Correlation of Relative Afferent Pupillary Defect and Retinal Nerve Fiber Layer Loss in Unilateral or Asymmetric Demyelinating Optic Neuropathy

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PURPOSE. To investigate the relationship between relative afferent pupillary defect (RAPD) and retinal nerve fiber layer (RNFL) thickness assessed by optical coherence tomography (OCT) in patients with unilateral or asymmetric demyelinating optic neuropathy.

METHODS. Seventy-two patients with unilateral or asymmetric demyelinating optic neuropathy were retrospectively evaluated. RAPD was measured by the swinging flashlight method using neutral density filters, and RNFL thickness was measured with the OCT. Relationships between RAPD and RNFL thickness difference/ratio between the two eyes (in superior, inferior, temporal, nasal quadrants and total thickness) were evaluated by linear regression. Coefficients of determination ($R^2$) were calculated using a multivariate model.

RESULTS. The mean RNFL thickness in the more affected eyes was $82.7 \pm 18.7 \mu m$, and in the fellow eyes it was $88.9 \pm 15.97 \mu m$ ($R^2 = 0.406; P < 0.0001$). RAPD size correlated significantly with both RNFL thickness difference (total: $R^2 = 0.191$, $P < 0.0001$; superior: $R^2 = 0.203$, $P < 0.0001$; inferior: $R^2 = 0.126$, $P = 0.002$; temporal: $R^2 = 0.059$, $P = 0.040$; nasal: $R^2 = 0.062$, $P = 0.035$) and RNFL thickness ratio (total: $R^2 = 0.325$, $P = 0.0001$; superior: $R^2 = 0.339$, $P < 0.0001$; inferior: $R^2 = 0.256$, $P < 0.0001$; temporal: $R^2 = 0.151$, $P = 0.0001$; nasal: $R^2 = 0.156$, $P = 0.001$).

CONCLUSIONS. RAPD as measured in log units significantly correlated with total and quadrant RNFL thickness differences and ratios. Total, superior, and inferior quadrant data produced the strongest correlations. (*Invest Ophthalmol Vis Sci.* 2010; 51:4013–4016) DOI:10.1167/iovs.09-4644

The relative afferent pupillary defect (RAPD) is an asymmetry in the pupillary light response and an important objective parameter for quantifying the loss of neuronal function in asymmetric or unilateral optic nerve or retinal disorders. Detection of RAPD is performed by alternately illuminating each eye while comparing the velocity and amplitude of the pupillary responses with the swinging flashlight test. Neutral density filters in 0.3 logarithmic unit steps aid in the detection and quantification of RAPD. The size of RAPD can be quantified by the density of the filter required to balance the response of each eye, typically ranging from 0.3 to 1.8 log units.

Optical coherence tomography (OCT) allows direct visualization and measurement of RNFL thickness and macular volume with micron-scale resolution. The OCT data analysis program generates values for average RNFL thickness that can be further divided into quadrants and clock hour sectors (12 zones) for more localized analyses. Normal values for RNFL thickness are available for age-stratified populations, with an average decline of approximately 0.17% per year. Several studies have used the OCT to evaluate retinal changes in patients with glaucoma and found that the visual field abnormalities in such patients are linked to changes in RNFL thickness. Nakanishi et al. estimated that at least 25% RNFL loss is required to have RAPD.

In this study we analyzed the relationship between RAPD and RNFL thickness (difference and ratio) in patients with unilateral or asymmetric demyelinating optic neuropathy.

METHODS. Seventy-two patients from the Neuro-ophthalmology Unit, Department of Neurology and Ophthalmology, Michigan State University, with unilateral or asymmetric demyelinating optic neuropathy who had RAPD confirmed and OCT performed in the same visit were retrospectively reviewed. In addition to RAPD, patients were included only if they were found to have other signs of optic neuropathy, such as decreased visual acuity, visual field defect, dyschromatopsia, and diminished contrast or brightness sensitivity. The study was a retrospective study with already established data, and it followed all the guidelines for experimental investigations required by the Institutional Review Board and Ethics Committee of Michigan State University.

Charts were reviewed, and all patients underwent complete ophthalmic examination, including visual acuity, slit lamp biomicroscopy, intraocular pressure measurement with Goldmann tonometry, and fundus examination. Patients were excluded if they had any other conditions that might affect the measurement of RAPD or OCT, such as glaucoma, cataract of more than 2 severity (can cause contralateral RAPD because of light scattering in the ipsilateral eye), mechanical iris dysfunction, myopia >6 D, or OCT of insufficient quality. All subjects who had acute optic neuropathy were included at least 6 months after the onset of optic neuropathy to ensure complete resolution of optic disc swelling, if any.

The RAPD measurement was performed by the investigators using the swinging flashlight method with neutral density filter quantification ranging from 0.3 to 1.8 log units in 0.3-log unit increments. While in a sitting position, patients were instructed to fixate on a distant target in a mesopic room, and then each eye was illuminated for 3 seconds. This method is best described by Kawasaki et al.

