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Thickness of retinal nerve fiber layer correlates with disease duration in parallel with corticospinal tract dysfunction in untreated multiple sclerosis

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Abstract—Optical coherence tomography (OCT) is an emerging clinical and research measure of retinal nerve fiber layer (RNFL) loss in multiple sclerosis (MS) and may reflect neurodegeneration. Few studies capture the effect of disease duration on the RNFL in subjects without exposure to disease-modulating therapies. We assessed the relationship of RNFL loss with disease duration in subjects with untreated MS and determined if such loss paralleled corticospinal tract dysfunction in MS. Subjects underwent OCT (n = 52) and visual testing (n = 60). Either they were either examined or they participated in a validated telephone interview so we could determine their Expanded Disability Status Scale (EDSS) scores. Both RNFL thickness (Spearman r_s = –0.47, $p < 0.001$) and EDSS scores (r_s = 0.51, $p < 0.001$) correlated with disease duration. RNFL thickness correlated with EDSS scores (r_s = –0.43, $p < 0.001$). In conclusion, RNFL loss correlates with disease duration and EDSS scores in subjects with untreated MS, indicating that OCT may capture neurodegeneration.

Key words: disease duration, disease-modifying therapy, Expanded Disability Status Scale, multiple sclerosis, neurodegeneration, optic nerve diseases, optical coherence tomography, rehabilitation, retinal nerve fiber layer, visual acuity.

INTRODUCTON

In multiple sclerosis (MS), both inflammatory demyelination and axonal loss in gray and white matter are observed early, even presymptomatically [1]. These losses lead to central nervous system (CNS) atrophy [2] and

Abbreviations: CI = confidence interval, CNS = central nervous system, DMT = disease-modifying therapy, EDSS = Expanded Disability Status Scale, HCVA = high-contrast visual acuity, LCVA = low-contrast visual acuity, logMAR = logarithm of minimum angle of resolution, MRI = magnetic resonance imaging, MS = multiple sclerosis, OCT = optical coherence tomography, ON = optic neuritis, OU = oculus uterque (both eyes), RNFL = retinal nerve fiber layer, RNFLt = RNFL thickness, RRMS = relapsing-remitting MS, VA = visual acuity.

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functional disability [3]. Standard outcome measures of relapse rate and magnetic resonance imaging (MRI) lesion load neither correlate well with functional decline nor reflect CNS neurodegeneration [4–5]. Optical coherence tomography (OCT) is under evaluation as an outcome measure of axonal degeneration for use in clinical trials and practice [6].

OCT is a noninvasive technique that uses infrared laser light to create cross-sectional images of the retina; this technique provides quantitative analysis of the retinal nerve fiber layer (RNFL) thickness (RNFLt), macular thickness, and macular volume. The mechanism and reliability of OCT are well described [7]. OCT detects changes in the RNFL, which contains unmyelinated axons subject to damage in glaucomatous and ischemic optic neuropathies [8]; more recently, OCT has been applied to optic neuritis (ON) [9]. Short-term follow-up studies after acute ON demonstrate an acute decrement of the peripapillary RNFLt that plateaus by 3 to 6 months [10]. OCT also detects changes in the macula after ON [11]. The calculated macular volume includes the inner macular thickness, which contains the retinal ganglion cells presumably affected after ON by a dying-back axonopathy, as seen in animal models [12]. Alternatively or additionally, primary neuronal degeneration may affect the retinal ganglion cells. OCT has been shown to correlate with functional optic nerve measures such as multifocal visual-evoked potentials [13] and low-contrast visual acuity (LCVA) [14].

As one of the longer white matter tracts in the CNS, the optic nerve is likely to show the effects of both acute inflammation and neurodegeneration early in MS. ON is the presenting symptom of MS in 25 to 50 percent of cases and eventually affects up to 80 percent of patients during the illness, causing significant morbidity [15]. RNFLt in subjects with MS without a history of ON is lower than in control subjects, indicating subclinical axonal loss [9,16]. Thus, OCT is an attractive candidate measure for capturing early changes in MS.

