Evaluation of Visual Structural and Functional Factors That Predict the Development of Multiple Sclerosis in Clinically Isolated Syndrome Patients

Consuelo Pérez-Rico,1 Lucia Ayuso-Peralta,2 Lluisa Rubio-Pérez,2 Isabel Roldán-Díaz,3 Juan Arevalo-Serrano,4 Dolores Jiménez-Jurado,5 and Román Blanco6

1Department of Ophthalmology, University Hospital Príncipe de Asturias and Department of Surgery, University of Alcalá, Madrid, Spain
2Department of Neurology, University Hospital Príncipe de Asturias, Alcalá de Henares, Madrid, Spain
3Department of Ophthalmology, University Hospital Príncipe de Asturias, Alcalá de Henares, Madrid, Spain
4Department of Medicine, University Hospital Príncipe de Asturias, Alcalá de Henares, Madrid, Spain
5Department of Radiology, University Hospital Príncipe de Asturias, Alcalá de Henares, Madrid, Spain
6Department of Surgery, University of Alcalá, Madrid, Spain

Correspondence: Consuelo Pérez-Rico, Department of Ophthalmology, University Hospital Príncipe de Asturias, Carretera Alcalá-Meco s/n, 28805 Alcalá de Henares, Madrid, Spain; cinta.perezrico@gmail.com.

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PURPOSE. To evaluate visual pathway structure and function in patients with clinical isolated syndrome (CIS) by using spectral-domain optical coherence tomography (OCT) and multifocal visual-evoked potentials (mfVEP), predicting CIS conversion to clinically definite multiple sclerosis (MS).

METHODS. This observational, longitudinal study assessed the eyes with no previous history of optic neuritis of 29 consecutive patients with CIS according to the McDonald criteria. The relationships of the mfVEP results with the clinical findings, and psychophysical (Humphrey perimetry) and structural (OCT) diagnostic test data were investigated.

RESULTS. The mfVEP amplitude responses (interocular and monocular probability analysis) showed abnormal cluster visual field defects in 48.3% of the CIS eyes, whereas mfVEP latency analysis showed significant delays in 20.7%. The OCT average retinal nerve fiber layer thickness (RNFLT) was significantly reduced compared with the control group (P = 0.02). Significant differences between CIS eyes with abnormal and normal mfVEP latencies were found for the OCT RNFLT (P < 0.001) with a longer latency being linked to more severe axonal damage. Using multivariate logistic regression analysis, OCT average RNFLT was found to be an independent predictor of clinically definitive MS diagnosis at 12 months.

CONCLUSIONS. The combined use of OCT and mfVEP is helpful to detect significant subclinical visual pathway abnormalities and axonal loss in CIS patients. Retinal axonal loss measured by OCT is an important prognostic factor of conversion to MS in patients with CIS in absence of symptomatic optic neuritis.

Keywords: clinically isolated syndrome, multifocal visual-evoked potentials, spectral-domain optical coherence tomography, subclinical retinal axonal loss

Patients presenting with clinically isolated syndrome (CIS) are at risk of developing multiple sclerosis (MS). More than 80% of CIS patients with lesions on magnetic resonance (MR) images go on to develop MS, and approximately 20% have a self-limited process.1 This may create a diagnostic and therapeutic dilemma, given the difficulty in predicting who will convert to MS.

Sensitive tests are needed for early detection of the disease as well as for evaluating the efficacy of current and new treatments so as to delay the progression of disability. Both structural and functional tests can be used to assess damage to the axons of the visual pathway in CIS patients,2,3 already demonstrated in proton-MR spectroscopy studies.4,5 Optical coherence tomography (OCT) has shown specific retinal alterations in MS patients. The retinal nerve fiber layer thickness (RNFLT) is significantly reduced in the clinically affected eyes of patients with MS and optic neuritis (ON) and in their unaffected fellow eyes, as well as in the eyes of patients with CIS or MS without ON.6–8 In addition, OCT RNFLT has been suggested to be a structural biomarker of axonal loss in MS,9,10 and has also been correlated with brain atrophy.11

Multifocal visual-evoked potentials (mfVEPs) provide a method to diagnose the optic pathway conditions by assessing visual-evoked potentials, not as a single global response, but rather as responses from multiple individual segments of the visual field.12 In addition to providing response amplitudes, the mfVEPs also provide information about nerve conduction velocity (latency) that is useful in assessing the extent of demyelination. Recently, mfVEP amplitude has been shown to be a functional biomarker of axonal loss in MS.13 Likewise, Klistorner et al.14 reported a strong topographical association between RNFLT and mfVEP amplitude in eyes affected by ON. Laron et al.7 reported that mfVEP shows greater sensitivity than OCT and Humphrey visual field (HVF) in detecting abnorma-
ities in both an ON eye and its fellow. Even more, prolonged latencies could indicate increased risk of clinically definite MS in a patient with CIS who has presented with only ON.2

