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# Baseline, one and three month changes in the peripapillary retinal nerve fiber layer in acute optic neuritis: Relation to baseline vision and MRI ☆

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ABSTRACT

*Objective:* Retinal nerve fiber layer (RNFL) loss occurs with MS or after optic neuritis. Acute RNFL alterations at presentation and changes over time have not been well documented. We analyzed regional RNFL changes using 2 methods, ocular coherence tomography (OCT) and scanning laser polarimetry (SLP), to study initial edema and early RNFL loss.

*Methods:* 40 subjects with unilateral acute optic neuritis, had prospective OCT and SLP RNFL thickness values organized into 4 quadrants. We compared affected with normal fellow and control eyes to determine RNFL thickening (≥10% of 95th percentile of controls) and thinning (≥10 μ less than fellow eye) at presentation, 1 and 3 months.

*Results:* RNFL thickening occurred in 27/33 eyes (82%) by OCT and in 21/34 eyes (62%) by SLP at baseline. At 1 month, RNFL thickening was common even as thinning developed in 15/23 (65%) of eyes by OCT and in 15/28 eyes (54%) by SLP. At 3 months, RNL was thinned by OCT in 14/24 (58%) and by SLP in 15/25 (60%) affected eyes (58%). Neither MRI optic nerve lesion nor vision at baseline correlated with optical image findings or vision outcome.

*Conclusions:* RNFL swelling, most likely due to axoplasmic stasis from blockade at the lesion site in optic neuritis, is seen with OCT better than SLP. RNFL swelling in some quadrants and loss in others occur at 1 month and is well seen with interocular comparison by both methods. Optical imaging provides pathophysiologic as well as quantitative information regarding axonal changes.



## 1. Introduction

Swelling of the optic disc is seen on clinical examination in approximately one third of eyes at presentation of acute optic neuritis. Available methods for imaging of the optic disc and peripapillary retinal nerve fiber layer (RNFL) can be utilized to demonstrate and quantify RNFL swelling and subsequent thinning due to demyelination. An earlier small case series showed a trend of thickening in the RNFL in eyes with acute optic neuritis eyes when compared with fellow asymptomatic eyes [2]. OCT studies performed months or longer after the onset of optic neuritis revealed reduction in the global mean RNFL that was more prevalent in eyes with persistent visual deficits [3,4]. Until recently, no large case series study of acute optic neuritis with ocular imaging at the time of presentation had been reported [5].

Although OCT is the most commonly used optical imaging modality to evaluate the RNFL, scanning laser polarimetry (SLP) studies also show RNFL losses in eyes with glaucoma and in multiple sclerosis (MS) patients [6–8]. Scaling differences between the two imaging techniques account for larger RNFL thickness measurements seen with OCT compared with SLP, but both are comparable for uncovering RNFL loss due to disease [9,10]. The temporal RNFL, possibly the quadrant most often disturbed in optic neuritis, was difficult to image with older SLP methods, and is seen better using newer methodology, called enhanced corneal compensation [11,12]. We prospectively investigated eyes with acute optic neuritis to further elaborate the RNFL changes at presentation, 1 and 3 months and to explore the relationship of these findings to changes in vision and MRI demonstrated lesions of affected optic nerves. Further, we sought to improve the sensitivity of uncovering more subtle abnormalities or alterations in the RNFL results by utilizing interocular comparisons and evaluating all 4 quadrants of collected data. We also explored whether additional or distinguishing features in RNFL alteration could be uncovered by comparing the

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measured OCT thickness and SLP retardation results at baseline 1 and 3 months.

## 2. Methods

We selected subjects with first-time unilateral acute demyelinating optic neuritis in the affected eye and vision loss less than 21 days. All study subjects had typical features of optic neuritis including a relative afferent pupillary defect in the affected eye [1]. None of the eyes had significant optic disc swelling or peripapillary hemorrhages or exudates on ophthalmoscopy. Mild swelling of the optic disc, noted by comparison to the fellow eye with smaller cup to disc ratio, was permitted. Thus, all patients in this series would be classified clinically as having retrobulbar optic neuritis. This is a consecutive case series of patients in the Neuro-Ophthalmology Service at New York Eye and Ear Infirmary and the INN at Roosevelt Hospital in New York City, and no eligible subjects declined to participate. Patients with prior optic neuritis in the affected eye, other optic nerve disorders, and optic atrophy by ophthalmoscopy in either eye were excluded. Given that for an attack of optic neuritis, either idiopathic or related to MS the outcomes are similar; subjects could have known MS and/or prior optic neuritis in the fellow eye. None of the patients with MS had long-standing (maximum duration 3 years) or secondary progressive disease or MRI evidence of cerebral atrophy.