The corticospinal tract is another long CNS white matter tract frequently affected in MS. Like the optic nerve, it is subject both to acute inflammation in the form of transverse myelitis and to neurodegeneration as seen by increasing gait dysfunction, MRI atrophy [2], and recently, gray matter demyelination on high-field MRI [17]. The Expanded Disability Status Scale (EDSS) is a standard measure of gait dysfunction and may correlate with other long tract signs, including RNFL loss and cognitive dysfunction [18], although it poorly predicts long-term disability [19] and its validity in relapsing-remitting MS (RRMS) has been recently challenged [20]. OCT may provide a more sensitive research and clinically applicable measure to capture neurodegeneration in MS.

Most studies using OCT have not accounted for the effects of disease-modifying therapies (DMTs) on the RNFL, which may be significant if similar to DMT effects in early MS [21]. We studied OCT in subjects with MS of varying disease durations and with no exposure to DMTs to test the hypothesis that in untreated MS, RNFLt loss occurs both over the course of disease and in parallel with corticospinal tract dysfunction reflecting CNS neurodegeneration.

METHODS

Subjects

The institutional review board approved all study procedures, and subjects gave their written informed consent. We recruited subjects over 18 years of age from the Thomas Jefferson University Comprehensive MS Center (Philadelphia, Pennsylvania) and the Neuro-Ophthalmology Service at Wills Eye Institute (Philadelphia, Pennsylvania) with no exposure to DMT. Subjects met revised McDonald criteria for MS [22]. We included subjects with clinically isolated syndrome if they fulfilled two or more modified Barkhof MRI criteria [23]. We determined disease-duration subject history. We considered neurological symptoms occurring before the diagnosis date to be caused by MS if they were of a typical nature (brainstem, spinal cord, visual, or multisystem), lasted for at least 24 hours, and were unexplained by other neurological or systemic conditions.

Exclusion criteria included any DMT use, including interferon beta preparations, glatiramer acetate, natalizumab, mitoxantrone, chemotherapeutics, or immunosuppressants. We did not consider corticosteroid treatment a DMT for the purpose of this study, although the effects of corticosteroids on RNFLt after ON are largely unknown. Of the subjects, 21 had been treated with corticosteroids before enrollment; only 4 had received corticosteroid treatment for acute ON in the year before enrollment. We delayed enrollment in subjects with acute ON for 3 to 6 months to allow the RNFL to stabilize [10] and for at least 1 month after intravenous corticosteroid treatment. We excluded subjects with comorbid systemic

diseases that could mimic MS, ocular disease that might affect the OCT results, or other abnormal fundoscopic findings unrelated to MS. We also excluded subjects with OCTs performed at nonparticipating facilities or who were unable to cooperate with testing.

The primary end point was to establish a correlation between RNFLt and disease duration. Secondary end points included establishing correlations between EDSS scores and disease duration, RNFLt and EDSS scores, and RNFLt and both high-contrast visual acuity (HCVA) and LCVA and determining the effects of ON history on these relationships. The study was powered on the primary end point only. We calculated a sample size of 45 subjects to achieve 80 percent power to detect a moderate Spearman rank correlation of 0.4 with a 5 percent two-sided test. After study initiation, data regarding the normal age-related RNFL decrement of 2 μm/decade over the age of 18 years became available [24]. We increased RNFLt by a factor of 2 μm for every decade over age 18 for each subject, and we recruited additional subjects to allow for a lower correlation coefficient. We did not age adjust macular data because limited data on normative age-related decrements exists [11].

Of the subjects, we screened 134, enrolled 83, and then excluded an additional 31 after enrollment, leaving 52 subjects. Screen failures were from lack of interest (n = 32), DMT use (n = 6), uncertainty of MS diagnosis (n = 4), ON within 3 months of OCT (n = 4), comorbid systemic or ocular disease (n = 3), clinically isolated syndrome failing MRI criteria (n = 1), and OCT from a nonparticipating facility (n = 1). Reasons for exclusion after enrollment were DMT use (n = 16), clinically isolated syndrome failing MRI criteria (n = 6), ON within 3 months of OCT (n = 5), lack of informed consent (n = 2), uncertainty of MS diagnosis (n = 1), and comorbid ocular disease (n = 1).

