Correlation of Retinal Nerve Fiber Layer Measured by Scanning Laser Polarimeter to Visual Field in Ischemic Optic Neuropathy

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Objective: To evaluate the relationship between retinal nerve fiber layer (RNFL) measurement with scanning laser polarimetry (SLP) and standard automated perimetry (SAP) in nonarteritic anterior ischemic optic neuropathy (NAION).

Methods: In this prospective observational case series, all subjects (28 eyes with NAION) underwent SAP and SLP. The RNFL retardation measurements and visual field test points were grouped into 6 corresponding sectors. The contralateral uninvolved eye was used as control. The relationship between RNFL retardation and SAP was evaluated with the Spearman nonparametric technique and linear regression analysis. The main outcome measure was correlation of SLP RNFL parameters and SAP.

Results: Global and sectoral SLP parameters showed a significant difference in affected eyes compared with controls. The strongest correlations were seen between mean deviation and number (r = -0.524; P = .004), ellipse modulation (r = 0.5026; P = .006), and maximum modulation (r = 0.526; P = .004). Superior sectoral visual field indexes showed a strong correlation with inferior RNFL changes (r = 0.522; P < .008). Linear regression confirmed a strong relationship between the superior sectoral visual field indexes and the inferior RNFL.

Conclusion: Scanning laser polarimetry was able to identify structural changes of the RNFL globally and in the inferior SLP sector with functional loss in NAION.

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METHODS

SUBJECTS

An observational case series was undertaken involving 28 patients with isolated unilateral NAION occurring at least 3 months prior to initial examination with acute optic disc swelling. They were recruited from the Neuro-Ophthalmology Service at Wills Eye Hospital between September 2000 and October 2003. Patients were considered eligible for recruitment if they had a diagnosis of unilateral NAION, with the initial disc swelling and the diagnosis documented and confirmed at Wills Eye Hospital by a neuro-ophthalmologist. The uninvolved eye was required to have normal ophthalmic assessment findings with a visual acuity of 20/40 or better. Patients with glaucoma, a family history of glaucoma, intraocular pressure of greater than 21 mm Hg in either eye, giant cell arteritis, other optic neuropathies, posterior segment diseases, corneal diseases, refractive surgery, or neurological diseases or systemic diseases with possible ocular involvement, such as diabetes mellitus, were excluded from the study. Patients were excluded if they had anetropia greater than 5 diopters (D) or astigmatism greater than 2.5 D. All patients had experience with VF testing and had undergone at least 2 prior tests with reliable results. Because there is a wide intersubject variability in the RNFL thickness, the unaffected eye was used as the control.

All patients underwent a complete neuro-ophthalmic examination performed by a neuro-ophthalmologist at the time of initial examination and on follow-up visits. This was followed by Swedish Interactive Threshold Algorithm (SITA) 24-2 standard automated perimetry (SAP) and SLP (GDx Nerve Fiber Analyzer with fixed corneal compensation [software version 2.0.09]; Laser Diagnostic Technologies), which were performed within 1 week of each other. The research adhered to the tenets of the Declaration of Helsinki. The institutional review committee had approved the research and informed consent had been obtained.

SCANNING LASER POLARIMETRY

The GDx is a confocal scanning laser ophthalmoscope with an integrated polarization modulator, a fixed corneal compensator, and a polarization detection unit. Details of its operation are described elsewhere. In all subjects, both eyes were scanned starting with the right eye. The pupils of the patients were undilated, and the room lights were left on. Three high-quality retardation images were acquired through the undilated pupil and the results were averaged for the analysis. The default sectors were defined as temporal (25° to 25°), superior (25° to 145°), nasal (145° to 215°), and inferior (215° to 335°), giving two 120° sectors, a 70° sector, and a 50° sector. The parameters automatically generated by the SLP software were evaluated. These were divided into parameters that represented a global assessment of the RNFL and parameters that represented the sectoral RNFL status. Global parameters were the number, symmetry, ellipse modulation, maximum modulation, and ellipse average. The number is a global measure derived from more than 200 other parameters that are analyzed by a neural network trained to discriminate between healthy and glaucomatous eyes. The maximum modulation and ellipse modulation are indicators of the difference between the thickest and thinnest parts of the RNFL. Sectoral parameters were superior maximum, inferior maximum, superior average, inferior average, temporal median (superior maximum–superior ratio), nasal median (superior maximum–superior nasal ratio), superior integral, (superior temporal ratio), inferior (inferior temporal ratio), and superior nasal ratio.

