Correlation between Morphological and Functional Retinal Impairment in Multiple Sclerosis Patients

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Purpose. To assess whether a correlation exists between optic nerve fiber layer (NFL) thickness and the retinal or visual pathway function in multiple sclerosis (MS) patients previously affected by optic neuritis.

Methods. Fourteen patients with a diagnosis of definite MS were examined. All had been affected by optic neuritis (MSON) with complete recovery of visual acuity (14 eyes included in study). These were compared with 14 eyes from 14 age-matched control subjects. NFL thickness was measured by optical coherence tomography (OCT). Three different measurements in each quadrant (superior, inferior, nasal, and temporal) were taken and averaged. The data in all quadrants (12 values averaged) were identified as NFL Overall, whereas the data obtained in the temporal quadrant only (3 values averaged) were identified as NFL Temporal. Retinal and visual pathway function was assessed by simultaneously recording pattern electroretinograms (PERGs) and visual evoked potentials (VEPs) using high-contrast (80%) checkerboard stimuli subtending 15 minutes and 60 minutes of the visual arc (min arc) and reversed at the rate of two reversals per second.

Results. In MSON eyes there was a significant ($P < 0.01$) reduction in NFL thickness in both NFL Overall and NFL Temporal evaluations compared with the values observed in control eyes. PERG, (15-min arc checks) and VEP (15-min arc and 60-min arc checks), showed a significant ($P < 0.01$) delay in latency and reduction in amplitude. NFL Overall and NFL Temporal values were significantly correlated ($P < 0.01$) to the PERG P50 latency and P50 to N95 amplitude recorded with 15-min arc checks. No correlations ($P > 0.01$) between NFL values and the other electrophysiological data (PERG recorded with 60-min arc checks and VEP recorded with 15-min arc and 60-min arc checks) were found.

Conclusions. There is a correlation between PERG changes and NFL thickness in MS patients previously affected by optic neuritis, but there is no correlation between VEP changes and NFL thickness. (*Invest Ophthalmol Vis Sci.* 1999;40:2520–2527)

Multiple Sclerosis (MS) patients showed a delay of cortical response revealed by visual evoked potential (VEP) recordings[1–10] and a functional impairment at the retinal level revealed by flash or pattern electroretinogram (PERG) recordings.[6,9,10–15] Abnormalities of transient PERGs, such as reduced amplitude and delayed latency, were observed in particular in MS patients previously affected by optic neuritis.[10,16–18] In animal studies, after section of the optic nerve and consequent retrograde ganglion cell degeneration, there is a progressive disappearance of the PERG response. These abnormalities have been ascribed to an impairment of the innermost retinal layers.[19] This interpretation of the PERG impairment in MS patients seems plausible, but the relationship between the structural and functional retinal alterations has never been thoroughly evaluated in humans.

A new noninvasive technology allowing cross-sectional imaging of the eye was recently introduced by Huang et al.,[20] Puliafito et al.,[21] and Hee et al.[22,23] This is an objective method of quantifying the nerve fiber layer (NFL) in vivo and of assessing the retinal thickness by optical coherence tomography (OCT).

In our study OCT, PERG, and VEP were performed in a group of MS patients previously affected by optic neuritis to assess whether a correlation exists between the structural (NFL thickness) and functional (PERG, VEP) findings.

Methods

Patients

Fourteen patients (six men and eight women; mean age, 34.1 ± 5.8 years) with a diagnosis of definite MS, according to the criteria proposed by Poser et al.,[24] who had been affected by optic neuritis, were enrolled in the study. When an MS patient had been affected by optic neuritis in both eyes (3/14), we studied the eye affected longer. Therefore, we considered 14 eyes from 14 MS patients (14 MSON eyes). It has been observed that the retrograde degeneration process may fully

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develop in 6 months.[25] Our patients were examined at least 12 months after the last optic neuritis episode.

An ophthalmologic examination, including anterior segment biomicroscopy, visual acuity, applanation tonometry and ophthalmoscopy, was performed in all subjects tested. Inclusion criteria for the study were refractive errors, when present, within −2 and +2 spherical diopters; intraocular pressure less than 18 mm Hg in both eyes (average of two measurements); no concomitant ocular or systemic disease; and complete recovery of visual acuity (10/10) after the optic neuritis episode.