Quantitative RNFL measurements were obtained using OCT (Stratus; software version 3.0.1; Carl Zeiss Meditec, Inc., Dublin, CA). The average RNFL thickness for the entire circumference and for each quadrant was obtained for both eyes. Repeated measurements were taken by the investigators until a good quality OCT was achieved for each eye (signal strength ≥6) with the disc centered in the 3.4-mm...
circle. The more affected eye was defined as the eye with positive RAPD regardless of the OCT measurement.

Statistical analysis was performed (SPSS; SPSS, Inc., Chicago, IL). The comparison of two independent continuous variables was made with unpaired t-test. Correlation coefficient and linear regression were used in assessing the relationship between RAPD and the following parameters: inter-eye difference of mean RNFL thickness; ratio of RNFL thickness in the fellow eye to the more affected eye.

RESULTS

Seventy-two patients were included in the analysis (mean age, 45.8 ± 10.3 years [range, 24–69 years]). Thirty-two percent (n = 25) of our patients were men, and sixty-eight percent (n = 49) were women. Optic neuropathy in this group was caused by demyelinating disease (95.9% [n = 69 patients], multiple sclerosis; 4.1% [n = 3], Devic neuromyelitis optica). RAPD was detected in the right eye in 64% of our patients.

Mean RNFL thickness was 82.74 ± 18.74 μm in the more affected eyes and 88.89 ± 13.97 μm in the fellow eyes, with significant difference between the sets of eyes (R² = 0.406; P < 0.0001). Mean quadrant RNFL thicknesses of the more affected eyes and the fellow eyes were 53.25 ± 18.60 and 57.95 ± 16.54 μm temporally (R² = 0.637; P < 0.0001), 71.23 ± 21.52 and 73.16 ± 17.73 μm nasally (R² = 0.585; P < 0.0001), 102.73 ± 24.27 and 112.79 ± 20.14 μm superiorly (R² = 0.505; P < 0.0001), and 103.70 ± 27.16 and 111.84 ± 20.15 μm inferiorly (R² = 0.666; P < 0.0001; Table 1).

The RAPD range was between 0.3 and 1.8 log units, with a mean of 0.525 log units. Eighty-six percent (n = 62) of our patients had a RAPD of ≤0.6 log units. The RAPD correlated significantly with both RNFL thickness difference (total: R² = 0.191, P < 0.0001 [Fig. 1]; superior: R² = 0.203, P < 0.0001; inferior: R² = 0.126, P = 0.002; temporal: R² = 0.059, P = 0.040; nasal: R² = 0.062, P = 0.035) and RNFL thickness ratio of the fellow eye to the more affected eye (total: R² = 0.325, P < 0.0001 [Fig. 2]; superior: R² = 0.339, P < 0.0001; inferior: R² = 0.256, P < 0.0001; temporal: R² = 0.151, P < 0.0001; nasal: R² = 0.156, P = 0.001).

DISCUSSION

This is the largest study to date correlating RAPD and RNFL thickness in patients with unilateral or asymmetric demyelinating optic neuropathy using the OCT. Coupling quantifiable measures of visual function such as RAPD using the swinging flashlight test with ocular imaging techniques such as OCT enables us to correlate structural changes in the visual system with function in patients with optic neuropathy.14

The annual incidence of optic neuritis is 1 to 5 cases per 100,000 population.15–19 and optic neuritis is the presenting manifestation of multiple sclerosis in approximately 19% of

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<th>Table 1. Average RNFL Thickness</th>
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<td>More Affected Eye (μm)</td>
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</tr>
<tr>
<td>Total RNFL thickness</td>
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<tr>
<td>Superior quadrant</td>
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![Figure 1. Relationship between RAPD (log units) and the difference in the total RNFL thickness (R² = 0.191; P < 0.0001).](image-url)
patients$^{20}$; 55% to 60% of patients with multiple sclerosis have evidence of optic neuropathy at some point during their disease.$^{21,22}$ These facts made our multiple sclerosis patients a good population in which to study the relationship between RAPD and RNFL.

The superior, inferior, and nasal quadrants of the peripapillary RNFL are largely composed of magnocellular ganglion cell axons. In contrast, the parvocellular ganglion cell axons, which are the major component of the papillomacular bundle, are concentrated in the temporal quadrant. More recently, the role of melanopsin-containing ganglion cells in the non-image-forming visual system, including the pupillary response and synchronization of the biological clock through suprachiasmatic nucleus connection, has been emphasized; however, the exact location, number, connections, and projections of these cells are still under investigation.$^{23-25}$