Figure 1. Test pattern of the Humphrey Field Analyzer 24-2 (Carl Zeiss Meditec) paradigm for a right eye (A) and a GDx Nerve Fiber Analyzer with variable corneal compensator (Laser Diagnostic Technologies, Inc, San Diego, Calif) retardation image of a right eye (B), with a measurement circle superimposed (the fixed corneal compensator has the exact same arrangement). In the present study, visual field test points and peripapillary GDx measurements were grouped in corresponding sectors, as suggested by Garway-Heath et al. Corresponding sectors were grayscale and named after the position of the sector in the GDx variable corneal compensator image in relation to the optic disc.

VF TESTING

Standard automated perimetry was performed with the SITA standard 24-2 program. All VF test results were reliable with less than 33% fixation losses, false-positive responses, and false-negative responses. Each VF was divided into 6 zones based on the optic disc–VF map described by Garway-Heath et al (Figure 1). Garway-Heath et al produced the first high-resolution map from structure to function. Using this map allowed a detailed comparison of structure (GDx image) and function (SAP) measures. This mapping allowed correlation of sectors of disc RNFL with sectors of the VF. Because sectoral SLP parameters are divided into 4 fixed sectors, the 2 superior (sectors 2 and 3) and 2 inferior (sectors 4 and 5) VF zones were combined to permit a direct 4-sector comparison between VFs and SLP. Thus, sector 1 (temporal VF, nasal optic disc 121° to 230°) corresponds to the nasal SLP measurements. Sectors 2 and 3 (superior and superior nasal VF, inferior optic disc sectors 231° to 270° and 271° to 310°) correspond to the inferior nasal and inferior temporal SLP measurements, respectively. Sectors 4 and 5 (inferior paracentral and inferior VF, superior disc sectors 41° to 80° and 81° to 120°) correspond to superior temporal and superior nasal SLP measurements, respectively. Sector 6 (macular VF, temporal disc 311° to 340°) corresponds to temporal parapapillary SLP measurements.

The mean deviation (MD) was calculated for each of the sectors from the raw retinal sensitivity on the VF printout. We then correlated SLP measurements with the global and sectoral MDs of the appropriate VF zones using linear and logarithmic regression based on the assumption that the RNFL is a predictor of VF sensitivity.

STATISTICAL ANALYSIS

The unaffected contralateral eyes were used as the control group. A Spearman ranked correlation coefficient (r) was calculated for each sector to measure the degree of association between SAP and SLP. A t test for related groups was used to compare affected with unaffected eyes. “Number” and “symmetry” are not normally distributed parameters; therefore, the sign test was used for these parameters. All tests were 2-tailed and a P value of <.05 was considered statistically significant because all comparisons were preplanned. However, a more conservative critical significance level could be adopted based
RESULTS

A total of 28 patients (13 men, 15 women) were evaluated. The mean ± SD age was 61 ± 11 years (range, 39-79 years). The mean time between initial examination and study enrollment was 4.1 months, ranging from 97 days to 159 days. At the final visit, the mean visual acuity was 0.06 logarithm of the minimum angle of resolution (logMAR) (approximately 20/30 Snellen equivalent) in the control eyes and 0.44 logMAR (20/60 Snellen equivalent) in the affected eyes ($P = .01$).

GLOBAL PARAMETERS

The MD of the affected group ranged from −26 to 0 dB with a mean ± SD of −11.74 ± 6.65 dB, while the unaffected MD ranged from −4.36 to 3.74 dB with a mean ± SD of −0.63 ± 2.03 dB. The difference was statistically significant ($P < .001$). All global SLP parameters with the exception of symmetry were significantly different between the affected and unaffected eyes (Table 1).

The relationship between SAP and SLP measurements is graphically presented in Figures 2, 3, 4, and 5 for global parameters in eyes with NAION. The global SLP parameters that significantly correlated with MD in affected eyes were number ($r = −0.524; P = .001$), maximum modulation ($r = 0.526; P = .004$), and ellipse modulation ($r = 0.5026; P = .006$) (Bonferroni correction $P < .008$). The correlation between RNFL loss and MD only modestly improved when the difference between affected and unaffected eyes was considered for both RNFL and VF loss; that is, the affected RNFL was subtracted from the unaffected RNFL and this value correlated with the difference between affected and unaffected VF sensitivities.