History of Optic Neuritis

Prior studies have shown an absolute difference in RNFLt based on individual eye ON history [10,14]. We obtained ON history in our study by subject report. Because ON history is subject to recall and other biases, we performed multivariate analyses considering the effect of individual eye ON history and thinner side RNFLt in the manner proposed by Sepulcre et al., presuming the thinner side is most affected by inflammation [25].

Retinal Imaging

OCT images were acquired with a Stratus OCT with (software version 4.0, Carl Zeiss Meditec, Inc; Dublin, California) by trained technicians at the Wills Eye Institute and Thomas Jefferson University, and Dr. Sergott reviewed them for quality. We dilated the subjects' pupils with 2.5 percent phenylephrine hydrochloride and 0.5 percent tropicamide if a small pupil sized impaired image quality [26].

We captured three 3.4-mm diameter Fast RNFL Protocol scans (scan length = 10.87 mm) centered on the optic disk for each eye. The Stratus OCT software calculated mean RNFLt values from each 360° scan, and we averaged the three means for each eye using Microsoft Excel (version 2003, Microsoft Corp; Redmond, Washington) to reduce the influence of technical error during scan acquisition. The Fast Macular Protocol (scan length = 6.0 mm, reliability within ±10 μm) used the average of six radial lines to compose a macular thickness/volume map. We reviewed additional fast optic disk and fast crosshair images to exclude other ocular pathologies. All images met the signal strength requirements of at least 7 (maximum 10) as per manufacturer recommendation.

Visual Testing

We measured the HCVA of each eye with appropriate refraction using a retro-illuminated Early Treatment Diabetic Retinopathy Study chart (Precision Vision; La Salle, Illinois) at 4 m, and we recorded 4 m as the logarithm of minimum angle of resolution (logMAR) acuity. We tested LCVA at 2 m and evaluated given data suggesting improved sensitivity for optic nerve dysfunction [27] using a 1.25 percent low contrast Sloan letter chart (Precision Vision). We determined the eye with greater visual impairment by logMAR value; we considered eyes with equal logMAR values equally impaired.

Corticospinal Tract Dysfunction

Dr. Spain examined Thomas Jefferson University subjects (n = 43) for their EDSS scores [28]. Because they were unavailable to be evaluated in the clinic, Wills Eye Institute subjects (n = 9) participated in a standardized and validated telephone interview conducted by Dr. Spain that established their EDSS scores [29].

Statistical Analysis

We used Spearman rank correlation to assess correlations between OCT parameters, EDSS scores, visual

acuity (VA), and disease duration. OCT parameters from each eye included the average RNFLt; the thickness of the temporal, inferior, nasal, and superior quadrants of the RNFL; the total macular volume; and the minimum and average thicknesses of the fovea. We age-adjusted RNFLt as described previously. We performed multivariate analyses to determine the effects of ON history as described previously. We used the Tukey test method to limit type 1 error from performing more than one statistical test; individual *p*-values of 0.025 and 0.018 limited the overall type 1 rate at 0.05 as indicated. We used analysis of variance to compare the mean RNFLt for both eyes (oculus uterque [OU]) between cohorts with and without ON history. We performed statistical analyses using JMP, version 8.0 (SAS Institute, Inc; Cary, North Carolina).

RESULTS

Table 1 shows subject demographics. Wills Eye Institute subjects ($n = 9$) were more likely to have RRMS (78% vs 53%), ON (100% vs 37%), a higher mean EDSS score (3.9 vs 3.0), and a lower mean RNFLt (75.57 µm vs 88.51 µm) than Thomas Jefferson University subjects ($n = 43$). We found no other systematic differences between recruitment sites. The distribution of subjects by disease duration demonstrated a wide spread, with 18 subjects in the 0- to 3-year duration group, 12 in the 4- to 6-year group, 8 in the 7- to 12-year group, and 14 in the >12-year group.

Table 1.
Subject demographics.

