

Measurement of the retinal nerve fibre layer with scanning laser polarimetry in patients with previous demyelinating optic neuritis

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Abstract

Objectives—Subjective visual deficits are common after demyelinating optic neuritis despite the frequent return of normal visual acuity. Visual and electrodiagnostic tests have demonstrated evidence of these persisting functional abnormalities, which are thought to be secondary to demyelination and variable axonal loss in the optic nerve. Scanning laser polarimetry (SLP) is a new image analysis technique which uses the polarising properties of the retinal nerve fibre layer (RNFL) to produce a quantitative measure of its thickness. This study was carried out to assess the prevalence, extent, and pattern of RNFL loss after demyelinating optic neuritis using SLP.

Methods—Twenty four patients with a history of previous demyelinating optic neuritis were re-examined. Examination included measurement of logmar visual acuity, Pelli-Robson contrast sensitivity, and the presence of a relative afferent pupil defect and optic atrophy. SLP was performed and a mean RNFL profile from a series of three images from each eye was constructed. This was compared with normative data from 20 age matched normal subjects. The lower 99.9% confidence limit of the normal data was calculated and used as the cut off criterion for abnormality.

Results—There were a total of 31 eyes with a history of demyelinating optic neuritis and SLP disclosed an abnormality in 29 (94%) of these. Twenty three eyes recovered an acuity of 0.0 or better, 21 of which had evidence of RNFL loss on polarimetry. Scanning laser polarimetry was the only abnormality found in nine of the 31 eyes (29%). The pattern and extent of RNFL loss was very variable and there was no significant difference in these indices between patients with multiple sclerosis compared with those with isolated demyelinating optic neuritis.

Conclusion—Scanning laser polarimetry can provide a quantitative measure of RNFL loss after demyelinating optic neuritis, demonstrating its occurrence in a high percentage of patients recovering normal visual acuity.

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Keywords: demyelinating optic neuritis; retinal nerve fibre layer; scanning laser polarimetry

Demyelinating optic neuritis is a common condition which generally has a characteristic course and a good prognosis for vision. About 75% of patients regain 6/6 vision but despite this, patients often complain of subjective visual deficits.^{1,2} Some visual tests can detect evidence of these residual functional abnormalities with variable sensitivity. Visual evoked responses have been used as an objective assessment of optic nerve function after recovery from demyelinating optic neuritis. Abnormal results have been demonstrated in 65% to 100% of cases recovering 6/6 vision or better.³⁻⁸ Similarly, Pelli-Robson contrast sensitivity, colour vision as tested with the Farnsworth-Munsell 100 hue test, and visual fields give abnormal results in 46%, 26%, and 20% of cases recovering 6/6 vision respectively.²

The precise aetiology of these persisting abnormalities is unknown but variable atrophy of the optic nerve and retinal nerve fibre layer (RNFL) has been well described in multiple sclerosis and after demyelinating optic neuritis. The mechanism resulting in axonal loss is unknown but may be due to the retrograde atrophy of axons within plaques of demyelination. Kerrison *et al* showed RNFL atrophy at postmortem histologically in 35 of 49 eyes of patients previously diagnosed as having multiple sclerosis.⁹ Frisen and Hoyt considered that RNFL loss was universal after demyelinating optic neuritis although they admitted that this was not always detectable using techniques available at that time.¹⁰ Ophthalmoscopically visible optic disc pallor and RNFL defects have been shown to result from the direct loss of axons.¹¹ Direct ophthalmoscopy and red free photography have enabled clinical observation of optic disc pallor in 50% to 71% of patients with a history of demyelinating optic neuritis and multiple sclerosis, and RNFL defects in up to 89%.^{8,12} However, it is known that RNFL atrophy is only detectable using red free photography after a 50% loss of neural tissue in a given area.¹¹ Furthermore the evaluation of optic disc characteristics and RNFL assessment using the above techniques is thought to be qualitative, subjective, and inconsistent even among experienced observers.¹³

Scanning laser polarimetry (SLP) is a new computerised image analysing technique which utilises the polarising properties of the RNFL to determine its thickness.¹⁴ Preliminary studies have investigated the use of SLP in the diagnosis of glaucoma with promising results.^{15,16} Comparison of the data from SLP in an individual patient to a normal age