This study was conducted with New York Eye and Ear Infirmary IRB approval. Subjects had assessment that included presence of a relative afferent pupillary defect in the affected eye, monocular best-corrected visual acuity (expressed in LogMAR notation; assigned finger count to no light perception a score range 2–4), color vision testing using pseudoisochromatic plates (expressed as a ratio of plates identified correctly/total number of plates tested), and threshold perimetry performed using the Humphrey Field Analyzer SITA 24–2 standard perimeter strategy using size III (expressed as mean deviation, MD, in decibels, db). Unless the patient had an MRI within the prior 6 months, a fat-suppressed gadolinium-enhanced MRI with short tau inversion recovery views of the optic nerve to chiasm and brain was performed [13].

We prospectively studied subjects at baseline (mean 6 days after vision loss began) 1 and 3 months. For SLP (GDx with enhanced corneal compensation research software, Zeiss-Meditec, Dublin, CA) [10,11], through an undilated pupil, an elliptical band was adjusted to permit maximum capture of the same peripapillary RNFL measurement between exams and eyes. Retardation values were determined within the band, which were re-sampled into 64 circumferential measures of RNFL thickness. Only SLP images centered on the disc, well focused, and with quality scores $\geq 7$ were analyzed (36/40 eyes at baseline). After pupillary dilation, the OCT (Stratus version 3; OCT 4 Software, fast RNFL protocol, Zeiss-Meditec, Dublin, CA), adjusted for refractive error, was used to obtain a set of three 3.4 mm diameter retinal scans, averaged to provide the RNFL thickness at 256 points along the circumference of the circular peripapillary scan in each eye. Only centered OCT data with signal strength scores $\geq 7$ were analyzed (38/40 eyes at baseline). All studies were performed on the same OCT and SLP equipment by one technician (GM). Macula OCTs are not reported but none had macula edema or thinning.

We analyzed the SLP and OCT RNFL thickness divided in 4 quadrants, temporal, superior, nasal and inferior. For OCT, each quadrant measurement was determined from the average of the corresponding 3 clock hour sectors. For SLP, the 64 RNFL data points were organized in groups of 16 points that were averaged for each quadrant measurement. We also evaluated the mean global RNFL thickness around the entire circumference for OCT and ellipse for SLP. Average and quadrant RNFL thicknesses are reported and compared with fellow normal and control eyes.

The fellow eye was considered asymptomatic or 'normal' and used for interocular comparison only if at baseline the eye had normal vision ($\geq$20/20, $\geq$95% color plates seen, MD$\geq -3.00$ db) and RNFL data that fell within the 5%–95% interval for population controls for OCT (also within 5%–95% of 81 Iowa controls, mean age 53.5 years). In addition, no included fellow eyes had baseline RNFL that was swollen (when compared with the 95th percentile of 81 Iowa controls or the normal database provided with the OCT3). Using the fellow eyes seemed to be a reasonable approach particularly in subjects without definitive MS since RNFL loss is not typically seen early in MS or patients with a clinically isolated syndrome [14].

We defined swelling for both OCT and SLP affected eye data using ratios of affected/fellow or affected/control eye RNFL measurements. Swelling was judged for SLP if 1 quadrant had a ratio $\geq 1.1$ (110%), since only 2% of 'normal' fellow eyes divided by the 95th percentile from normal RNFL had 1 quadrant or the global average $\geq 1.1$ (10% thicker). Swelling was judged for OCT if 1 quadrant sector ratio was $\geq 1.1$, since only 2.5% of 'normal' fellow eyes divided by the 95th percentile of unaffected eyes and only 2.4% of Iowa control eyes divided by 95th percentile of these controls had 1 quadrant $\geq 1.1$.

For global RNFL averages, either for SLP or OCT, swelling was defined when the measurement was thicker than the 95th percentile of the age matched normal database provided with each machine. RNFL was also judged swollen if the SLP average was greater than 59.4 μ (95th percentile of 'normal' fellow eyes) or if the OCT average was greater than 114 μ (95th percentile of control eyes).

RNFL thinning (derived by subtracting thickness of corresponding fellow quadrant from affected eye) was judged if 1 quadrant (for OCT) or 1 quadrant (for SLP) was $\geq 10$ μ thinner in an affected eye. For OCT this criterion occurred in only 2.5% of fellow eyes after subtracting the 5th percentile of fellow eyes and in only 1.2% of control eyes after subtracting the 5th percentile of the Iowa control eyes. For SLP only no fellow eyes met this criterion after subtracting the 5th percentile of baseline fellow eyes.

For the global RNFL averages, OCT or SLP was thinned if the result of subtracting the fellow from the affected eye measurement was $\geq 10$ μ. RNFL thinning was also judged if the SLP average fell below 42.4 μ (5th percentile of 'normal' fellow eyes) or if the OCT average fell below 84 μ (5th percentile of control eyes).