Variable	Number (%)
Total	52 (100)
Thomas Jefferson University	43 (83)
Wills Eye Institute	9 (17)
Female	43 (83)
Age (yr, mean ± SD)	43.2 ± 11.1 (range 23–72)
Type of MS	
Clinically Isolated Syndrome	11 (21)
Relapsing-Remitting	30 (58)
Secondary Progressive	3 (6)
Primary Progressive	8 (15)
History of Optic Neuritis	24 (46)
Disease Duration (yr, mean ± SD)	9.3 ± 10.3
Disease Duration (yr, median)	5.5 (range 0.2–45.0)
EDSS Score (mean ± SD)	3.2 ± 1.6
EDSS Score (median)	3.0 (range 1.0–6.5)

EDSS = Expanded Disability Status Scale, MS = multiple sclerosis, SD = standard deviation.

The RNFLt OU correlated significantly with MS disease duration (Spearman $r_s = –0.47$, $p < 0.001$) (**Figure 1(a)** and **Table 2**). Other OCT parameters, including macular volumes and foveal thicknesses, did not demonstrate superior correlations with disease duration compared with the RNFLt (**Table 2**). The inferior quadrant RNFLt had the strongest correlation with disease duration than any other sector, although all were significant (data not shown). While some studies suggest a greater absolute RNFLt loss in the temporal sector [30], others do not [31]; as yet, little data exist to suggest differing regional rates of RNFL decline.

Corticospinal tract dysfunction as captured by EDSS also correlated with disease duration ($r_s = 0.51$, $p < 0.001$) (**Figure 1(b)** and **Table 2**). Finally, RNFLt OU correlated with EDSS scores ($r_s = –0.43$, $p < 0.001$) (**Figure 1(c)** and **Table 3**).

We performed multivariate analyses to determine the effects of individual eye ON history and the thinner RNFLt on the correlations between RNFLt and EDSS scores with disease duration. While RNFLt differed significantly between eyes with a history of ON (75.81 µm, 95% confidence interval [CI] 69.96–81.65 µm) compared with no history (90.93 µm, 95% CI 87.98–93.87 µm; $p < 0.001$) and between thinner (80.30 µm, 95% CI 76.38–84.21 µm) and thicker side (92.25 µm, 95% CI 88.34–96.16 µm; $p < 0.001$), neither had a significant affect on the relationship between RNFLt or EDSS scores and disease duration (**Table 4**). Of note, 6 of the 24 subjects with known ON had been affected bilaterally, thereby decreasing a possible ON effect. Interestingly, the ON eye did not always demonstrate a more impaired OCT; of 18 subjects with monocular ON, 4 had a thinner RNFLt and 5 had a lesser macular volume in the opposite eye.

As a proof of concept, VA worsened at a lower RNFLt. HCVA was shown to correlate with RNFLt ($r_s = –0.53$, $p < 0.001$, $n = 51$) (**Table 3**), as did LCVA ($r_s = –0.34$, $p = 0.002$), although we tested fewer subjects using LCVA ($n = 39$). Both ON history and thinner-side RNFLt influenced the VA results, as shown by multivariate analyses (**Table 4**), although none reached significance after we applied the Tukey test for multiple analyses.

A categorical difference existed between subject cohort-based ON history. The mean RNFLt OU 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; $p < 0.001$) (**Figure 2**). The distinction in baseline RNFLt based on subject ON

