Original Article

Optical Coherence Tomography and Subclinical Optical Neuritis in Longitudinally Extensive Transverse Myelitis

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Abstract

Objective: The aim is to compare the retinal nerve fiber layer (RNFL) thickness of longitudinally extensive transverse myelitis (LETM) eyes without previous optic neuritis with that of healthy control subjects. **Methods:** Over 20 LETM eyes and 20 normal control eyes were included in the study and subjected to optical coherence tomography to evaluate and compare the RNFL thickness. **Result**: Significant RNFL thinning was observed at 8 o'clock position in LETM eyes as compared to the control eyes ($P = 0.038$). No significant differences were seen in other RNFL measurements. **Conclusion**: Even in the absence of previous optic neuritis LETM can lead to subclinical axonal damage leading to focal RNFL thinning.

Keywords: Multiple sclerosis, neuromyelitis optica, optic neuritis, optical coherence tomography, transverse myelitis

Introduction

The term "transverse myelitis" describes a heterogeneous group of inflammatory disorders that are characterized by acute or subacute motor, sensory, and autonomic (bladder, bowel, and sexual) spinal cord dysfunction. Most commonly, there is partial involvement of a small segment of the spinal cord (spanning fewer than two vertebral segments), often in the context of multiple sclerosis (MS). The term longitudinal extensive transverse myelitis (LETM) is used when lesion extends over three or more vertebral segments on the sagittal spinal magnetic reasoning imaging (MRI) and is located centrally within the spinal cord.[1] LETM, although rare, is clinically important as it is often associated with catastrophic clinical consequences, and without early recognition and treatment, many patients are left with severe disability. While LETM is classically associated with neuromyelitis optica (NMO), there are many other causes. These include various other autoimmune and inflammatory diseases that involve the central nervous system (CNS) such as MS, sarcoidosis, or Sjogren's syndrome or in infectious diseases with CNS involvement. Patients with a malignancy, metabolic disturbances, or traumatic spinal cord injury can also present with longitudinal spinal lesions. Some of these are readily treatable. Therefore, early recognition and etiological diagnosis are warranted for optimizing outcome and in some cases commencing appropriate treatment to prevent future attacks.

Optical coherence tomography (OCT) is an established technique used in the setting of glaucoma and other retinal diseases to measure retinal nerve fiber layer (RNFL) thickness and macular volume (MV), a measurement that may provide information relating to the size and number of retinal ganglion cell (RGC) bodies.[2] OCT can measure the thickness of the retinal layers using the echo-time-delay of low-frequency infrared light from a low coherence light source. Several previous studies have shown the RNFL thinning in MS eyes, in both with or without previous history of optic neuritis;[3-5] more thinning in progressive MS than in relapsing remitting MS.[6] NMO is associated with more widespread axonal injury in the affected optic nerves and therefore, a thinner overall average RNFL compared to MS, with particular involvement of the superior and inferior quadrants.[7,8]

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Earlier studies showed no subclinical axonal damage in LETM eyes without any previous history of optic neuritis. One study carried out by Ratchford *et al*. demonstrated significant RNFL thinning in nonoptic neuritis MS eyes as well as greater thinning in NMO optic neuritic eyes as compared to MS optic neuritic eyes.[8] However, no difference was found between controls and 17 nonoptic neuritis eyes of patients with LETM or 8 nonoptic neuritis eyes of patients with NMO. Similarly, de Seze *et al*. did not find any subclinical RNFL loss in the eyes of patients with extensive myelitis who were positive for anti-NMO antibodies.[9] Later on, in 2011, Moura *et al*. reported significant thinning of RNFL in the nasal quadrant and in the 3 o'clock segment on comparing OCT of 26 patients with idiopathic LETM without previous episodes of ON Optic neuritis to that of control eyes.[10]

Here, in this study, we utilized OCT to measure and compare the average (360°), quadrantic (90°) and segmental (30°) RNFL thickness of LETM eyes without previous optic neuritis with that of normal healthy control eyes to evaluate whether any correlation exists.

