect of CNS, it remains to be determined whether one would be able to get an accurate overview of the entire CNS based on a single region.

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