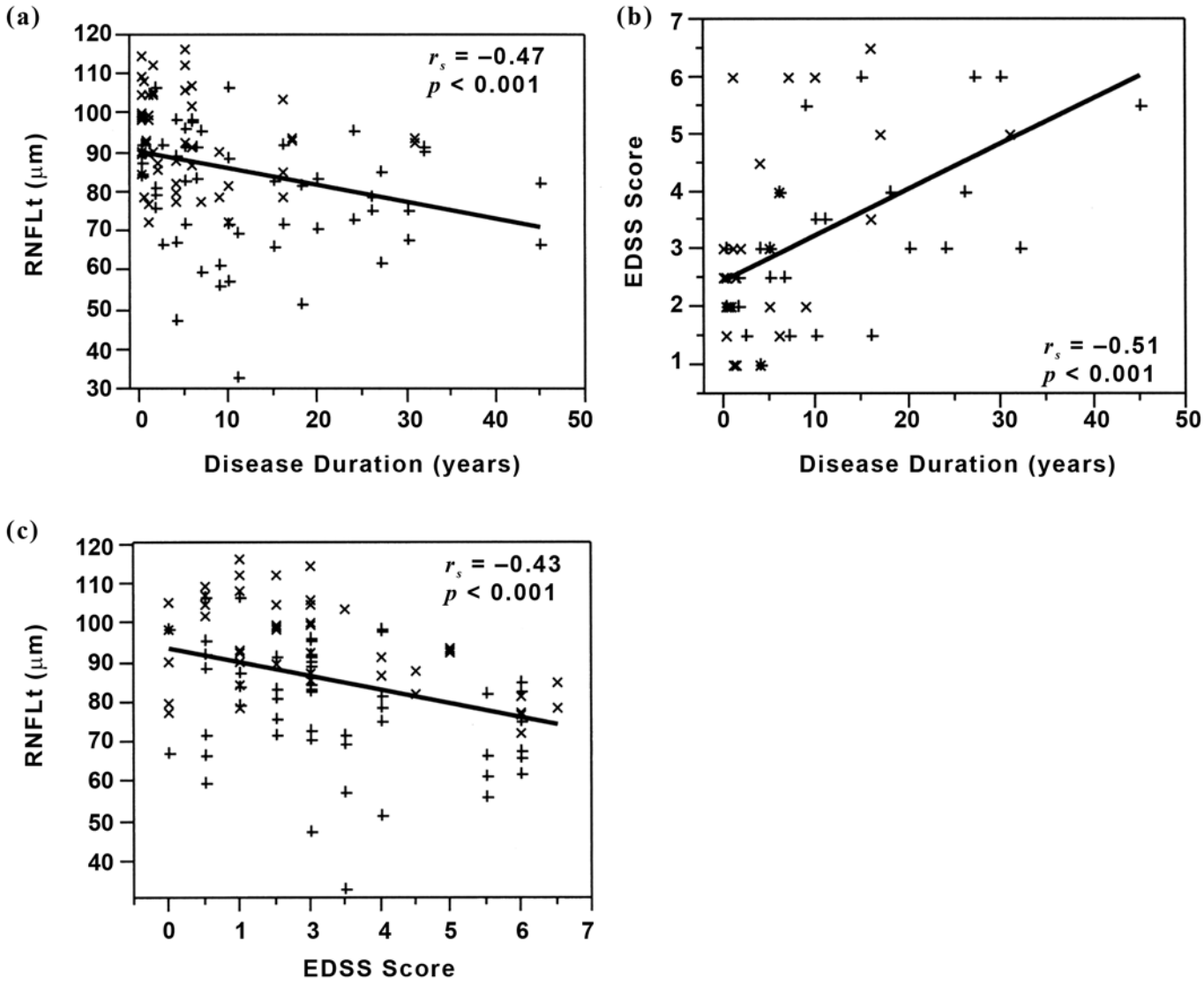

Figure 1.
(a) Retinal nerve fiber layer thickness (RNFLt) of both eyes correlates with disease duration. **(b)** Expanded Disability Status Scale (EDSS) scores correlates with disease duration. **(c)** RNFLt of both eyes correlates with EDSS scores. "+" = subject history of optic neuritis (ON), "×" = no subject history of ON.

history may have implications for using OCT as an outcome measure in populations with MS heterogeneous in ON status.

DISCUSSION

Few studies have assessed RNFL loss in subjects with MS who had not received DMTs. We found that in MS, a greater correlation existed between RNFL loss and desease duration than could be accounted for by age alone, corroborating other recent studies [25,32]. In addition, the functional measure EDSS also correlated with disease duration, supporting the hypothesis that long white matter tracts (optic nerve and corticospinal tracts) are frequently affected by symptomatic inflammation and insidious neurodegeneration.