The 14 MSON eyes were compared with 14 eyes from 14 age-matched control subjects. In MS patients affected by unilateral optic neuritis (11/14), we considered the fellow eye (11 MS contralateral eye, MSCE) a further control. OCT, PERG, and VEP were assessed both in MS patients and in control subjects.

Informed consent was received from all subjects involved in the study. The research followed the tenets of the Declaration of Helsinki, and the protocol was approved by the local ethics committee .

OCT Examination

OCT, including a fiber optic delivery system coupled with a slit biomicroscope (Humphrey, San Leandro, CA), was used. This system provides the operator with a video camera view of the scanning probe beam on the fundus and OCT imaging acquired in real time on a computer monitor. After dilation with 1% tropicamide, each eye was scanned three times using a circle size of 3.4 mm (1.7-mm radius). Near-infrared light (84-nm wavelength) was used. Throughout scanning, the patient kept the eyes constantly fixed on an internal target provided by the equipment. The measurements were obtained from three nonconsecutive scans (i.e., the patient was allowed to rest for a few seconds before repositioning to proceed to the following scan).

The OCT software was an automated computer algorithm that identifies the anterior and posterior border of the retina, making it possible to calculate NFL and total retinal thickness by quadrant and by clock hour. Retinal thickness was determined by computer as the distance between the first reflection at the vitreoretinal interface and the anterior boundary of the second reflective layer corresponding to the retinal pigment epithelium and the choriocapillaris. NFL thickness was automatically assessed by computer assuming the correlation with the red highly reflective layer at the vitreoretinal interface.[26]

The average values of three different measurements per quadrant (superior, inferior, nasal, and temporal) were calculated. The overall data obtained in all quadrants (12 values averaged) were identified as NFL Overall, and the data obtained in the temporal quadrant only (3 values averaged) were identified as NFL Temporal. NFL Temporal was taken to evaluate the temporal fiber in which the papillomacular bundle fibers are included.[27]

Electrophysiological Examination

In accordance with procedures in previously published studies,[28–30] simultaneous PERG and VEP recordings were performed using the following methods. The subjects under examination were seated in a semidark, acoustically isolated room in front of the display surrounded by a uniform field of luminance of 5 cd/m^2. Before the experiment, each subject was adapted to the ambient room light for 10 minutes. The pupil diameter was approximately 5 mm. Mydriatic or miotic drugs were never used. Stimulation was monocular after occlusion of the other eye. Visual stimuli were checkerboard patterns (contrast 80%, mean luminance 110 cd/m^2) generated on a TV monitor and reversed in contrast at the rate of two reversals per second. Two check sizes were used as visual stimuli: At the viewing distance of 114 cm the check edges subtended 60 and 15 minutes of visual angle (min arc). The screen of the monitor subtended 18° and a small red target (0.5°) was placed in the center of the stimulus field to maintain stable fixation. The refraction of all subjects was corrected for viewing distance.

PERG Recordings

The bioelectric signal was recorded by a small Ag-AgCl skin electrode placed over the lower eyelid. PERGs were derived bipolarly between the stimulated (active electrode) and the patched (reference electrode) eye using the method previously described.[31] The ground electrode was at Fpz. The interelectrode resistance was lower than 3 kΩ. The signal was amplified (gain 50,000), filtered (band-pass 1–30 Hz), and averaged with automatic rejection of artifacts (200 events free from artifacts were averaged for every trial) by BM 6000 (Biomedica Mangoni, Pisa, Italy). The analysis time was 250 msec. The transient PERG response is characterized by a number of waves with three subsequent peaks of negative (N), positive (P), and negative polarity, respectively. In normal subjects these peaks have the following latencies: 35, 50 and 95 msec (N35, P50, N95).

VEP Recordings

Cup-shaped Ag-AgCl electrodes were fixed with collodion in the following positions: active electrode in Oz, reference electrode in Fpz, and ground in the left arm. The interelectrode resistance was kept below 3 kΩ. The bioelectric signal was amplified (gain 20,000), filtered (band-pass 1–100 Hz), and averaged (200 events free from artifacts were averaged for every trial) by BM 6000. The analysis time was 250 msec. The transient VEP response is characterized by a number of waves with three subsequent peaks of negative, positive, and negative polarity, respectively. In normal subjects these peaks have the following latencies: 75, 100, and 145 msec (N75, P100, N145).