Methods

This was an observational cross-sectional study. Patients were recruited in the study from out- and in-patient Department of Neurology, Sir Sundar lal hospital, Banaras Hindu University (BHU), Varanasi, India. Informed written consent was obtained from all the participants. The study protocol and consent process were approved by Institute of Medical Sciences, BHU.

Patients attending neurology OPD and admitted in Neurology ward from October 2013 to March 2015 were included in the study. The neurological inclusion criteria for the study was the occurrence of sensory, motor, or autonomic dysfunction attributable to the spinal cord, with bilateral signs or symptoms and inflammation within the spinal cord demonstrated by gadolinium enhancement on MRI, and spinal cord abnormality involving three or more vertebral segments. The neurological exclusion criteria were MRI evidence of compressive myelopathy, brain MRI suggestive of MS or acute disseminated encephalomyelitis and clinical profile suggesting infection, connective tissue disorders, malignancy, trauma, or radiation injury as the etiology for the spinal cord dysfunction.

The ophthalmological exclusion criteria were history of glaucoma, corrected visual acuity <6/6, optic neuropathy, age-related macular degeneration, or other relevant retinal and/or optic nerve disease.

On the basis of these inclusion and exclusion criteria, a total of twenty patients of idiopathic LETM without previous history of optic neuritis and 20 normal healthy controls (from patient attendants and hospital staff) were selected and subjected to complete ophthalmologic examination. Visual field, visual evoked potential, and optic coherence tomography were also performed within a maximum period of 5 days. All the control subjects had a normal ophthalmic examination and visual field. Other serological and necessary investigations done to exclude patients of LETM having infective, connective tissue disorder, metabolic, or malignancy as an etiology. Only one eye from each patient was randomly selected for the study. Similarly, one eye from each healthy subject was included in the analysis, and selection between the right and left eye was performed such that it matched the selection in the patients with LETM.

Optical coherence tomography

Retinal imaging of all the subjects were performed using the OCT equipment (Carl Zeiss, Meditec, Dublin, CA, USA) after papillary dilatation. OCT was performed at our ophthalmology department by one of our ophthalmology resident doctor. The fast RNFL thickness protocol, which calculates the average of three circumferential scans around the optic disc, was used to compute the overall average RNFL for each eye. The nontested eye was covered with a patch to improve the internal fixation. Only scans with signal strength of 7 or above (maximum 10), indicating a high-quality scan, was considered as acceptable for analysis. Fundus photographs were routinely obtained to ensure proper centering of the scan, which is critical for accurate results and reproducibility. Average RNFL thickness for 360° around the optic disc, and for the superior, nasal, inferior, and temporal quadrants around the optic disc as well as in the twelve 30° segments (with 3 o'clock position as nasal) were recorded for each eye of patients and controls.

Statistical analysis

The RNFL thickness parameters of LETM eyes and control eyes were compared using Student's *t*-test; significance of the data shown by *P* value. Histogram analysis and the shapiro-wilk test confirmed that the distributions satisfied the normality assumption.

Results

A total of 20 randomly selected eyes from 20 idiopathic LETM patients without previous history of optic neuritis and 20 eyes from healthy control subjects were included for final analysis. The mean age ± standard deviation was 29 ± 13.61 years (range 11–65) in the LETM group and 30 ± 12.24 years (Range 11–64) in the control group. Male-to-female ratio was 1:1.36 in both LETM and control group. Visual evoked potential (VEP) was normal in both case and control patients.

Table 1 shows the RFNL thickness measurements and its comparison of LETM eyes with that of control eyes. No significant difference was observed in average or quadrantic RNFL thickness. The only significant RNFL thinning that was found was in the 8 0'clock position ($P = 0.038$). We also divided patients in age groups below or above 30 years and in male and female sex and their comparison was done with the control using one-way ANOVA but found no statistical difference. Clinical and MRI findings also showed no statistical significance with RNFL thinning.