Spearman values were utilized to determine potential correlations. We also performed Wilcoxon signed rank tests to compare the actual OCT and SLP thickness measurements for quadrants between affected and fellow eyes at baseline. The paired *t*-test was used to evaluate differences in quadrant data for OCT and SLP baseline and 1 and 3 month data. Two-tailed significance was used in all calculations.

## 3. Results

We studied 40 subjects, 6 men and 34 women, with a mean age 32 years (median 31.6 years) at an average of 6.4 days (sd 4.0) after the onset of vision loss. Twelve subjects had relapsing remitting MS, diagnosed by Poser criteria, for a mean of 1.4 years (sd .69, range 1–3 years) and 10 were taking interferon or glutarimer acetate. Prior optic neuritis in the fellow eye occurred in 9 subjects (7 of who had MS). Affected eye baseline and follow up visual performance are detailed in Table 1. Intravenous methylprednisolone was given for 3 days after the baseline evaluation in 38 patients. Of the 38 patients, the 28 without MS were treated with oral prednisone at 1 mg/kg/day for 2 weeks after the intravenous methylprednisolone.

An MRI was performed in 24 patients and none had signs of cerebral atrophy. An optic nerve lesion was seen in 23/24 MRI studies. All 23 had abnormal enhancement of the affected optic nerve with gadolinium and abnormal bright signal on the STIR sequences. The mean lesion length was 11 mm, $+/-6$ mm. The proximal limit of the lesion approximated the posterior sclera by $\leq 5$ mm in 11 MRI's. The 12 other lesions had a mean of 12 mm (range 8–20 mm) distance from the globe.

**Table 1**
Affected eye visual performance at study time points.

| | Baseline | 1 month | 3 months |
|---|---|---|---|
| *Visual acuity, LogMAR units* | | | |
| Mean, +/−sd | 1.02, +/−1.02 | 0.39, +/−0.72 | 0.13, +/−0.45 |
| No. ≤20/50 (0.4) | 28 | 9 | |
| No. ≥20/20 (0.0) | 5 | 19 | |
| *Color vision — ratio identified/total* | | | |
| Mean, +/−sd | 0.38, +/−0.44 | 0.67, +/−0.44 | −.82, +/−0.36 |
| No. 0.0 | 0.2 | 0.8 | |
| No. 1.0 | 0.09 | 0.19 | |
| *Mean deviation, db* | | | |
| Mean, +/−sd | −18.48, +/−10.89 | −7.82, +/−9.81 | −3.82, +/−6.22 |
| No. ≤−15.0 | 20 | 5 | |
| No. ≥−3.0 | 3 | 15 | |

**Table 2**

| | Temporal quadrant | Superior quadrant | Nasal quadrant | Inferior quadrant | Global average |
|---|---|---|---|---|---|
| Mean OCT at baseline for 38 affected eye in microns | 77.08 | 152.58 | 89.62 | 158.41 | 115.28 |
| SD | 19.30 | 37.94 | 28.38 | 33.47 | 23.25 |
| Mean SLP at baseline for 36 affected eye in microns | 23.37 | 66.53 | 46.30 | 70.10 | 52.13 |
| SD | 8.57 | 12.35 | 10.62 | 11.38 | 5.95 |
| Mean OCT at baseline for 38 fellow eye in microns | 63.28 | 128.72 | 82.84 | 117.09 | 97.98 |
| SD | 13.51 | 18.23 | 19.46 | 19.88 | 13.85 |
| Mean SLP at baseline for 36 fellow eye in microns | 23.13 | 63.66 | 45.09 | 67.31 | 50.49 |
| SD | 7.27 | 10.03 | 8.38 | 9.39 | 5.69 |
| Mean OCT for 33 affected/ fellow eye at baseline | 1.25 | 1.19 | 1.11 | 1.38 | 1.19 |
| SD | 0.33 | 0.29 | 0.36 | 0.31 | 0.22 |
| Mean SLP for 34 affected/ fellow eye at baseline | 1.08 | 1.06 | 1.04 | 1.06 | 1.04 |
| SD | 0.46 | 0.21 | 0.20 | 0.20 | 0.10 |
| Number of swollen quadrants by OCT at baseline (33 eyes) | 21 | 17 | 16 | 26 | |
| Number of swollen quadrants by SLP at baseline (34 eyes) | 13 | 16 | 10 | 14 | |
| Number of thinned quadrants by OCT at 1 month (23 eyes) | 7 | 7 | 10 | 3 | |
| Number of thinned quadrants by SLP at 1 month (28 eyes) | 2 | 6 | 4 | 5 | |
| Number of thinned quadrants by OCT at 3 months (24 eyes) | 4 | 10 | 7 | 11 | |
| Number of thinned quadrants by SLP at 3 months (25 eyes) | 4 | 8 | 7 | 11 | |