In the recording session, simultaneous PERGs and VEPs were recorded at least twice, and the resultant waveforms were superimposed to check the repeatability of the results. We accepted PERG and VEP signals with a signal-to-noise ratio higher than 2. The noise was measured by recording the bioelectric signals (200 averaged events) while the monitor was screened by a cardboard. Noise less than 0.1 μV (mean 0.086 μV) was observed in all subjects tested. For all PERGs and VEPs the peak latency and the peak amplitude of each of the averaged waves were measured directly on the display by means of a pair of cursors.

Statistics

The data are reported as mean values ± 1 SD. The differences between control and MSON and MSCE eyes and between MSON and MSCE eyes were statistically evaluated with one-way analysis of variance for repeated measures. To assess whether a correlation exists between OCT and electrophysiological parameters, linear regression analysis (Pearson's test)

TABLE 1. Clinical, Morphologic, and Electrophysiological Data

	Eye	Sex	Age (y)	Time Elapsed Since Last ON Episode (m)	NFL Overall (μm)	NFL Temporal (μm)	P50 (msec) 15 min arc	P50 (msec) 60 min arc	N35–P50 (μV) 15 min arc	N35–P50 (μV) 60 min arc	P50–N95 (μV) 15 min arc	P50–N95 (μV) 60 min arc	P100 (msec) 15 min arc	P100 (msec) 60 min arc	N75–P100 (μV) 15 min arc	N75–P100 (μV) 60 min arc
Control subjects																
PV	R	M	37	—	92.5	68.9	57	56	1.3	1.1	1.8	1.8	106	106	7.5	6.3
DI	L	M	41	—	96.1	73.4	50	52	1.2	0.6	1.6	1.5	100	99	5.3	7.3
GF	R	F	37	—	96.3	78.3	46	56	1.5	0.8	1.8	1.3	98	102	8.7	8.3
GS	R	F	34	—	110.4	85.2	63	60	1.1	1.0	1.4	1.6	107	103	8.9	6.1
DF	R	F	29	—	107.3	71.1	58	59	1.3	1.2	1.7	1.7	108	102	7.5	8.2
BV	R	F	27	—	104.2	74.2	60	58	1.4	1.0	2.0	1.8	110	103	5.6	5.7
ND	R	M	29	—	110.2	72.8	67	62	1.8	1.0	2.3	1.2	111	104	6.3	7.0
RA	L	F	35	—	107.2	82.3	56	59	1.2	0.7	1.8	1.4	106	107	6.4	6.7
TR	R	F	37	—	118.3	81.4	60	58	1.2	0.9	1.7	1.6	107	103	6.2	7.1
AS	R	M	40	—	117.4	86.3	58	56	1.8	0.8	2.0	1.7	102	102	6.0	7.2
FN	L	F	41	—	116.4	96.2	50	52	1.3	0.7	1.9	1.2	110	102	7.4	8.7
MV	L	M	39	—	125.3	92.1	56	54	1.5	1.2	2.0	1.9	102	99	5.7	6.3
FT	L	F	33	—	126.6	102.3	58	51	1.2	1.0	1.7	1.5	108	97	7.5	8.2
OT	L	M	32	—	127.4	106.5	59	59	1.1	1.1	1.6	1.3	110	105	7.6	8.2
MSON																
AD	R	F	38	24	35.58	15.30	86	64	0.7	0.5	0.5	0.7	143	134	1.2	1.6
CI	L	M	40	15	47.10	24.00	72	60	0.8	1.2	0.8	1.7	121	131	5.1	2.6
AO	L	F	28	24	52.20	23.30	64	66	1.0	0.5	0.4	0.8	130	125	3.2	4.5
LA	L	F	26	24	55.10	50.00	66	64	0.5	0.8	0.5	0.9	119	130	1.7	3.1
LD	R	M	27	24	57.10	39.30	57	60	0.3	0.8	0.8	1.3	116	124	2.6	2.5
OP	L	M	36	12	57.20	48.30	70	58	0.5	0.8	0.8	2.5	148	142	2.4	2.6
CE	L	M	40	12	58.75	63.00	62	59	0.8	1.3	0.8	1.6	120	110	1.1	3.5
AS	R	F	37	24	59.42	30.00	64	64	0.8	0.7	0.8	0.7	128	137	2.4	1.4
OR	R	F	35	12	61.00	53.00	66	59	1.2	0.6	1.0	1.1	145	119	3.0	2.7
CF	L	F	41	24	64.75	24.00	70	52	0.6	1.0	0.8	1.2	128	152	2.3	1.1
AA	L	M	29	18	70.10	49.70	63	60	0.7	0.4	1.0	0.8	126	147	4.8	6.0
PD	R	F	42	24	70.50	48.00	62	59	0.5	0.5	1.2	1.4	130	151	4.0	3.6
AG	L	M	30	24	71.10	50.30	62	60	0.9	1.0	1.4	1.4	133	133	1.9	8.0
RM	L	F	28	19	77.10	63.30	59	53	1.5	1.1	2.0	1.8	119	112	2.6	3.0
MSCE																
LA	R	F	26	—	77.5	57.7	60	55	1.3	1.0	1.7	1.2	112	109	4.9	5.3
LD	L	M	27	—	78.7	59.3	59	53	1.1	1.1	1.3	1.3	114	110	4.5	6.2
OP	R	M	36	—	76.5	52.3	62	57	1.5	1.1	1.7	1.6	112	111	6.6	6.7
CE	R	M	40	—	82.9	77.6	66	61	1.6	0.8	2.0	1.8	117	116	4.3	5.1
AS	L	F	37	—	64.4	67.6	58	55	1.1	1.1	1.6	1.0	112	110	9.4	8.7
OR	L	F	35	—	86.1	75.3	60	58	1.3	0.9	1.5	1.2	108	109	8.2	8.5
CF	R	F	41	—	76.3	70.1	58	53	1.5	0.9	1.8	1.3	110	105	6.3	7.2
AA	R	M	29	—	78.8	68.6	57	56	1.1	0.9	1.7	1.3	109	107	6.2	7.7
PD	L	F	42	—	87.8	86.3	59	54	1.2	1.0	1.9	1.4	109	105	5.7	6.3
AG	R	M	30	—	98.7	87.4	58	56	1.1	1.0	1.6	1.2	108	103	4.5	5.2
RM	R	F	28	—	102.3	98.3	59	53	1.0	0.9	1.5	1.2	115	111	8.2	7.2