SECTORAL PARAMETERS

The VF indexes in all sectors of affected eyes were significantly depressed compared with the contralateral unaffected eyes ($P < .001$) (Table 3). The majority of the sectoral SLP parameters of affected eyes were significantly different from unaffected eyes (all $P < .001$), with the exception of those that represented the temporal and nasal regions. In healthy, unaffected eyes, no statistically significant correlations between SAP and SLP measurements were found in any sector ($P = .39$).

When the relation between structure and function was evaluated using the sectoral SLP parameters with their corresponding VF sectors, only those representing the inferior RNFL region showed significant association with

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Table 1. Global VF Indexes and RNFL Parameters by SLP Between Affected NAION Eye and Contralateral Normal Eye

<table>
<thead>
<tr>
<th>Mean ± SD</th>
<th>Normal Eye (n = 28)</th>
<th>Involved NAION Eye (n = 28)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VF MD, dB</td>
<td>−0.63 ± 2.03</td>
<td>−11.74 ± 6.65</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Number</td>
<td>23.42 ± 17.34</td>
<td>52.25 ± 19.49</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ellipse modulation</td>
<td>2.37 ± 0.62</td>
<td>1.86 ± 0.62</td>
<td>.001</td>
</tr>
<tr>
<td>Average thickness</td>
<td>65.19 ± 12.18</td>
<td>58.29 ± 10.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ellipse average, µm</td>
<td>68.96 ± 11.78</td>
<td>58.21 ± 10.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Maximum modulation</td>
<td>1.50 ± 0.52</td>
<td>1.03 ± 0.39</td>
<td>.001</td>
</tr>
<tr>
<td>Symmetry</td>
<td>0.90 ± 0.13</td>
<td>0.85 ± 0.15</td>
<td>.27</td>
</tr>
</tbody>
</table>

Abbreviations: MD, mean deviation; NAION, nonarteritic anterior ischemic optic neuropathy; RNFL, retinal nerve fiber layer; SLP, scanning laser polarimetry; VF, visual field.

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Figure 2. Correlation between visual field mean deviation (MD) and GDx Nerve Fiber Analyzer (Laser Diagnostic Technologies, Inc, San Diego, Calif) global parameter “number” (affected eyes). $r = −0.524$.

Figure 3. Correlation between visual field mean deviation (MD) and GDx Nerve Fiber Analyzer (Laser Diagnostic Technologies, Inc, San Diego, Calif) global parameter “maximum modulation” (affected eyes). $r = 0.526$. 

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the corresponding superior VFs (Table 4). This included inferior deviation from normal ($r = 0.522; P = .008$), inferior average ($r = 0.517; P = .005$), and inferior maximum ($r = 0.564; P = .002$). Interestingly, inferior maximum and inferior average also correlated with nasal VF sector ($r = 0.624; P < .001$ and $r = 0.611; P = .001$, respectively). The relation of structure and function was not identifiable between any of the other sectors, including superior RNFL and the corresponding inferior VF. 

Table 5 tabulates the qualitative interpretation of the VF defect along with the quantitative VF raw sensitivities and the GDx RNFL parameters. Figure 6 shows the fit with a least-squares linear regression model for the relationship between RNFL and decibel–differential light sensitivity with $r = 0.683$ ($P < .001$). Figure 7 illustrates results for a patient with NAION studied with SLP and the corresponding VF defect.

In glaucoma, there is a correlation between structural measures of optic neuropathy, which is measured with SLP, and functional loss, which is measured with SAP. Scanning laser polarimetry (both with fixed corneal compensation and variable corneal compensation) has also been shown to differentiate patients with glaucoma from normal individuals with sensitivities and specificities of 72% to 78% and 56% to 92%, respectively. However, to date, there is a paucity of studies.
that quantitate RNFL loss in nonglaucomatous optic neuropathies. The appearance of the optic nerve in NAION has not been evaluated quantitatively beyond a case report; rather it is usually subjectively described by estimating the degree and extent of pallor or qualitatively commenting on defects in the nerve fiber layer. Moreover, no available studies have been performed that quantitatively correlate RNFL loss in nonglaucomatous optic neuropathies with a corresponding decrease in VF sensitivities. To our knowledge, this study is the first to demonstrate that when examined with SLP, eyes affected with NAION show defects in the RNFL that can be identified both with the global and the sectoral SLP parameters. Furthermore, to our knowledge, this study is also the first to quantify a relationship between changes of the RNFL and corresponding changes in VF sensitivity in NAION.