In this context, our study examined the relationship between OCT RNFLT and the amplitude and latency of mfVEPs in eyes of CIS patients without ON history so as to evaluate any visual pathway damage. Optical coherence tomography RNFLT was used as a marker of axonal degeneration, and mfVEP latency as a marker of demyelination, whereas mfVEP amplitude was used to assess the combined effect of inflammation and axonal loss. Although baseline MR imaging findings are known to have the best predictive value in evaluating the risk of CIS conversion to MS,13 we also assessed other prognostic factors (OCT and mfVEP) as alternatives to MR imaging in investigating the risk of conversion to MS in CIS patients.

PATIENTS AND METHODS
This observational, longitudinal study assessed 29 consecutive patients (10 men and 19 women; median age: 33.4 years) with CIS. The study included patients with CIS having a first clinical episode suggestive of central nervous system (CNS) demyelination involving the optic nerve, brainstem, spinal cord, or other topography, not attributable to other inflammatory diseases, but lacking radiological evidence of dissemination in time of lesions.16 Exclusion criteria were bilateral, acute, or atypical ON presentation; a refractive error of more than 5 diopters equivalent sphere; and a history of any other ocular (e.g., glaucoma, cataract, or macular diseases) or systemic disease that could affect the visual system. The study protocol was approved by the local institutional review board and adhered to the tenets of the Declaration of Helsinki, and all participants provided informed consent.

The study group (CIS eyes), included one eye each, randomly selected, from 20 CIS patients with no history of ON and the unaffected fellow eyes of 9 CIS patients with a history of unilateral ON, giving a total of 29 eyes. Diagnosis of ON was based on clinical findings, such as unilateral visual loss, pain with eye movement, relative afferent pupillary defect, and color vision deficiency. As a control normative group, one eye each, randomly selected, from 26 age-matched healthy subjects (7 men and 19 women; median age: 32.2 years) with a normal disease that could affect the visual system. The study protocol was approved by the local institutional review board and adhered to the tenets of the Declaration of Helsinki, and all participants provided informed consent.

Brain and spine MR imaging studies were performed with a 1.5-T Philips Gyroscan MR Unit (Philips Medical Systems, Best, The Netherlands) using conventional T1, T2, proton density, fluid-attenuated inversion-recovery, and double inversion-recovery weighted sequences with and without gadolinium. The total number of lesions with a diameter larger than 3 mm, and dissemination in space (DIS) and dissemination in time (DIT) criteria were assessed.16 Patients with CIS were included in the study within 3 months of their first clinical event and they were evaluated every 3 months. Magnetic resonance imaging studies were performed at baseline, and 5 and 12 months.

Disability was recorded for each patient using the Expanded Disability Status Scale (EDSS) score. All participants underwent an ophthalmologic examination that included best-corrected visual acuity (BCVA) with high-contrast Snellen acuity chart, pupillary reflexes, slit-lamp biomicroscopy, applanation tonometry and fundoscopy. A Swedish Interactive Threshold Algorithm-standard (SITA-standard 24-2) program automated perimetry was performed (Humphrey Visual Field Analyzer II; Carl Zeiss Meditec, Inc., Dublin, CA, USA). Spectral-domain OCT examinations were performed with the Cirrus HD-OCT Model 4000 (Carl Zeiss Meditec, Inc.).

Multifocal Visual-Evoked Potential Recordings and Analysis
The mfVEP recordings were obtained using VERIS software 5.9 (Electro-Diagnostic Imaging, San Mateo, CA, USA). The stimulus was a scaled dartboard with a diameter of 44.5°, containing 60 sectors, each with 16 alternating checks, 8 white (luminance: 200 cd/m²) and 8 black (luminance: <3 cd/m²), with a Michelson contrast of approximately 99%. The sectors were cortically scaled with eccentricity to stimulate approximately equal areas of the visual cortex.17 The dartboard pattern reversed according to a pseudorandom m-sequence at a frame rate of 75.18