* Fifteen- and 60-min are check sizes used.

was adopted. In both statistical analyses, $P < 0.01$ was considered significant.

RESULTS

The main clinical, morphologic, and electrophysiological data pertaining to control subjects and MS patients are reported in Table 1. The statistical results are shown in Tables 2 and 3.

OCT Examination

Examples of nerve fiber layer (NFL) assessment in one MSON eye and in one control eye are shown in Figure 1. In control eyes we found NFL thickness within 92.5 and 127.4 μm (mean, 111.11 $\pm$ 11.42 μm) in the NFL Overall evaluation and within 68.9 and 106.5 μm (mean, 83.64 $\pm$ 11.87 μm) in the NFL Temporal evaluation. In MSON eyes we observed NFL thickness within 35.58 and 77.10 μm (mean, 59.79 $\pm$ 10.80 μm) in the NFL Overall evaluation and within 15.30 and 63.30 μm

TABLE 2. Electrophysiological Parameters

	PERG P50 Latency (msec)		PERG N35–P50 Amplitude (μV)		PERG P50–N95 Amplitude (μV)		VEP P100 Latency (msec)		VEP N75–P100 Amplitude (μV)	
	15 min arc	60 min arc	15 min arc	60 min arc	15 min arc	60 min arc	15 min arc	60 min arc	15 min arc	60 min arc
Control and MSON eyes										
Controls (n = 14)	57.7 ± 5.08	56.6 ± 3.32	1.35 ± 0.23	0.94 ± 0.19	1.81 ± 0.22	1.54 ± 0.23	106.07 ± 4.07	102.43 ± 2.74	6.90 ± 1.13	7.24 ± 0.95
MSON (n = 14)	65.93 ± 7.14*	59.86 ± 3.96†	0.77 ± 0.31*	0.80 ± 0.29†	0.91 ± 0.41*	1.28 ± 0.51†	129.0 ± 10.4*	131.93 ± 13.2*	2.74 ± 1.21*	3.30 ± 1.85*
MSON and MSCE eyes										
MSON (n = 11)	63.73 ± 4.08	58.91 ± 3.73	0.75 ± 0.35	0.82 ± 0.27	1.01 ± 0.41	1.34 ± 0.51	128.36 ± 10.4	132.42 ± 14.9	2.62 ± 1.03	3.41 ± 1.99
MSCE (n = 11)	59.64 ± 2.50‡†	55.55 ± 3.73§†	1.25 ± 0.20‡†	0.97 ± 0.10§†	1.66 ± 0.20‡†	1.32 ± 0.22§†	111.45 ± 2.98‡*	108.73 ± 3.61‡†	6.25 ± 1.72‡†	6.74 ± 1.26‡†