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Table 1 Demographic profile of the patients

Patient category (n = 24)	Unilateral/bilateral DON	Age (mean, (range) y)	Sex	Time interval after last DON episode (mean, (range) y)
10 Clinically definite or probable MS	5 Unilateral 5 Bilateral	37 (32–52 years)	1 M 9 F	4.5 (1–9)
14 Isolated DON	12 Unilateral 2 Bilateral	39 (29–56)	3 M 11 F	5.2 (1–10)
Normals		37 (30–55)	4 M 16 F	

DOM=demyelinating optic neuritis; MS=multiple sclerosis.

matched database provides the potential to detect, quantify, and locate areas of RNFL loss. This study was designed to assess the prevalence, extent, and pattern of RNFL loss in patients, as measured with the SLP, in a cohort of patients who had recovered from an episode of demyelinating optic neuritis in at least one eye. Furthermore, it was carried out to compare this RNFL assessment with the findings of other clinical tests and to determine the sensitivity of SLP in the detection of optic nerve abnormalities as compared with the other methods.

Method

Approval from the local ethics committee was obtained along with informed consent from all of the patients. Forty five patients were chosen at random from those who had attended the Bristol Eye Hospital with a documented history of demyelinating optic neuritis in the preceding 10 years. The original diagnosis was based on the criteria summarised by Glaser.¹⁷ Patients were excluded if there was a history of any other eye abnormality and if there was a history of more than one episode of optic neuritis in either eye.

Twenty five of these patients were able to attend for re-examination. This included the assessment of visual acuity, Pelli-Robson contrast sensitivity, the presence of optic disc pallor and a relative afferent pupillary defect, and scanning laser polarimetry on both eyes.

Visual acuity was tested with a full refraction in place, on a retroilluminated Bailey-Lovie chart at a distance of 4 m. Acuity was recorded

in Logmar units. An acuity of 0.0 (equivalent to 6/6 on a Snellen chart) or lower was considered normal.

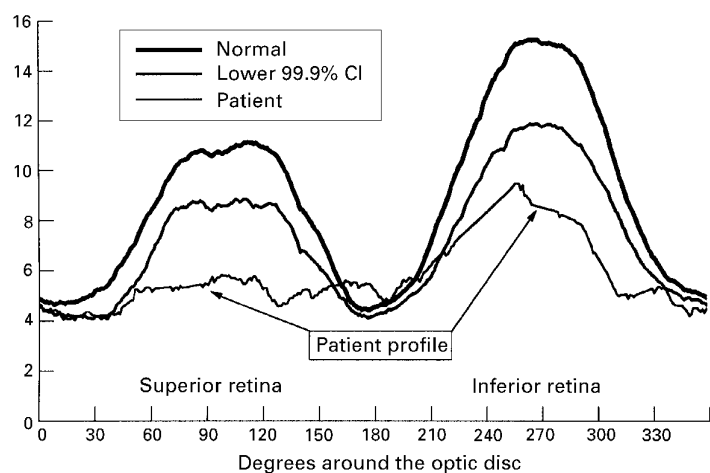
Contrast sensitivity was measured at a testing distance of 1 m on a standard Pelli-Robson chart. The chart consists of 16 rows of upper case letters of a constant size, arranged in triplets. Each triplet contains letters of equal contrast and each successive triplet declines in contrast in 0.15 log unit steps. The score was recorded as the lowest line at which the patient was able to correctly identify two of the three letters. A score of line 12 or higher was considered normal.^{18, 19} Previous studies have shown that the results of the Pelli-Robson test are highly correlated with peak contrast sensitivity measured with a sine wave grating.²⁰

Optic disc pallor was assessed using a direct ophthalmoscope and graded as absent, mild, moderate, or severe. The presence of a relative afferent pupillary defect was sought and measured using a neutral density filter as described previously.²¹ In addition to the above assessments, a general ophthalmic examination including the measurement of the intraocular pressure was carried out to exclude the presence of any other significant ocular disease.