All global SLP parameters (with the exception of symmetry) were significantly different between affected and unaffected eyes. Our findings in NAION are similar to studies using SLP in glaucoma, with “number” and “maximum modulation” demonstrating the strongest correlation. The modulation parameters are theoretically more reliable, correcting for individual variation in the RNFL thickness, average, and ellipse average were not correlated with VF MD, in keeping with the findings of Lan et al. The impact of a fixed corneal compensator improperly compensating for intersubject variability in corneal birefringence is the most likely explanation. Additionally, normal VF findings can be associated with a wide range of RNFL measurements. Thus, for a global parameter such as “average” to be significantly reduced in some subjects, a certain amount of RNFL damage must occur; hence, small focal RNFL or optic nerve head damage might be overlooked.

Scanning laser polarimetry demonstrated attenuation of the RNFL in the superior and inferior sectors in...
the right eye and a contralateral unaffected left eye. Note the flattening of the superior retinal nerve fiber layer hump.

Another contributing factor may be a “floor effect,” described by Schlottmann et al, which is when an RNFL of less than 20 µm is not detected. This would result in the detection of noise from other structures rather than signal from the remaining superior RNFL. In the present study, the superior RNFL was significantly thinner than the inferior (mean ± SD, 14.21 ± 8.41 µm vs 19.11 ± 10.55 µm), with the majority of affected eyes less than 20 µm. The MD was also more depressed in the inferior field (−15 dB) than the superior field (−8 dB) when compared with normal eyes. This loss of VF sensitivity, particularly in the inferior VF, may in fact equate to almost total loss of the superior RNFL.

Finally, the lack of correlation could be partly explained by the arbitrary division of sectors of the SLP and VF map. The division of the VF map is not based on altitudinal pattern. Therefore, measurements of the superior and inferior VF sectors are approximates that exclude half of the nasal and temporal fields that cross over into the respective superior or inferior hemifields. Moreover, the structure-function mapping used in this study attributes only 4 points to the temporal field and thus only 2 points for the superotemporal and inferotemporal fields. The nasal field is not sectorially represented on its own. Therefore, there may not be enough points to detect functional loss in such an analysis.

In summary, to our knowledge, this study is the first to quantitatively measure the attenuation of the RNFL with SLP in a group of patients who had a previous episode of NAION. It demonstrates a partial topographic correlation of optic nerve structure with MD, where magnitude of focal RNFL attenuation was related to the magnitude of the decreased VF sensitivity.

The ability to objectively measure the degree of damage to the optic nerve directly, rather than indirectly by the amount of VF damage, marks a juncture in the study of nonglaucomatous optic neuropathies. This study has shown that there is a quantitative relation between structure and function in an optic neuropathy other than glau-

Figure 7. GDx Nerve Fiber Analyzer (Laser Diagnostic Technologies, Inc, San Diego, Calif) data for a patient with nonarteritic anterior ischemic optic neuropathy in the right eye and a contralateral unaffected left eye. Note the flattening of the superior retinal nerve fiber layer hump.

The temporal and nasal SLP and VF sectors were not significantly different between the affected and unaffected eyes. The inferior SLP indexes showed a significant correlation with the MD, reflecting that a significant sectoral RNFL defect can result in both sectoral and global loss of VF sensitivity. Similar correlations between sectoral parameters and MD have been reported in glaucomatous eyes. The inferior sectoral SLP parameters were also strongly correlated with the superior VF indexes, reflecting that VF defects in NAION tend to be altitudinal defects.

Surprisingly, no structure-function relationship was found between the superior RNFL segment and the corresponding inferior VF sectors. A similar finding was found in glaucomatous eyes using SLP, where inferior SLP indexes correlated strongly with superior VF indexes and superior SLP indexes did not correlate with inferior VF indexes. Recently, others have also identified weaker correlations between the inferior VF indexes and corresponding superior SLP indexes.

There are several possibilities that may account for this lack of correlation. The strength of the correlation in all the sectors may be affected by the fixed corneal compensator, which has been shown to affect the discriminative power of SLP in mild to moderate glaucoma. The fixed corneal compensator introduces an error in measurements by erroneously compensating for corneal birefringence where the axis and magnitude of birefringence differ from population mode values. The introduction of the variable corneal compensator to achieve individualized corneal compensation has improved the relationship between the RNFL measured with SLP and the VF test. Inadequate (under) corneal compensation may result in a general increase in full-field retardation that may translate to spuriously high RNFL retardation, decreasing structure-function associations.
coma. Future research should further investigate the structure-function relationship of neuro-ophthalmic conditions and determine whether these technologies may provide us with diagnostic and prognostic information to improve patient care.

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REFERENCES