Three channels of continuous VEP recordings were obtained with gold cup electrodes. For the midline channel, the electrodes were placed 4 cm above the inion (active), at the inion (reference), and on the forehead (ground). For the other two channels, the same ground and reference electrodes were used, but the active electrodes were placed 1 cm above and 4 cm lateral to the inion on either side. By taking the difference between pairs of channels, three additional “derived” channels were obtained. The records were amplified with the high- and low-frequency cutoffs set at 5 and 100 Hz, respectively (half-amplitude preamplifier PS11J; Grass Instruments, Rockland, MA, USA), and sampled at 1200 Hz (every 0.83 ms). The impedance was less than 5 K for all subjects. In a single session, 2-7 minute recordings were obtained from monocular stimulation of each eye and were averaged for analysis. Second-order kernel best-channel responses were then extracted.19,20 This averaging, as well as all other analyses, was computed with custom-made programs written in commercial software (Matlab; Mathworks, Inc., Natick, MA, USA).21 Response amplitudes were calculated by obtaining the root mean square (RMS) of the amplitude for each mfVEP response over time intervals from 45 to 150 ms. Signal-to-noise ratios were calculated for each response by dividing the RMS of the signal window by the average of the 60 RMS values of the noise-only window. Each of these values was compared with values from the normative group subjects22 and monocular probability plots were derived. Interocular amplitude differences for each patient were also calculated by taking the logarithm of the interocular ratio at each location21 and the interocular probability plot was derived. The amplitude probability plot was color-coded with saturated red squares (left eye) and saturated blue squares (right eye), with a significant difference being determined at P < 0.01 and, for desaturated colors, at P < 0.05.

Monocular and interocular latencies were measured as the temporal shift producing the best cross-correlation value between the corresponding responses of the patient’s eye and a template based on control eyes (monocular analysis) or between the corresponding responses from two eyes (interocular analysis). The latency probability plots were colored-coded in a manner similar to the amplitude plots using ovals instead of squares.

To evaluate the mfVEP and HVF total deviation results, we analyzed cluster defects: a defective cluster had two or more contiguous points at P < 0.01, or three or more contiguous points at P < 0.05, with at least one point at P < 0.01.25

Statistical Analysis
All data are expressed as the median and interquartile amplitude. Statistical analysis and study design were based on the recommendations for ophthalmological research.23 Differences in proportions were evaluated by the χ² test or Fisher’s exact test, as appropriate. Differences of two means were evaluated by the Student’s t-test if the normal distribution
TABLE 1. Baseline Characteristics Data Summary in CIS Patients, n = 29

<table>
<thead>
<tr>
<th>Age, y</th>
<th>33.4 (7.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>10/19</td>
</tr>
<tr>
<td>Kurtzke EDSS</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Oligoclonal bands in CSF</td>
<td>20 (69%)</td>
</tr>
<tr>
<td>High IgG level in CSF</td>
<td>15 (51.7%)</td>
</tr>
<tr>
<td>No. of MR imaging lesions</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (24.2%)</td>
</tr>
<tr>
<td>1–3</td>
<td>4 (13.8%)</td>
</tr>
<tr>
<td>4–8</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>≥9</td>
<td>9 (31%)</td>
</tr>
</tbody>
</table>

Data in median (interquartile amplitude) and percentages. One patient refused lumbar puncture.

predicting development of MS in CIS

The most relevant ophthalmological, perimetric, and OCT data are shown in Table 2. No significant differences in the BCVA were found between the CIS and control groups (P < 0.297). Also, HVF indices did not show significant differences between the CIS and control eyes (mean deviation, –1.2 [2.0] vs. –1.0 [1.5] dB; P = 0.183 and pattern standard deviation, 1.6 [0.6] vs. 1.5 [0.8] dB; P = 0.147). Interestingly, significant differences in the average RNFLT measured by OCT were found between both the CIS group and the control normative group (99.9 [20] vs. 105.8 [17.5] μm; P = 0.02), whereas no significant differences were observed in the temporal RNFLT (68 [19] vs. 70 [18] μm; P = 0.476) or macular volume (6.9 [0.7] vs. 7.0 [0.5] mm³; P = 0.495) (Table 2).

Table 3 lays out the changes detected by mfVEP in the CIS patients’ visual function. When the mfVEP amplitude responses were analyzed combining the interocular and monocular probability plots, OCT, and HVF tests were able to detect significant visual field defects only in 17.2% of the CIS eyes, respectively. An example of mfVEP probability plots, OCT, and HVF total deviation results for a CIS patient is shown in the Figure. Significant differences between eyes with abnormal and normal mfVEP latencies were found for the OCT RNFLT in the CIS group eyes (P < 0.001) with a longer latency being linked to more severe axonal damage.

Conversion of CIS to MS was established if the patient sustained a second clinical neurological event or if the follow-up MR imaging revealed DIS and DIT. In our study, 16 (55.2%) CIS patients converted to MS at 6 months (median time in months; 6.1 [5.8]), and 19 (65.5%) CIS patients converted at 12 months (median time in months; 12.6 [2.2]). The results of the univariate binary logistic regression analysis of the predictor variables from CIS conversion to McDonald MS are shown in Table 4. In backward stepwise multivariate binary logistic regression analysis, after adjustment for other covariates, the OCT average RNFLT at baseline (OR: 1.12; 95% confidence interval: 1.0 to 1.26; P = 0.043) was found to be an independent predictor of McDonald MS diagnosis at 12 months. All other variables, such as MR imaging lesions, oligoclonal bands in CSF, OCT temporal RNFLT, and mfVEP amplitude and latency, did not show any statistically predictive value of MS conversion.