While RNFL and EDSS scores correlated with each other, as has been shown in other studies [25,32], comparison of their relative sensitivities to change over the

Table 2.
Spearman correlation coefficients (r_s) and *p*-values between optical coherence tomography (OCT) parameters and disease duration (in years) and between Expanded Disability Status Scale (EDSS) scores and disease duration. Significance set at $p < 0.025$ for multiple comparisons (Tukey test).

Outcome Measure	Disease Duration	
	r_s	*p*-Value
OCT Parameter		
RNFLt OU (μm)	–0.47	<0.001
RNFLt Inferier Quadrant OU (μm)	–0.55	0.001
Total Macular Volume OU (mm^3)	–0.30	0.002
Fovea Minimum Thickness OU (μm)	0.22	0.026
Fovea Thickness OU (μm)	—	—
EDSS	0.51	<0.001

NS = not significant, OU = oculus uterque (both eyes), RNFLt = retinal nerve fiber layer thickness.

Table 3.
Spearman correlation coefficients (r_s) and *p*-values between retinal nerve fiber layer thickness (RNFLt) of both eyes (oculus uterque [OU]), Expanded Disability Status Scale (EDSS) scores, and both high- and low-contrast visual acuities (HCVA and LCVA, respectively). Significance set at $p < 0.05$.

Outcome Measure	RNFLt OU (μm)	EDSS
EDSS	$r_s = –0.43$	—
	$p < 0.001$	—
HCVA	$r_s = –0.53$	$r_s = 0.48$
	$p < 0.001$	$p < 0.001$
LCVA	$r_s = –0.34$	$r_s = 0.15$
	$p = 0.002$	$p = 0.18$

short term cannot be evaluated in this cross-sectional design. Furthermore, OCT is a continuous physiological measure, while EDSS is an ordinal functional measure and thus not directly comparable. This study does, however, provide baseline data for a prospective study of RNFL loss in subjects with untreated MS to assess the true rates of loss regarding ON history and sensitivity to short-term changes. Rates of RNFL loss need to be assessed in conjunction with whole brain or gray matter atrophy measures [3] and more sensitive measures of corticospinal tract dysfunction than the EDSS [19–20] so we can gain a comprehensive measure of the neurodegenerative component of MS. Only then can neuroprotective strategies for preserving vision, gait, cognition, and the other debilitating effects of MS be more confidently tested.

We found that peripapillary RNFL measures produced stronger correlations with disease duration than did macular measures of thickness [11] or volume [33], which have been found in other studies to be more sensitive to the effects of ON. Further elucidation is required.

Correlations between RNFLt OU and disease duration were relatively modest. Exclusion of subjects with clinically isolated syndrome based on MRI criteria may have biased the subjects with shorter disease duration toward those with more advanced disease and potentially more RNFL involvement than a true early MS cohort. Additionally, some of the subjects with longer disease duration, having chosen not to initiate DMT, may have been biased toward less severe disease and potentially less RNFL loss. The cross-sectional design of the study and heterogeneous subject population regarding MS type and stage of disease may also have influenced the strength of correlations.

Multivariate analysis using individual eye ON history and thinner RNFLt side did not affect the relationships of RNFLt and EDSS scores to disease duration, although this study was not powered to address these secondary outcomes. This finding may indicate that subclinical ON and/or ongoing neurodegeneration affect both optic nerves sufficiently to negate the influence of symptomatic ON. Interestingly, OCT data contradicted the recalled history of ON in one-quarter of subjects with lesser RNFLt in the reportedly unaffected eye. A larger prospective study of RNFL loss is necessary to determine the character and tempo of neurodegeneration given ON history. At a given time point, using the averaged RNFLt OU may prove a more useful global measure of disease burden. The smaller baseline RNFLt among subjects with a history of ON as found in other trials may require subject stratification by subject history of ON rather than individual eye history of ON in clinical trials [25].

Table 4.
Multivariate analyses to determine if factors of individual eye optic neuritis (ON) history or thinner retinal nerve fiber layer (RNFL) interacted with correlations between RNFL thickness (RNFLt) and disease duration, between Expanded Disability Status Scale (EDSS) scores and disease duration, and between RNFLt and both high- and low-contrast visual acuities (HCVA and LCVA, respectively). Significance set at $p < 0.018$ for multiple comparisons (Tukey test).