At baseline, the average thickness across quadrants was greater in affected than in fellow or control eyes and more readily seen on OCT (38 eyes) than SLP (36 eyes) (Fig. 1, Table 2). Fig. 2a and bshows the optical imaging from a case without clinically apparent swelling of the optic disc at presentation. For both OCT and SLP, thickening was more apparent across quadrants when affected/fellow eye ratios were calculated (Fig. 3), which revealed swelling in 27/33 eyes (82%) on OCT and in 21/34 eyes (62%) on SLP. The number of quadrants with swelling was greater for each quadrant using OCT (Table 2). For Wilcoxon signed ranks, OCT quadrants for affected eyes compared with fellow eyes were positive (thicker) in temporal ($p=0.001$), superior ($p=0.002$), and inferior ($p=0.001$). For Wilcoxon signed ranks, SLP on quadrants for affected eyes compared with fellow eyes were significantly more positive. For eyes with high quality data for both OCT and SLP in the same subjects, 21/27 eyes (78%) met criteria for being swollen. The number or location of quadrants swollen did not correlate between OCT and SLP in individual subjects. The average number of swollen quadrants was 2.5, sd 1.3 for OCT ($p=0.001$, compared with SLP) and 1.5, sd 0.9 for SLP. The number of quadrants swollen was well correlated with the amount of global thickening for both OCT ($r=0.57$, $p=0.001$) and SLP ($r=0.51$, $p=0.002$). Quadrant ratios of affected/control eye group data upper 95th percentile for individual quadrants showed swelling for OCT in 14/33 (42%) eyes and for SLP in 2/34 (6%) eyes.

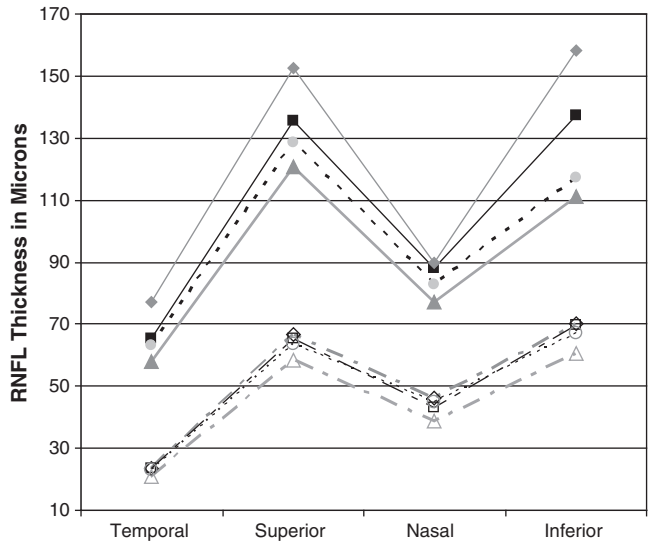


**Fig. 1.** Actual RNFL thickness values for OCT (data for 38 eyes) and SLP (data for 36 eyes) for affected eyes across 4 quadrants and for fellow eyes (baseline only, circles, dotted lines) at baseline. OCT (solid markers, solid lines) shown with baseline (diamond), 1 month (square), and 3 months (triangle) for affected eyes. SLP (open markers, broken line) shown with baseline (diamond), 1 month (square), and 3 months (triangle) for affected eyes.

At baseline, the actual global average measures of RNFL thickness revealed thickening (swelling) in 11 eyes (33%) for OCT (mean 113.89 μ, sd 22.3 for affected and 97.65 μ, sd 16.1 for fellow eyes, $p=0.01$) and in 4 eyes (12%) for SLP (mean 52.31 μ, sd 5.8 for affected eyes and 50.48 μ, sd 5.7 for fellow eyes, $p=0.19$). The ratio of affected/fellow eye RNFL global average thickness, showed swelling in 50% by OCT and in 19% by SLP. No affected eye had the baseline OCT and SLP global averages below normal nor was the difference from the fellow eye below zero.

At baseline, there were no correlations with the optic nerve lesion length or proximity to the globe on MRI or visual acuity, color vision, or mean deviation of threshold perimetry and the number of swollen quadrants by OCT or SLP. There were no correlations with the number of quadrants with thickening or severe swelling at baseline and visual performance at baseline or at 1 month.