Scanning laser polarimetry was performed using a Nerve Fiber Analyser (Laser Diagnostic Technologies Inc, San Diego, California). The birefringence of the RNFL is measured by a confocal scanning laser ophthalmoscope which has a polarisation modulator, corneal polarisation compensator, and polarisation detection unit integrated into the system. The polarisation state of the near infrared (780 nm wavelength) diode laser is altered by the birefringent RNFL and this is displayed as a 15 by 15° field of view image of the optic nerve head and peripapillary retina.¹⁴

The change in the polarisation state, measured as the retardation in degrees, is converted in a linear fashion to the thickness of the RNFL and displayed in microns. Three measurements of each eye were made in a single session without pupillary dilation. The average time to perform a complete examination was 10 minutes. The thickness of the RNFL was retrieved from the image by placing a concentric circular zone (width of 1.5 to 2.0 optic disc diameters) within the peripapillary region and centred on the optic disc.

The resultant RNFL polar profile, comprising 360 individual values (one value per angular degree) was retrieved from each image and a mean profile for the series of three images from each eye was constructed and calculated. The within observer reproducibility for this



Polarmetric retardation angle (1° = approximately $7.4 \mu\text{m}$ of RNFL thickness¹⁴) v degrees around the optic disc illustrating three resultant profiles of RNFLs: a mean normal profile (thick line), the corresponding lower 99.9% confidence limit profile (medium line), and a profile of a patient with diffuse severe RNFL loss after demyelinating optic neuritis (thin line).

Table 2 Sensitivity of the tests used in this study

Visual acuity n (%)	Contrast sensitivity n (%)	RAPD detectable n (%)	Optic disc pallor n (%)	Scanning laser polarimetry n (%)
8 (26)	10 (32)	12 (39)	17 (55)	29 (94)

Sensitivity represents the prevalence of abnormal values in the 31 eyes with previous demyelinating optic neuritis; RAPD = relative afferent pupil defect.

instrument has been previously reported to be around 5%.^{15 23 24} This value represents the area under the profile (or integral) coefficient of variation (CV)—that is, the SD of three or more measurements divided by the mean of those measurements and expressed as a percentage. We have previously reported within observer reproducibility CVs of less than 10% for individual degrees comprising a polar profile and about 5% for the integral CV.²² The blood vessels were removed from the profile by using our own algorithm and the final profile was compared with our normative data by standardising the two profiles via the temporal and nasal 30°. The area under the profile (integral) was used as the measure of thickness of the RNFL. The normal data were created from an age matched group of 20 patients (table 1). Normal subjects were included in the study if there was no family history of glaucoma, they had had no previous intraocular pressure rise, and no history of ocular trauma or any retinal or optic nerve disease. They all had a best corrected visual acuity of 6/9 or better, normal anterior segments on slit lamp biomicroscopy, intraocular pressure of less than 22 mm Hg (Goldmann tonometer), normal optic nerve head appearances on slit lamp biomicroscopy, and no glaucomatous visual field defects on Humphrey 24-2 full threshold automated perimetry. The lower 99.9% confidence limit from the normal data was calculated and used as the cut off criterion for abnormality (figure). A profile was therefore defined as abnormal by the presence of an RNFL defect, which measured 1% or more, below the 99.9% lower confidence limit of the normal database. The defect was quantified by expressing it as a percentage of the mean for the integral of the normal database.

The clinical examination and the scanning laser polarimetry were performed by separate

examiners and both were blind to the history at the time of the examination. A history was taken and the case notes were reviewed to ascertain the timing and laterality of the previous demyelinating optic neuritis. The age matched normal patients were imaged concurrently with the study patients and again the examiner was blind as to whether these patients were within the normal group or were study patients to reduce any possible bias during imaging. About half of the study patients had had a diagnosis of multiple sclerosis made in the past and this was categorised according to the criteria of Poser *et al.*²⁵

Spearman rank correlation coefficients were used to estimate the linear correlation between the polarimetry results and the other clinical tests. The sensitivity of each test (the percentage of abnormal results) was calculated. The incremental detection value of each non-visual acuity test (for example, the number of patients with normal visual acuity who had an abnormal score on a non-visual acuity test divided by the number of patients with normal visual acuity) was also calculated. The χ^2 test was used to look for differences in the pattern and extent of RNFL loss between those with definite and probable multiple sclerosis and those with isolated demyelinating optic neuritis. Only the affected eye or the right eye in cases of previous bilateral optic neuritis were used for this analysis to avoid the effects of between eye correlation. A focal nerve fibre layer defect was defined as a defect of less than 45° and a diffuse defect as a one of 45° or more in circumferential peripapillary extent.