Data are means ± SD by one-way analysis of variance versus control eyes; 15- and 60-min are check sizes were used.
* $P < 0.001$ vs. control.
† Not significant ($P > 0.001$) vs. control.
‡ $P < 0.001$ vs. MSON.
§ Not significant ($P > 0.01$) vs. MSON.

TABLE 3. Linear Regression and Correlation between Electrophysiological Parameters and NFL Overall or NFL Temporal Evaluated in MS Eyes Previously Affected by Optic Neuritis

	PERG P50 Latency		PERG N35–P50 Amplitude		PERG P50–N95 Amplitude		VEP P100 Latency		VEP N75–P100 Amplitude	
Versus	15 min arc*	60 min arc	15 min arc	60 min arc	15 min arc	60 min arc	15 min arc	60 min arc	15 min arc	60 min arc
NFL Overall										
Correlation coefficient (r)	−0.744	−0.592	0.294	0.120	0.794	0.235	−0.234	−0.080	0.192	0.481
t:	−3.866	−2.546	1.068	0.422	4.531	0.840	−0.835	−0.280	0.681	1.902
P	0.002	0.025	0.306	0.680	<0.001	0.417	0.419	0.784	0.508	0.081
NFL Temporal										
Correlation coefficient (r)	−0.635	−0.364	0.268	0.268	0.607	0.424	−0.171	−0.391	0.107	0.404
t:	−2.849	−1.355	0.966	0.965	2.652	1.621	−0.602	−1.473	0.373	1.529
P	0.010	0.200	0.352	0.353	0.020	0.130	0.558	0.166	0.715	0.151

* Check size used.