At 1 month, the mean RNFL measurements for OCT and SLP were less than at presentation (not significant) for all quadrants but were still thicker than for fellow eyes (Fig. 1). The affected/fellow eye analysis showed thickening of 1 or more quadrants in 18/23 by OCT and in 24/28 by SLP. Quadrant comparison (by subtraction of fellow eye quadrants) showed thinning by OCT in 15/23 affected eyes (65%) and by SLP in 15/28 affected eyes (54%) (Fig. 4); and affected eyes had thinning in an average of in 1.83 quadrants, sd 0.86 by OCT and 1.8 quadrants, sd 0.44 by SLP. In thinned quadrants, the average loss was 23.4 μ, sd 15.1 by OCT and 16.1 μ, sd 6.8 by SLP (Fig. 4). Thinned quadrants were seen more frequently by OCT (Table 2, Fig. 4). Thickening remained in other quadrants in 18/23 eyes (78%, 10 of

which also had quadrants thinned in the same eye) by OCT and in 24/28 eyes (86%, 4 of which also had quadrants thinned in the same eye) by SLP. Paired *t*-test results showed for all affected eyes reduction of thickening compared with baseline affected eye in temporal and inferior quadrants($p \leq 0.01$) for OCT and in the nasal quadrant ($p = 0.03$) for SLP at 1 month. In contrast to affected eyes, the fellow asymptomatic eyes had no significant difference for any quadrant at 1 month compared with baseline.

At 1 month, the mean for global average was 104.6 μ (sd 24.2) for OCT and 50.9 μ (sd 6.8) for SLP. The affected/fellow eye quadrant ratios were less than at baseline (Fig. 3). The affected minus the fellow eye RNFL global average was thinned in 6/23 eyes for OCT (mean 5.83 μ, sd 18.6 for all eyes) and in 0/28 eyes for SLP (mean 0.50 μ, sd 5.3 for all eyes). The OCT global average was less than 84 μ in 4 affected eyes (16%). The SLP global average was less than 42.4 μ in 3/28 affected eyes (11%).

There were no correlations with the optic nerve lesion length or proximity to the globe on MRI or baseline visual performance and the number of quadrants thinned at 1 month on OCT and SLP.

At 3 months, the mean RNFL measurements for OCT and SLP were less than at presentation and 1 month as well as for fellow eyes (Fig. 1). The affected/fellow eye analysis (Fig. 3) showed thickening of 1 or more quadrants in 11/24 (45%) by OCT and in 12/25 (50%) by SLP. Paired *t* test showed RNFL quadrant thickness was significantly thinned compared with fellow eye for SLP determinations for temporal ($p = 0.05$), superior ($p = 0.01$) nasal ($p = 0.02$), and inferior ($p = 0.03$) quadrants. By OCT, only the superior quadrant was significantly ($p = 0.01$) thinned on this analysis. Quadrant comparison (by subtraction of fellow eye quadrants) showed thinning by OCT in 14/24 affected eyes (58%) and by SLP in 15/25 affected eyes (60%) (Fig. 4); and affected eyes had thinning in an average of in 2, sd 1.0, quadrants by OCT and 1.8, sd 0.9, quadrants by SLP. In thinned quadrants, the average loss was 23.8 μ, sd 21.0 by OCT and 18.2 μ, sd 7.0 by SLP (Fig. 4). Thinned quadrant frequency was similar for OCT and SLP (Table 2, Fig. 4). Paired *t*-test results showed that at 3 months all affected eyes had significant reduction of thickening compared with baseline affected eye in all quadrants for both SLP (range, $p = 0.003$ to 0.035) and OCT (range, $p = 0.001$ to 0.013) except for the nasal quadrant by OCT. In contrast to affected eyes, the fellow asymptomatic eyes had no significant difference for any quadrant at 3 months compared with baseline.

At 3 months, the mean for global average was 90.1 μ (sd 17.7) for OCT and 45.4 μ (sd 6.3) for SLP. The affected minus the fellow eye RNFL global average was thinned in 8/24 eyes for OCT (mean −5.7 μ, sd 18.0x for all eyes) and in 5/25 eyes for SLP (mean −5.0 μ, sd 8.0 for all eyes). The OCT global average was less than 84 μ in 7 affected eyes (29%). The SLP global average was less than 42.4 μ in 7 affected eyes (28%).

There were no correlations with the optic nerve lesion length or proximity to the globe on MRI or baseline visual performance and the number of quadrants thinned at 3 months on OCT and SLP. At 3 months, RNFL loss in the global average OCT correlated with visual acuity ($r = -0.59$, $p = 0.01$), color vision ($r = 0.44$, $p = 0.05$), and mean deviation ($r = 0.78$, $p = 0.01$) At 3 months, RNFL loss in the global average SLP correlated with visual acuity ($r = -0.55$, $p = 0.01$), color vision ($r = 0.44$, $p = 0.03$), and mean deviation ($r = 0.57$, $p = 0.01$).