DISCUSSION

In the present study, our results showed that mfVEP amplitude and latency responses from clinically unaffected eyes of CIS patients were significantly abnormal. The presence of these anomalous mfVEP responses from CIS patients in the absence of ON could be the electrophysiological evidence of widespread subclinical inflammation in CNS even at very early stages of MS. In addition, there was also significant atrophy of the retinal nerve fiber layer measured by OCT in the group of CIS patients’ eyes. Taken together, our results provide a good opportunity to assess the relationship between structure and function.
function of the CNS in patients with CIS and to establish patients' neurologic impairment.

A unique benefit of the mfVEP is its ability to expose a subclinical lesion in the clinically unaffected eyes in MS, not detected with structural and psychophysical diagnostic techniques. Laron et al. demonstrated that the mfVEP was more sensitive in detecting abnormality than the HVF and OCT in both affected and unaffected eyes of MS patients with an ON history and in MS patients with no clinical history of ON in either eye. Our study, in CIS patients without ON, concurs with these findings and with those of other reports. This result is expected because mfVEP, by virtue of the latency measurements, detects demyelination, whereas OCT does not. Prolongation of the latency is a surrogate marker of visual pathway demyelination, and demyelination is intimately related to axonal loss in MS. Myelin plays a vital role in providing trophic support to axons and protecting them from inflammatory mediators and immune cells. Our study has established a significant relationship between mfVEP latency and OCT RWNFLT in eyes of CIS patients without history of ON, with a longer latency being linked to more severe axonal damage. In this regard, this result is comparable to that obtained by Klistorner et al. in the clinically unaffected eyes of MS patients. The association of delayed latency with RNFLT reduction supports the concept that demyelination may play an important role in promoting axonal loss.

Previous studies using OCT to examine retinal axonal degeneration in CIS found no differences in RNFLT between unaffected eyes of CIS patients and controls. Our results are in agreement with those of other investigators showing that OCT average RNFLT parameter appeared to be consistently thinner in CIS eyes, indicating that retinal axonal loss occurs early before established clinically definite MS and in the absence of symptomatic ON. However, in contrast with the other study, we were not able to detect any significant OCT temporal axonal loss in our sample of CIS patients. Temporal-predominant peripapillary retinal nerve fiber layer thinning is characteristic in MS, but the cause of this pattern of thinning is unknown. In this sense, still more research is needed to understand the predominant patterns of retinal axonal loss in MS.

Another objective of this study was to identify that OCT and mfVEP potential prognostic factors predict CIS conversion to clinically definite MS. Using multivariate logistic regression analysis, OCT average RNFLT was found to be an independent predictor of McDonald MS diagnosis at 12 months. A preliminary study by Outteryck et al., in CIS patients with and without ON, reported that retinal axonal loss measured by OCT at the earliest clinical stage of MS, did not predict conversion to MS at 6 months. This study was performed with time-domain OCT to measure RNFLT, which provides lower resolution than spectral-domain OCT and.

### Table 4. Results of Univariate Binary Logistic Regression Analysis of Predictors of McDonald MS at 12 Months

<table>
<thead>
<tr>
<th>Predictors of McDonald MS</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR imaging lesions</td>
<td>-</td>
<td>-</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>CSF oligoclonal bands</td>
<td>7.2</td>
<td>0.53–96.63</td>
<td>0.136</td>
</tr>
<tr>
<td>OCT average RNFLT</td>
<td>1.17</td>
<td>1.0–1.26</td>
<td>0.043</td>
</tr>
<tr>
<td>OCT temporal RNFLT</td>
<td>1.11</td>
<td>0.99–1.24</td>
<td>0.071</td>
</tr>
<tr>
<td>mfVEP amplitude</td>
<td>0.76</td>
<td>0.06–8.66</td>
<td>&gt;0.20</td>
</tr>
<tr>
<td>mfVEP latency</td>
<td>0.77</td>
<td>0.09–6.44</td>
<td>&gt;0.20</td>
</tr>
</tbody>
</table>

CI, confidence interval.
possibly, 6 months may not be a sufficiently long follow-up period to declare whether OCT predicts conversion to MS.

In summary, a significant incidence of subclinical optic nerve involvement was detected in CIS eyes by means of the OCT and mfVEP. Retinal axonal loss measured by OCT is an important prognostic factor that must be considered in CIS patients in the absence of symptomatic ON, as it promotes conversion of CIS to clinically definitive MS. Extended follow-up of these patients and a larger cohort remain necessary to confirm these findings.

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