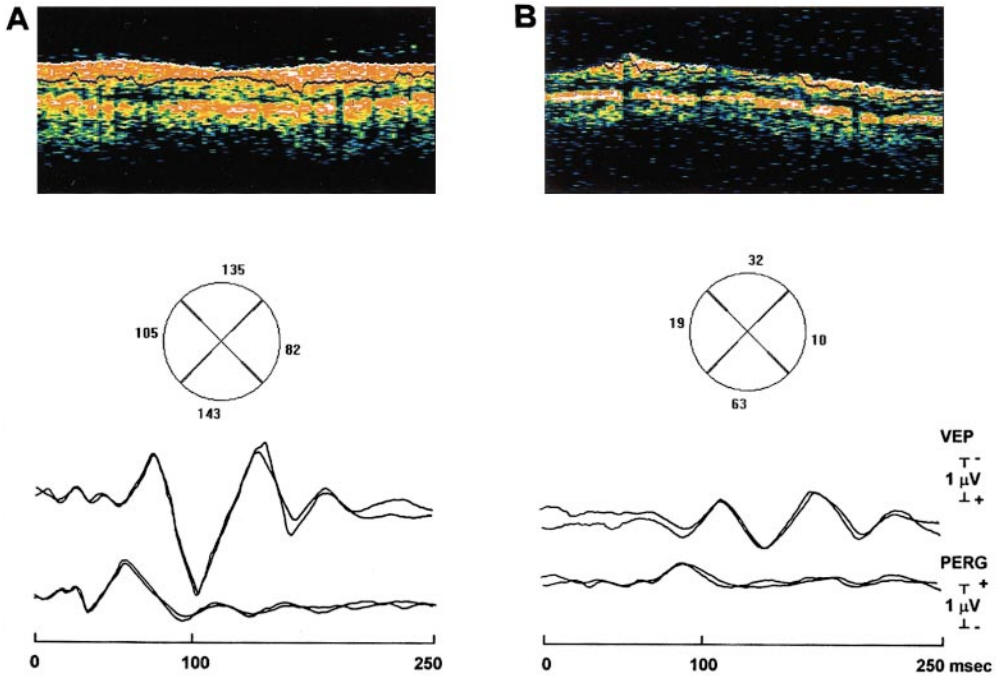

FIGURE 1. (**A**) Control left eye. *Top*: circular OCT taken in cylindrical section of tissue surrounding the optic disc. The anteriormost red reflection indicates the NFL. *Middle*: the NFL thicknesses are reported as averages in micrometers over each peripapillary quadrant (in a clockwise direction: superior, temporal, inferior, and nasal). *Bottom*: VEP and PERG recordings obtained in response to 15-min arc checks of visual stimuli. (**B**) Right eye of MS patient previously affected by optic neuritis. *Top*: OCT shows a marked decrease of the NFL reflection. *Middle*: the NFL thickness is thinned in each quadrant (in a clockwise direction: superior, nasal, inferior, and temporal) compared with the control eye. *Bottom:* in comparison with the control eye, in the MSON eye it was possible to observe VEP and PERG recordings (obtained in response to 15-min arc checks) with delayed latencies and reduced amplitudes.

(mean, 41.54 ± 15.55 μm) in the NFL Temporal evaluation. NFL thickness was significantly reduced when compared with those of control subjects (NFL Overall: $F(1,26) = 149.25$, $P < 0.01$; NFL Temporal: $F(1,26) = 64.84$, $P < 0.01$) and when compared with MSCE eyes (NFL Overall: $F(1,20) = 23.33$, $P < 0.01$; NFL Temporal: $F(1,20) = 21.07$, $P < 0.01$).

In MSCE eyes we found NFL thickness within 64.4 and 102.3 μm (mean, 82.73 ± 10.73 μm) in the NFL Overall evaluation and within 52.30 and 98.30 μm (mean: 72.77 ± 13.99 μm) in the NFL Temporal evaluation. We observed a significant reduction of the NFL Overall thickness values when compared with those of control subjects ($F(1,23) = 40.09$, $P < 0.01$), whereas NFL Temporal thickness was similar to that of control subjects ($F(1,23) = 4.42$, $P = 0.047$).

PERG and VEP Evaluation

Examples of PERG and VEP recordings from control and MSON eyes are shown in Figure 1.

PERGs

Using 60 min arc checks, MSON eyes showed P50 latency, N35 to P50 and P50 to N95 amplitudes with values similar to those of control eyes and to those of MSCE eyes ($P > 0.01$). Using 15 min arc checks, the P50 latency was significantly delayed compared with that in the control eyes and MSCE eyes; N35 to P50 and P50 to N95 amplitudes were significantly reduced compared with those in control and MSCE eyes. No significant differences were found between MSCE and control eyes.

VEPs

In MSON eyes, the VEP obtained in response to 60-min arc and 15-min arc checks showed P100 latencies significantly delayed and N75 to P100 amplitudes significantly reduced when compared with control and MSCE eyes. In MSCE eyes, the VEP obtained in response to 15-min arc checks showed P100 latency significantly delayed compared with that of control subjects. The P100 latency obtained with 60-min arc checks and the N75–P100 amplitudes obtained at 60-min arc and 15-min arc checks were similar to those of control subjects.

OCT versus PERG and VEP

The correlation between NFL thickness and PERG and VEP parameters is shown in Figures 2 and 3 and in Table 3. In MSON eyes the NFL Overall and NFL Temporal values were significantly correlated ($P < 0.01$) to the PERG P50 latency and PERG P50 to N95 amplitude (15-min arc checks). No correlation ($P > 0.01$) between NFL values and the other electrophysiological data (PERG N35–P50 amplitude recorded with 15-min arc checks, PERG parameters recorded with 60-min arc checks or VEP recorded with 60-min arc and 15-min arc checks) was found. In control and MSCE eyes, no significant correlation between electrophysiological parameters and NFL thickness was observed.

DISCUSSION

The purpose of our work was to evaluate whether a correlation exists between NFL thickness and the retinal (PERG) or visual