Table 1: Mean retinal nerve fiber layer (μm)±standard deviation for 20 eyes from patients with longitudinally extensive transverse myelitis and 20 eyes from normal controls

	Mean±SD		*P*
	LETM*	Control	
Average	84.0625±18.3465	90.6875±8.6542	0.201
Superior quadrant	113.87±22.687	109.46±17.524	0.575
Nasal quadrant	75.27±17.265	69.31±15.462	0.348
Inferior quadrant	120.67±26.038	110.85±15.491	0.246
Temporal quadrant	57.53±13.685	67.77±13.657	0.059
12 o'clock	124.00±28.720	114.08±28.643	0.370
1 o' clock	104.27±28.964	101.85±20.546	0.804
2 o'clock	93.53±30.319	79.15±20.157	0.158
3 o' clock	63.73±14.094	60.77±18.534	0.635
4 o' clock	68.13±13.742	67.69±14.557	0.935
5 o' clock	107.80±30.564	98.69±15.729	0.342
6 o' clock	139.27±35.385	123.62±26.126	0.201
7 o' clock	114.27±32.460	110.69±20.520	0.735
8 o'clock	52.875±19.123	64.687±10.351	0.038
9 o'clock	49.07±12.601	58.38±18.099	0.122
10 o' clock	66.00±18.178	77.23±11.833	0.068
11 o' clock	112.87±25.796	112.62±21.188	0.978

*P<0.05 is significant, SD=Standard deviation, LETM=Longitudinally extensive transverse myelitis

Discussion

Compared with idiopathic acute transverse myelitis (ATM), LETM is a rare condition; nevertheless, LETM is increasingly recognized as a unique clinical entity that should be distinguished from ATM and other longitudinal spinal lesions. The clinical presentation of a patient with LETM is often dramatic and can consist of paraparesis or tetraparesis, sensory disturbances, and gait, bladder, bowel and/or sexual dysfunction. LETM is the most important parameter in the diagnostic criteria of neuromyelitis optica spectrum disorder (NMOSD).[11] There is widespread demyelination, axonal damage, and extensive necrosis of neural tissue in NMOSD as well as in idiopathic LETM and recurrences are common. As compared to MS, NMOSD has got more devastating outcome and early diagnosis is pertinent as both has got different line of management and early institution of treatment can lead to prevention of severe neurologic deficit and favorable outcome.

OCT is used to monitor RGC axon loss in glaucoma, diabetic retinopathy, traumatic optic neuropathy, chiasmal lesions, and optic neuritis.[4,5,12-14] Its use has been quite extensively studied in MS in various studies. Kerrison *et al*., using histopathologic analysis, demonstrated a loss of RNFL thickness in the temporal quadrant in MS-affected eyes.[15] This temporal predominance of thinning is due to preferential affection of the papillomacular bundle in MS patients.[16] Another possible explanation is as the temporal RNFL thickness is thin to begin with, loss of RNFL in this region may lead to easier recognition of pallor than in other sectors, which have thicker baseline RNFL.[17] The first OCT study in optic neuritis was published in 1999 by Parisi *et al*. and compared average peripapillary RNFL thickness in 14 MS-related optic neuritis patients, at least 1 year after the optic neuritis, and in 14 controls. Not surprisingly, they found a significant thinning of the RNFL average thickness and RNFL temporal thickness in the optic neuritis group compared to controls (by an average of 46%, $P < 0.01$), and to the fellow-eye (nonaffected) of these MS patients (by an average of 28%, $P < 0.01$).[18] This preferential temporal quadrant involvement in Ms was also demonstrated by other investigators like Gundogan *et al*.[19] in 2007 and Bock *et al*.[20]

MS is a progressive disease in which subclinical RNFL thinning may occur, even in patients who have not been clinically diagnosed with optic neuritis.[3,18,21,22] In the absence of optic neuritis, retrograde transsynaptic RGC degeneration due to MS lesions within the posterior optic pathways could cause RNFL loss. Khanifar *et al*. in 2010 demonstrated progressive peripapillary RNFL thinning with increased duration of disease of more than 5 years, even in MS patients who do not manifest overt optic neuritis.[23] In MS patients without optic neuritis, axonal loss seems to correlate better with MRI parameters than in those that have suffered optic neuritis.[24,25] RNFL thickness correlates with brain atrophy more strongly in relapsing-remitting multiple sclerosis (RRMS) than in secondary progressive multiple sclerosis. These results suggest that the RNFL thinning reflects pathology that extends beyond local injury to the optic nerve by optic neuritis and OCT can be used for disease progression and treatment response in MS.