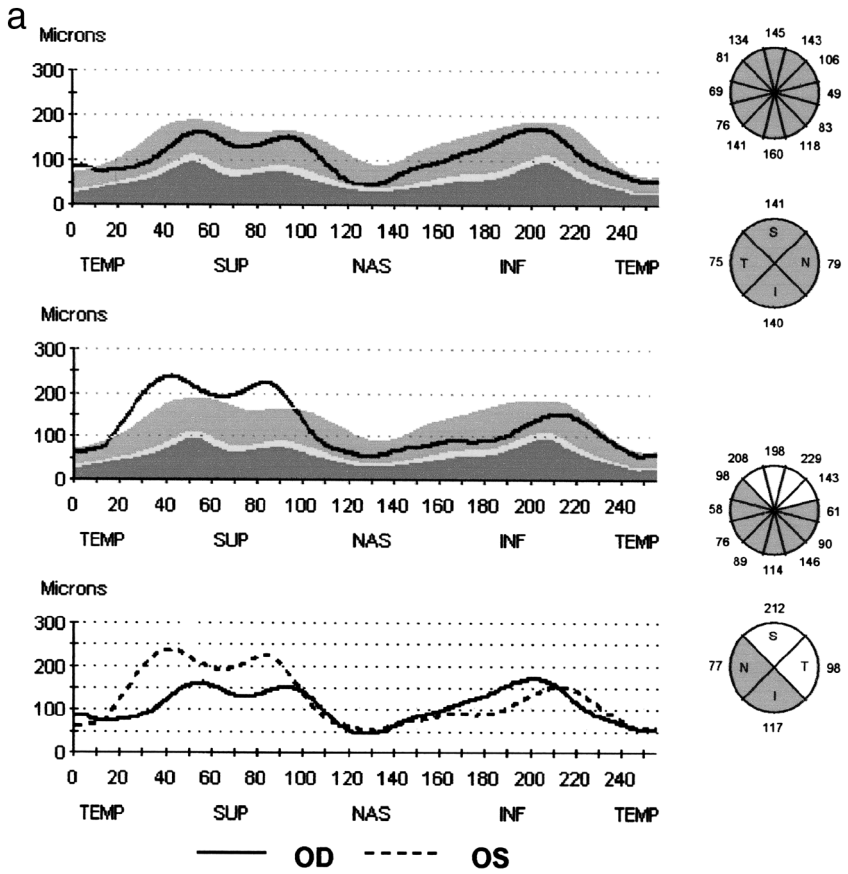


**Fig. 2.** a) Example of OCT RNFL (light gray 5–95th percentile, white 1–5th percentile, dark gray <1 percentile) finding for left eye at baseline compared with normal right eye. Even against the normative database the superior RNL is thickened. b) Example of SLP RNFL (fundus image top, RNFL thickness map middle, RNFL thickness measures bottom) finding for the affected left eye at baseline showing thickening across most quadrants compared with normal right eye. However, the RNFL is not thicker than the normative database.