In a study performed in patients with optic neuropathy of various etiologies (anterior ION, posterior ION, compressive optic neuropathy, and traumatic optic neuropathy), Nakanaishi et al.$^{11}$ concluded that substantial retinal ganglion cell damage is required for the development of RAPD, and they estimated 25% RNFL loss in the affected eyes compared with the unaffected eyes before RAPD was clinically detected. In that study, they did not find a significant correlation between quadrant RNFL thickness ratio and RAPD and attributed that to the variability in visual field defects and small sample size. In another study performed by the same group but in patients with asymmetric glaucoma, Tatsusmi et al.$^{12}$ found that RAPD was clinically detectable when the average total RNFL thickness was reduced by 27% in the more affected eyes compared with the fellow eyes. In that study, they used 0.6 log units as the minimal clinically detectable RAPD and found that the correlation between RAPD and quadrant RNFL thickness ratio was strongest in the inferior quadrant, followed by superior, temporal, and nasal quadrants.$^{12}$

Our study clearly demonstrated that the size of RAPD is significantly correlated with both RNFL thickness difference and ratio of the total and all RNFL quadrants. The strongest correlations were found with the total, superior, and inferior quadrants. These results are in good agreement with those of Tatsusmi et al.$^{12}$ especially if we accept the fact that glaucoma is a group of intraocular diseases that affect the vertical segments of the optic disc (inferior more than superior quadrant) more than the horizontal segments, whereas demyelinating diseases are systemic diseases that should have a generalized effect in optic disc RNFL, with the thicker segments (superior and inferior quadrants) having the most effect.

In rhesus monkeys that underwent laser ablation of macular tissue, Kerrison et al.$^{26}$ found that a 0.6-log unit RAPD was detected only when the lasered area incorporated the entire area within the arcades, suggesting that near total loss of parvocellular ganglion cell axons and partial loss of the magnocellular ganglion cell axons occurred. They concluded that a 0.6-log unit RAPD developed after unilateral RNFL loss of 25% to 50% and postulated that this threshold effect might have been caused by the redundancy in the anterior visual pathways. The neuroanatomic substrate for this redundancy may be attributed to the overlapping receptive fields and the pattern of retinal ganglion cell loss, whether it is focal and complete or diffuse and partial.$^{27,28}$

Our findings collectively made us wonder whether the parvocellular ganglion cell axons were not the major contributors to the bulk of the afferent pupillary response and about the exact contribution of both magnocellular ganglion cell axons and melanopsin-containing ganglion cell axons to this response. In our study, 33% ($n = 24$) of patients had RNFL thickness within normal limits in both eyes ($>88.9 \mu m$) and a RAPD range between 0.3 ($n = 16$), 0.6 ($n = 7$), and 0.9 ($n = 1$) log units. In addition, RNFL thickness was greater in the affected eyes in 30% ($n = 21$) of patients. These results do not totally agree with the previous studies, which concluded that a significant amount of RNFL loss (25%–50%) was needed for detectable RAPD and could be explained by qualitative cell (ganglion cell) contribution to the occurrence and size of RAPD.

Interestingly, we found that the more affected eye (with RAPD) actually had a thicker total RNFL than the fellow eye in 30% ($n = 21$) of our patients and equal thickness in 5% ($n =
4). Of these affected eyes, 52% had a total RNFL thickness of >88.9 μm (mean RNFL thickness in the nonaffected eyes in our patient population) with a RAPD range between 0.3 (61%), 0.6 (31%), and 0.9 (8%) log units. Three patients who had equal RNFL had 0.6-log units RAPD, and the fourth patient had 0.3-log units RAPD.

Further statistical analysis was performed for this particular group to see whether any of the four quadrant RNFL thickness ratios had significant correlation with RAPD, but none of them was significant (total: $R^2 = 0.001$, $P = 0.96$; superior: $R^2 = 0.27$, $P = 0.442$; inferior: $R^2 = 0.012$, $P = 0.605$; temporal: $R^2 = 0.056$, $P = 0.267$; nasal: $R^2 = 0.001$, $P = 0.912$).

Given that 30% of our patients had thicker RNFL in the affected than the nonaffected eye and that both the superior and the inferior quadrants had the most significant correlations even though they did not carry the papillomacular bundle, we think this supports the hypothesis that in a human visual pathway, not only does the quantitative asymmetry in RNFL thickness relate to RAPD, but perhaps the differential effect on the various retinal ganglion cell types (parvocellular, magnocellular, melanopsin-containing) is responsible for both the occurrence and the size of RAPD. Further studies should be performed to identify the exact location of these retinal ganglion cell types and their role in the afferent pupillary reflex.

One limitation of our study was that all our patients had demyelinating disease; accordingly, the results may not be generalized to other causes of optic neuropathy. Further studies should be conducted to find the relation between RAPD and RNFL thickness in patients with nondemyelinating causes of optic neuropathy.

In summary, the size of RAPD was found to significantly correlate with both the difference in RNFL thickness and the ratio of the RNFL thickness in the fellow eyes to the more affected eyes globally and in all quadrants; the total, superior, and inferior quadrant RNFL demonstrated the strongest correlations with the degree of RAPD. Our findings indicate that the size of RAPD may predict the degree of RNFL loss.

Acknowledgments

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References