Several studies have shown that the optic nerve damage in optic neuritis of NMO eyes is greater than that of MS eyes.[8,26] Naismith *et al*. in 2010 demonstrated that the superior and inferior quadrants were affected to a greater magnitude in NMO than MS, whereas the temporal quadrants were not demonstrably different.[7] While the subclinical axonal loss and thereby RNFL thinning is a proven fact in MS eyes, the same in NMOSD patients is a controversial issue. Several studies in the past had shown that NMOSD patients without a history of ON had normal RNFL[8,9,27,28] suggesting there by that subclinical optic neuritis in NMOSD is uncommon. One of the studies conducted by Ratchford *et al*.[8] in 2009 evaluated average MV and RNFL thickness by OCT in patients with MS, NMO, and LETM with and without previous episodes of ON. They found significant RNFL thinning in NMO ON eyes relative to both RRMS ON eyes and control eyes and proposed >15 μm RNFL loss after ON in a non-MS patient should prompt consideration of an NMOSD and suggested OCT as a tool for differentiating NMO from MS. While in eyes without a history of ON, statistically significant difference was found only for RRMS eyes (n = 338) as compared to control, indicating subclinical involvement, no difference was found between controls and 17 non-ON eyes of patients with LETM or 8 non-ON eyes of patients with NMO. Similarly, de Seze *et al*.[9] did not find any subclinical RNFL loss in eyes of patients with extensive

myelitis (only four patients with isolated myelitis) who were positive for anti-NMO antibodies. In both the above studies, the sample size for LETM patients was small and also they measured only the average RNFL thickness which may have led to the result that subclinical optic nerve damage does not occur in LETM. In 2011, Moura *et al*.[10] reported significant thinning of RNFL in the nasal quadrant and in the 3-o'clock segment ($P = 0.04$ and $P = 0.006$, respectively) on comparing OCT of 26 patients with idiopathic LETM without previous episodes of ON to that of control eyes.

In the present study conducted by us, we evaluated patients with LETM without any previous history of optic neuritis for subclinical axonal damage of optic nerve leading to RNFL thinning using OCT. Our study shows that the RNFL is significantly smaller in 8 o'clock segment in LETM eyes than in control eyes ($P = 0.038$) [Figure 1] No other quadrant or segment of the optic disc presented any significant difference. This finding supports the hypothesis of subclinical damage of optic nerve in LETM and that it causes focal RNFL thinning rather than generalized axonal loss as proposed by Moura