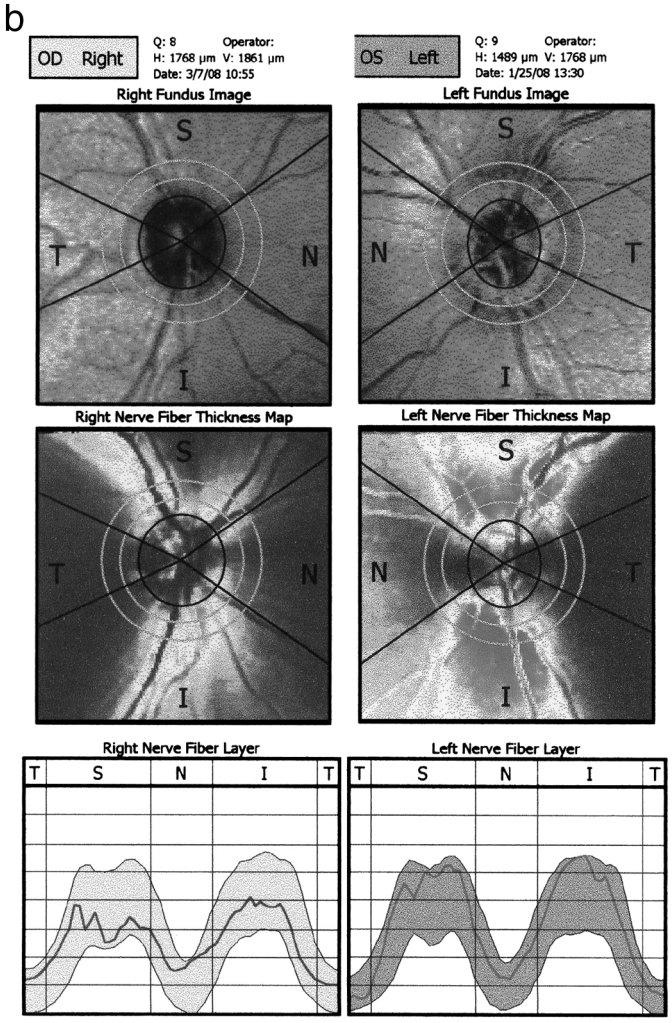


**Fig. 2** (*continued*).

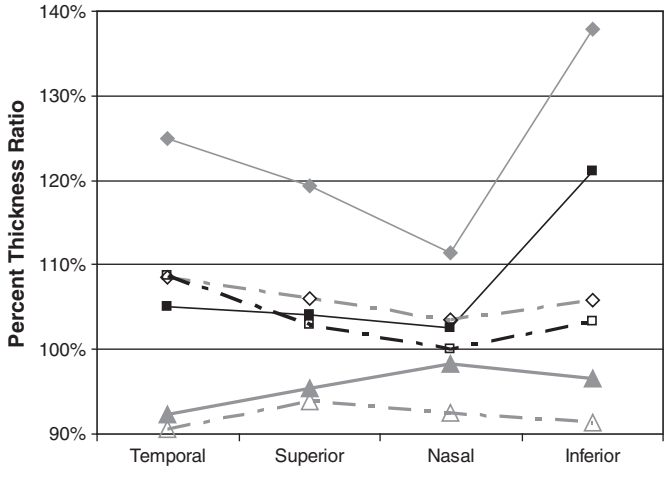


**Fig. 3.** Average OCT (data for 33 eyes) and SLP (data for 34 eyes) for affected eye values divided by fellow eye values across quadrants expressed as percentage. OCT (solid markers, solid lines) shown with baseline (diamond), 1 month (square), and 3 months (triangle) for affected eyes. SLP (open markers, broken line) shown with baseline (diamond), 1 month (square), and 3 months (triangle) for affected eyes.

## 4. Discussion

Quadrant analysis and comparison to fellow eye measurements revealed RNFL thickening, suggestive of swelling, in 82% by OCT and 62% by SLP of acutely affected eyes at presentation with first time optic neuritis. OCT was clearly superior to SLP in demonstrating the extent of RNFL baseline thickening. Interocular comparison of RNFL thickness is superior to the typically-used difference in quadrants from age-matched controls in industry databases for OCT and SLP and for OCT values obtained from our own controls (Iowa control eyes). Comparing the affected to the 'normal' fellow eye also increased the sensitivity of demonstrating thickening for the OCT and SLP global average RNFL above simple comparison with the databases for control eyes. Quadrant swelling was infrequently comparable for OCT and SLP, and OCT revealed significantly more swollen quadrants, particularly temporal and inferior, than SLP. Our use of interocular comparison to fellow asymptomatic eyes (if injured from prior demyelination) could have inflated the frequency of swelling in the affected eyes, but it would reduce our likelihood of uncovering early thinning or axonal loss (see below). We suggest that the fellow eyes used for comparison had no active demyelination since the RNFL measures across quadrants were stable over time. In addition, prior studies of patients with a single demyelinating episode, called clinically isolated syndrome, have shown that asymptomatic eyes have normal RNFL measurements [14]. We originally reported results from these study subjects and showed swelling of the RNFL in 85% via

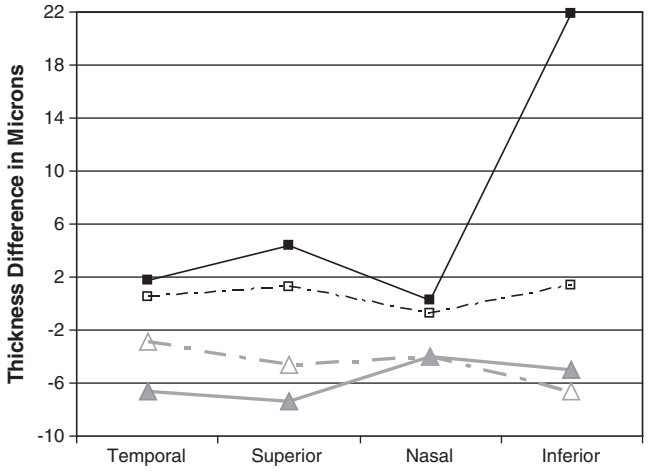


**Fig. 4.** For all affected eyes, the average number of micron difference at 1 and 3 months between the affected and fellow eye RNFL thickness (affected eye value–fellow eye value for each subject) for each quadrant. OCT (solid markers, solid lines) results shown for 1 month (square) and 3 months (triangle). SLP (open markers, broken line) results shown for 1 month (square) and 3 months (triangle). Values below zero suggest a loss of RNFL.

OCT and 88% via SLP of acute optic neuritis, using interocular comparison of sectors but variability for clock hour sectors limited reliability and consistent results (Kupersmith M, et al. Neurology:2008; 70 (Suppl 1): A128; Kupersmith et al. Neurology 2009;72; (suppl 3): A98). Recently, in a study with 41 patients, using analysis of quadrants, Kallenbach et al. reported swelling of the RNFL in approximately 38% of affected eye [5]. Most importantly, subjects were first evaluated as late as 28 days after the onset of vision loss so swelling might have partially resolved and RNFL loss could have reduced the frequency of reported swelling as demonstrated in our study. Additionally the Kallenbach study compared the affected and fellow eyes using Student *t*-test rather than paired *t*-test or interocular comparison, which could have further reduced the uncovering of RNFL swelling.