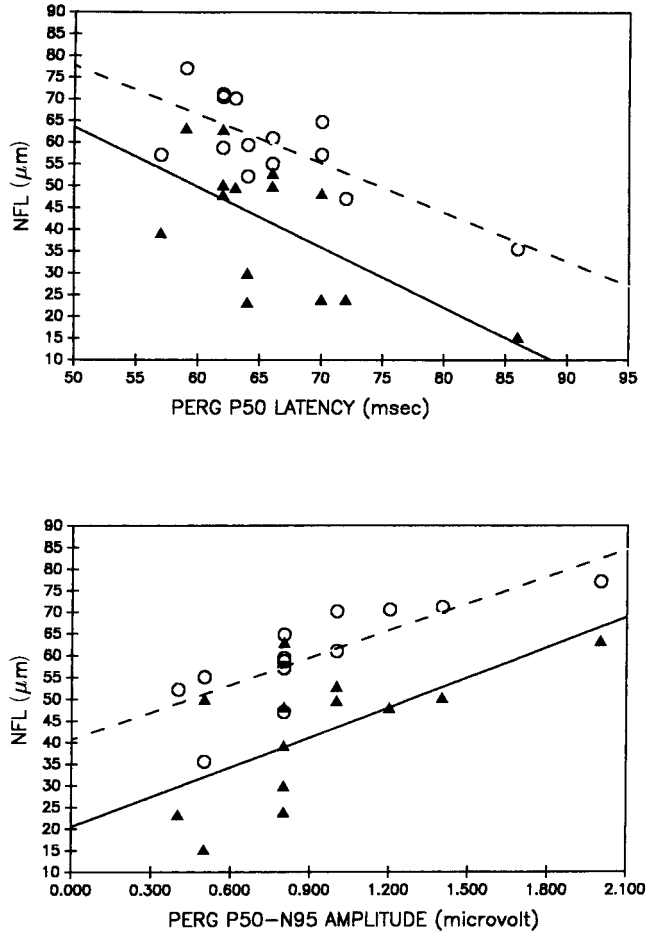

FIGURE 2. NFL thickness plotted against PERG P50 latency and PERG P50 to N95 amplitude in MS patients (*dashed line*, NFL Overall; *solid line,* NFL Temporal). Data refer to PERGs recorded using checkerboard stimuli subtending 15 minutes of the visual arc. For regression analysis, see Table 2. (○), NFL Overall; (▲), NFL Temporal.

pathway (VEP) function in MS patients previously affected by optic neuritis. NFL thickness was assessed by OCT. This is a reliable method when evaluating retinal morphology in humans in vivo[20–23] and has been successfully used in glaucoma patients in whom a reduction of NFL thickness indicates an optic nerve fiber impairment,[26] as seen in several histologic studies.[32–35] Our control subjects displayed NFL thickness values similar to those observed in normal subjects by Shuman et al.[26]

We observed a significant reduction of NFL thickness in MSON eyes that conforms with previous studies performed using different methods of retinal fiber assessment.[36–39] This reduction could be because of a loss of those axons that form the head of the optic nerve. A high frequency of transected axons in the affected brain area in MS patients was observed in a recent neuropathologic study.[40] It is likely that a similar degree of axonal involvement may develop in the optic nerve affected by the inflammatory process. Retrograde degeneration could then lead to the morphologic changes that we have observed.

It is worth noting that in MSON eyes NFL Overall and NFL Temporal reduced thicknesses were significantly correlated with the delayed P50 latencies and reduced P50 to N95 amplitudes and were not significantly correlated with reduced N35 to P50 amplitudes of PERG response to 15-min arc checks. These significant correlations can be understood based on previous studies of the sites of the PERG sources. Maffei and Fiorentini,[19,41] after section of the optic nerve in cats with consequent axonal retrograde degeneration, observed a progressive reduction in amplitude and disappearance of the ERG response when evoked by patterned stimuli, whereas the ERG response evoked by homogeneous luminance stimuli was preserved. Hollander et al.[42] found that ganglion cell shrinkage and ganglion cell loss in peripheral retina (particularly in the temporal area) began 3 weeks after section of the optic nerve, and these histologic findings were paralleled by the PERG reduction in amplitude. This was confirmed by experiments performed in monkeys by Maffei et al.[43] On the basis of these animal models, the integrity of ganglion cells and their fibers seems to be essential for generation of a normal PERG response.[44]

That there was no correlation between NFL Overall and NFL Temporal thickness and N35 to P50 amplitudes suggests, in agreement with Holder,[14] that not all the P50 component arises in the innermost retinal layer. When we used a large check size (60-min arc checks), the mean values of PERG