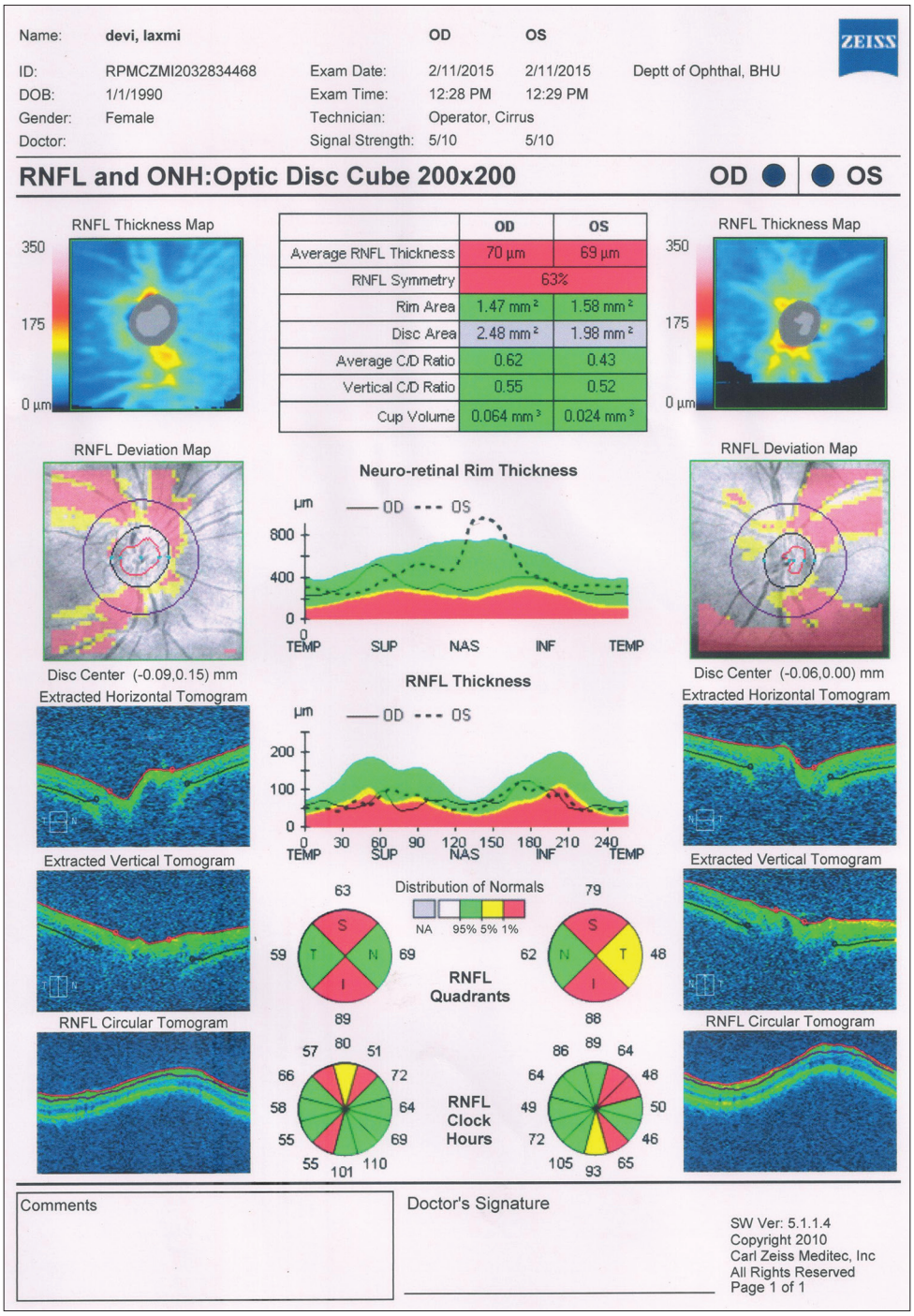

Figure 1: Optical coherence tomography showing thinning of retinal nerve fiber layer in three patients

et al., 2011. We found significant thinning only in 8 o'clock segment and not in any other quadrant and that too was in the different segment as compared to that reported by Moura *et al*. (3 o'clock). This can be due to relatively smaller sample size (n = 20), different ethnicity of the subjects or its quite possible that subclinical focal axonal loss does occur in LETM eyes but does not follow any particular segmental distribution. However, one thing is evident by this study that LETM can cause subclinical optic neuritis leading to focal RNFL damage and thinning. This focal axonal loss represented here in segmental RNFL thinning can occur in any segment and probably does not follow any particular distribution. Furthermore as VEP was normal in all our patients despite RNFL thinning, OCT seems more sensitive, and it has got the potential to replace VEP in clinical practice.

Conclusion

Therefore, RNFL measurements using OCT could potentially be used to identify subclinical axonal damage in patients with idiopathic LETM before episodes of optic neuritis occur. However, our study was a cross-sectional study and no follow-up was done, so further longitudinal study with larger sample size is required to get more information on the potential uses of OCT and RNFL thinning in the evaluation of idiopathic LETM and NMO.

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Conflicts of interest

There are no conflicts of interest.

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