Results

Of the 25 patients able to attend for re-examination, we were unable to image one patient on the polarimeter because of a superior rectus palsy with poor and unstable fixation. We excluded this patient from further analysis. The intraocular pressure was less than 21 mm Hg in all of the remaining eyes with no evidence of glaucoma or other eye disease which could affect the RNFL.

Ten of the 24 patients had clinically definite or probable multiple sclerosis whereas the other 14 had had an isolated episode of optic

Table 3 Incremental detection values (n (%))

	Total No	Abnormal visual acuity	Abnormal contrast sensitivity	RAPD present	Optic disc pallor present	Abnormal polarimetry
Normal visual acuity	23 (74)*	NA	5 (22)	7 (30)	10 (43)	21 (91)†
Normal contrast sensitivity	21 (68)	3 (14)	NA	7 (33)	8 (38)	20 (95)
Normal pupil reactions	19 (61)	3 (16)	5 (26)	NA	8 (42)	17 (89)
Normal optic disc	14 (45)	1 (7)	1 (7)	3 (21)	NA	12 (86)
Normal polarimetry	2 (6)	0	1 (50)	0	0	NA

Results based on eyes with a previous episode of demyelinating optic neuritis (n = 31).

*Of the 31 eyes with a history of optic neuritis 23 (74%) had normal visual acuity.

†Of the 23 eyes with normal visual acuity 21 (91%) had abnormal polarimetry.

NA=not applicable.

Table 4 Correlation between polarimetry and the other tests used in the study

Scanning laser polarimetry	Visual acuity	Contrast sensitivity	Pupil reactions	Optic disc appearance
All eyes with previous DON (n = 31) p Value	+0.30 > 0.7	-0.11 > 0.9	-0.42 > 0.6	+0.07 > 0.9
Patients with previous unilateral DON (n = 17) p Value	+0.23 > 0.8	+0.1 > 0.9	+0.20 > 0.8	+0.07 p > 0.9

DON=demyelinating optic neuritis.

Table 5 Findings in the 17 eyes with no previous history of demyelinating optic neuritis

Category	Eyes (n)	Abnormality in any of the four tests (n (%))	RNFL loss (n (%))
Clinically definite or probable MS	5	3 (60)	2 (40)
Isolated DON group	12	6 (50)	6 (50)*

*Two of these eyes also had abnormal contrast sensitivity.
MS=multiple sclerosis; DON=demyelinating optic neuritis

neuritis in one or both eyes. Seven patients had had episodes of optic neuritis affecting both eyes. There were 31 eyes with a previous history of demyelinating optic neuritis. Table 1 shows the age, sex, and time interval after the episodes of optic neuritis.

Table 2 shows the sensitivity (the percentage of abnormal values) recorded for each of the clinical tests. A visual acuity of less than 0.0 (6/6 on Snellen) was found in only eight eyes (26%) whereas scanning laser polarimetry disclosed an abnormality in 29 eyes (94%).

Twenty three eyes recovered an acuity of 0.0 or better, 21 of which had evidence of RNFL loss on polarimetry. Similar values were found for patients with normal contrast sensitivity, pupil reactions, and optic disc appearance (table 3). Scanning laser polarimetry was the only abnormality found in nine of the 31 eyes (29%). One eye had reduced contrast sensitivity as the only abnormality whereas there were no test abnormalities at all in one further eye. There was no significant correlation between the polarimetry scores and the other clinical tests (table 4).

There was a diffuse pattern of RNFL loss in 16 patients and a more focal pattern in seven (one patient with previous unilateral demyelinating optic neuritis had no evidence of RNFL loss), although the actual pattern of loss was extremely variable. The extent of the RNFL loss after demyelinating optic neuritis varied from 0% to 42% of the mean area of total nerve fibre layer of our normal population, with a mean of 9%. There was no significant difference in the extent ($\chi^2=0.056$, $p>0.90$) or pattern ($\chi^2=0.174$, $p>0.5$) of RNFL loss between patients with multiple sclerosis or isolated demyelinating optic neuritis.