Parameter	Mean Parameter Estimate ± Standard Error	*p*-Value
RNFLt and Disease Duration by ON History	0.038 ± 0.248	0.09
RNFLt and Disease Duration by Thinner Side	–0.021 ± 0.149b	0.87
EDSS and Disease Duration by ON History	1.009 ± 1.784	0.57
EDSS and Disease Duration by Thinner Side	–0.671 ± 0.471	0.16
RNFLt and HCVA by ON History	9.251 ± 4.202	0.03
RNFLt and HCVA by Thinner Side	–6.198 ± 2.731	0.03
RNFLt and LCVA by ON History	0.752 ± 5.857	0.90
RNFLt and LCVA by Thinner Side	–5.938 ± 3.258	0.08

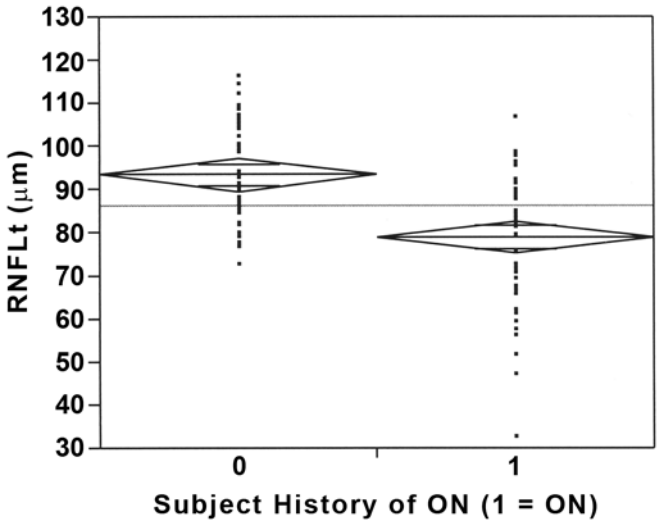

Figure 2.
Subjects with history of optic neuritis (ON) (1) had significantly lower mean retinal nerve fiber layer thickness (RNFLt) in both eyes (79.06 μm, 95% confidence interval [CI] 75.31–82.81 μm) than subjects without history of ON (93.49 μm, 95% CI 89.74–97.23 μm; $p < 0.001$).

As proof of concept, we found worse VA to correlate with a lower RNFLt and a more impaired EDSS score, with stronger correlations for HCVA than LCVA likely influenced by the unequal numbers tested (**Table 3**). Overall, correlations between RNFLt and VA measures were sensitive to the effects of ON and thinner RNFLt side, although the study was underpowered to these secondary outcomes. The poorer visual outcomes at lower RNFLt underscore the need to measure and preserve retinal axons.

Larger prospective studies that include more sensitive measures of corticospinal tract dysfunction than the EDSS, coupled with advanced neuroimaging techniques and, ideally, histopathological investigations, will help detect differences in the pattern and rate of RNFL loss by disease subtype and ON history, pointing to underlying pathological mechanisms of neurodegeneration [3,34]. Studies comparing DMT-exposed (including corticosteroids) and non-DMT-exposed subjects may help detect treatment effect on the RNFL. Finally, improvements to the current 8 to 10 μm resolution of the Stratus OCT will have greater power to differentiate neurodegeneration from normal age-related losses to the RNFL, as well as any potential DMT effects on preserving crucial visual function in MS.

CONCLUSIONS

In summary, we found RNFLt to correlate with disease duration in parallel with corticospinal tract dysfunction, as measured by the EDSS in a population with MS untreated by DMTs. Subjects with ON history had a lower baseline RNFLt. This study suggests that OCT may prove to be a useful instrument for capturing the CNS effects of inflammation and neurodegeneration for use in both clinical trials and practice.

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Study concept and design: R. C. Sergott, T. P. Leist.
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Drafting of manuscript: R. I. Spain.
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