Both optical imaging methods have wide normal ranges for global averages and for quadrant values. In our study, the temporal quadrant was the most variable for SLP, but not for OCT, in both affected and fellow eyes at presentation and at 1 month. Accurate SLP measurement of the temporal quadrants remains problematic even when using the enhanced corneal compensation adjustment. The large standard deviation for both methods in affected eyes was expected given that the range of swelling is variable and without an upper limit. Given the tighter range, for most quadrants the fellow eye standard deviations were smaller than for the affected eye for both OCT and SLP.

The proximity of the lesion seen on MRI was not related to the swelling of the RNFL at baseline or thinning of the RNFL at 1 month. Our data demonstrate that RNFL thickening can occur when the demyelinating lesion is remote from the globe. These data suggest that axoplasmic blockade at the lesion site may cause stasis of axoplasmic flow proximal to the lesion, at the optic nerve head, resulting in the observed RNFL thickening. The number of quadrants thickened and severity of swelling of the RNFL for OCT or SLP do not seem to be associated with increased severity of visual loss at presentation or poor recovery of vision. This further supports the concept that the swelling is a secondary phenomenon, perhaps due to axoplasmic stasis in the inflamed retrobulbar optic nerve rather than a result of intraocular extension of inflammation or a cytotoxic edema.

Given that clinically observed swelling of the optic disc occurs in approximately one third of eyes with acute optic neuritis [1], we anticipated that RNFL swelling would be seen on OCT. The apparent, albeit minor, thickening seen on SLP was unanticipated given the insensitivity of SLP showing edema. OCT showed more thickening and more quadrants swollen than by SLP. This difference may reflect a relative insensitivity of SLP imaging to changes in extracellular water or edema in the peripapillary RNFL, which was previously reported in anterior ischemic optic neuropathy [15]. SLP measurements are obtained with methodology that differs from OCT. SLP RNL values are determined by the birefringence properties in the retina, which arise almost exclusively from the RNFL and is due to the array of parallel cylindrical organelles such as axonal membranes, microtubules, and neurofilaments [16,17]. The RNFL birefringence induces reflected light polarized along bundles of nerve fibers to be delayed and this slowing is termed retardance. The retardance is proportional to the RNFL thickness and decreases with RNFL thinning [18] or microtubule loss [19]. This suggests the observed thickening is not solely due to interstitial edema or increase in intra-axonal water content, such as occurs with papilledema [20]. Increased retardance could be due in part to amplified axoplasmic flow of organelles in response to the retrobulbar optic nerve injury or subsequent dilation of these axons. In contrast to the current study, a prior report, using a less sensitive fixed corneal compensation SLP method and no interocular comparison, failed to demonstrate significant RNFL thickening in acute optic neuritis [15].

We found evidence of RNFL thinning by OCT and SLP at 4 to 5 weeks after the onset of vision loss. This suggests a loss of axons in quadrants even in eyes where swelling persisted in other quadrants. Without the persistent swelling it is possible that more axonal loss would have been demonstrated. It may be that SLP changes in birefringence, similar to what occurs with the experimental colchicine model [18] may be demonstrated prior to OCT demonstration of RNFL thinning but our study did not show it. However, our first measurements after presentation were obtained at 1 month, possibly after any difference between methods might have been revealed. The timing for observing RNFL thinning in optic neuritis is comparable to the earliest RNFL losses seen after traumatic optic neuropathy OCT [21] and SLP [22]. In our study, eyes with MRI lesions closer to the globe did not show RNFL thinning earlier than those with lesions more remote.

RNFL loss at 3 months occurred in approximately 60% of affected eyes. Thinning occurred in all quadrants, was not selective and was equally well demonstrated with OCT and SLP. Quadrant and interocular analyses were superior in showing RNFL thinning compared with using actual global averages, which showed less than 30% of eyes had deficits. Both methods showed global average RNFL loss that correlated with visual performance at 3 months.

Imaging of the peripapillary RNFL in demyelinating disease provides an in vivo look into the pathological process, particularly in acute cases. The implications for our findings need further investigation and evaluations performed early may have predictive capabilities. We suggest that OCT and SLP imaging of the RNFL in MS can reveal more than just axonal loss, following injury. Given the wide range of values for normal RNFL thickness, from either averaging all sectors or from measurements of individual quadrants, comparing affected with 'normal' fellow eye measurements across quadrants clearly increases the sensitivity of detecting swelling and early thinning of the RNFL.

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