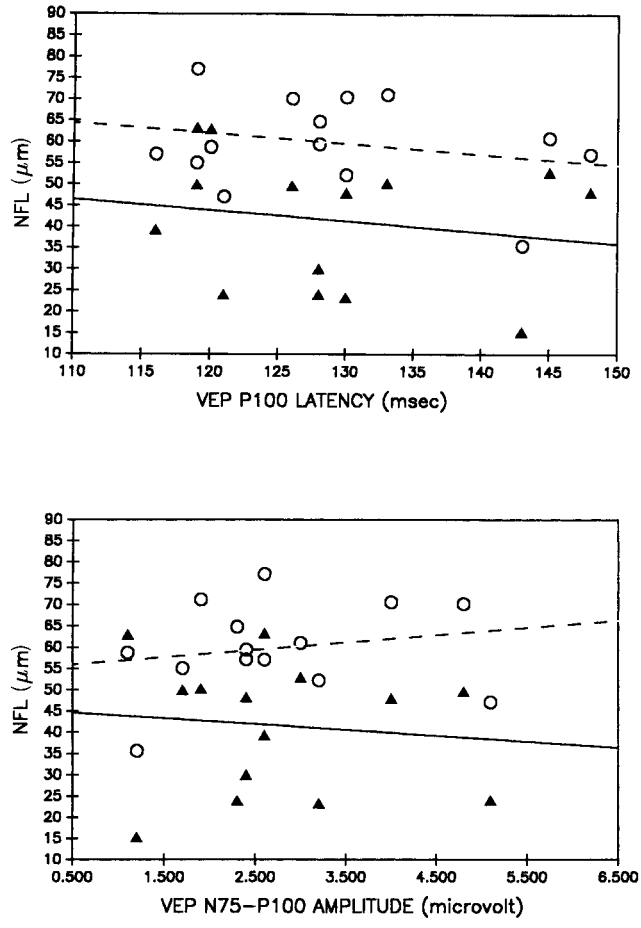

FIGURE 3. NFL thickness plotted against VEP P100 latency and VEP N75 to P100 amplitude in MS patients (*dashed line*, NFL Overall; *solid line,* NFL Temporal). Data refer to VEPs recorded using checkerboard stimuli subtending 15 minutes of the visual arc. For regression analysis, see Table 2. (○), NFL Overall; (▲), NFL Temporal.

parameters obtained in MSON eyes were not significantly different from those of control subjects. In addition, no correlation was observed between the electrophysiological and morphologic parameters. The dependence of transient PERG response on the spatial frequency of the visual stimulus has been described by Tobimatsu et al.[45] in cats after section of the optic nerve. They found, after the retrograde degeneration of ganglion cells, an impairment of transient PERG in response to small check size stimulation, whereas the PERG response evoked by large-check stimulation was not significantly modified. According to these investigators, it is likely that, when using large checks, the transient PERG signal reflects not only the innermost retinal layers function, but also the response of those retinal elements that are sensitive to uniform luminance changes (preganglionic cells located in more distal retinal layers).

Our results in MSON eyes may therefore be interpreted as follows: The loss of retinal fibers may induce changes in the transient PERG response to small checks (15 min arc), whereas it does not modify PERG response to large checks (60-min arc), because this signal may reflect the preganglionic bioelectrical activity also.

In MSCE eyes without a history of optic neuritis, we observed a reduction in NFL Overall thickness with sparing of NFL Temporal thickness. The P50 latencies and the N35 to P50 and P50 to N95 amplitudes were delayed and reduced (but not significantly) when compared with those of control subjects, and no correlation between PERG parameters and NFL Overall and NFL Temporal thickness was observed. This finding could suggest that some degree of axonal involvement may develop at the retinal level in MS patients, even in the absence of clinical symptoms and electrophysiological abnormalities.

In MSON and MSCE eyes we observed that the NLF Overall and NFL Temporal thicknesses were not related to the visual cortical responses evoked by 60-min arc or 15-min arc check size stimuli, although delayed VEP P100 latencies and reduced VEP N75 to P100 amplitudes were found. Our VEP results indicate that MSON and MSCE eyes display impaired neural conduction in the visual pathways, which is in agreement with several previous studies.[1–10] The absence of correlation between NFL thickness and VEP responses could be explained by considering that the abnormal visual cortical response observed in MS patients may result both from an impaired retinal function and a delayed neural conduction in the postretinal visual pathways.[1–10,16]

In conclusion, our results indicate that there is a correlation between PERG changes and NFL thickness, but there is no correlation between VEP changes and NFL thickness in MS patients previously affected by optic neuritis.

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