All 17 patients with previous unilateral demyelinating optic neuritis had subjectively considered their fellow eye (with no history of demyelinating optic neuritis) to be completely normal with no visual complaints. Evidence of nerve fibre layer loss was found in eight (47%) of these eyes (table 5). Abnormalities were found in two (40%) of the patients with definite or probable multiple sclerosis and six (50%) of the patients with isolated demyelinating optic neuritis.

Discussion

Using the SLP we were able to demonstrate and quantify the presence of RNFL loss in a very high percentage (94%) of cases after demyelinating optic neuritis. This value is similar to those previously reported for the presence of abnormal visually evoked responses (65%-100%).³⁻⁸ However, the exact relation between the latency and amplitude of visual evoked response and RNFL loss is not

known. It is also similar to values for RNFL loss as assessed with red free photography (50%-89%),^{8,12} while also giving a quantitative and repeatable measure of nerve fibre loss. The sensitivity of SLP is considerably higher than other commonly performed clinical tests such as contrast sensitivity. Indeed in 29% of our cases RNFL loss as shown with SLP was the only abnormality found. However, two patients with demyelinating optic neuritis showed no abnormalities on SLP. There are two possible explanations for this finding. Axonal loss may not be universal after demyelinating optic neuritis and therefore demyelination may occur on its own in some patients. Alternatively, the extent of axonal loss after demyelinating optic neuritis may be below the sensitivity of the SLP. Certainly the extent of axonal loss may have been insufficient to lower the retinal nerve fibre layer profile below our normal range in an individual eye.

The detection of abnormalities using SLP in the fellow normal eyes was also similar to previous studies using visually evoked responses (30-82%),^{5,8} and red free photography (45-68%),^{8,12} and also again higher than other clinical tests of visual function. The occurrence of fellow eye abnormalities probably represents subclinical episodes of demyelination or subclinical bilateral involvement at the time of the initial episode of unilateral optic neuritis. With its speed and ease of use SLP may prove to be a good alternative to visual evoked responses in the diagnosis of multiple sclerosis in identifying the site of a second lesion in an otherwise visually asymptomatic person with no history of optic neuritis. However, as with evoked responses, RNFL loss is not specific for demyelination.

We found no consistent pattern of RNFL loss after demyelinating optic neuritis which concurs with the findings using red free ophthalmoscopy and the absence of a characteristic field defect after demyelinating optic neuritis. Similarly, there was no significant difference in the extent and pattern of RNFL loss in patients with definite or probable multiple sclerosis against those with isolated demyelinating optic neuritis suggesting a similar pathogenesis.

The lack of correlation between SLP and visual acuity or contrast sensitivity is similar to the previously shown absence of correlation between VER latency and these two measures. There are several possible reasons for this finding. We used a global value of RNFL loss whereas abnormalities in visual function can be focal. Furthermore the exact relation between RNFL structure and visual function is not known and may vary between patients.²⁶ A relatively low correlation has also been reported between SLP and visual fields.^{16,27}

There was no significant correlation between the nerve fibre analysis and optic disc pallor or a relative afferent pupil defect. The presence of a relative afferent pupil defect is by definition made in relation to the contralateral eye and an assessment of optic disc pallor is often judged relative to the contralateral eye. The analysis was therefore repeated and limited to the 17

eyes with unilateral previous demyelinating optic neuritis. Despite this, there was no significant correlation. The presence of sub-clinical contralateral ocular abnormalities and the subjective and variable nature of assessment of optic disc pallor may partly explain this finding. Furthermore, the presence and magnitude of a relative afferent pupil defect will depend not only on the degree of axonal loss but also on the conduction delay resulting from demyelination.

The correlation between SLP and RNFL assessment using red free photography has been shown to be maximal at $r=0.53$,¹⁵ and the information obtained with SLP and photography do not seem to be equivalent. The reasons for these disparities are not entirely clear. However, the reproducibility of SLP is high and the information obtained using this technique is quantitative in nature. A recent study has shown a sensitivity of 96% for the detection of glaucoma by SLP.¹⁶ The results of this study suggest that SLP may be a very useful adjunctive investigation in the diagnosis of patients with multiple sclerosis and patients with previous demyelinating optic neuritis, and may also provide valuable information regarding the basic pathology of these conditions. Further investigation with longitudinal studies would be of great interest.

We have no financial or proprietary interest in the scanning laser polarimeter (Nerve Fiber Analyser) or Laser Diagnostic Technologies Inc.

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