Optical Coherence Tomography in Clinically Isolated Syndrome

No Evidence of Subclinical Retinal Axonal Loss

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Background: Optical coherence tomography has emerged as a new tool for quantifying axonal loss in multiple sclerosis (MS). A reduction in retinal nerve fiber layer (RNFL) thickness is correlated with Expanded Disability Status Scale score and brain atrophy.

Objective: To investigate RNFL and macular volume measurements using optical coherence tomography in the clinically isolated syndrome population.

Design: Prospective case series.

Settings: Neurologic clinics at the university hospitals of Lille and Strasbourg (France).

Participants: Fifty-six consecutive patients with clinically isolated syndrome (18 with optic neuritis and 38 without optic neuritis) and 32 control subjects.

Main Outcome Measures: Macular volume and RNFL thickness.

Results: Mean (SD) overall RNFL thickness (98.98 [10.26] µm) and macular volume (6.86 [0.32] µm³) in the clinically isolated syndrome population were not significantly different compared with the controls (98.71 [9.08] µm and 6.92 [0.38] µm³, respectively). No link was noted between atrophy of the RNFL or macula and conversion to MS at 6 months.

Conclusions: Optical coherence tomography does not reveal retinal axonal loss at the earliest clinical stage of MS and does not predict conversion to MS at 6 months.


Multiple sclerosis (MS) is an inflammatory demyelinating and neurodegenerative disease of the central nervous system. Axonal impairment has been shown to occur in MS since the publication of postmortem descriptions of the disease. More recent pathologic studies have confirmed that axonal loss is a prominent feature of the disease. Cerebral proton magnetic resonance spectroscopy (H-MRS) studies have shown that patients with MS have a significant decrease of N-acetylaspartate in T2-visible lesions and in normal-appearing white and gray matter. In clinically isolated syndrome (CIS), which represents the earliest clinical stage of the disease, axonal impairment and irreversible axonal loss have already been demonstrated in H-MRS studies. Optical coherence tomography (OCT) has emerged as a new tool enabling axonal loss to be quantified in MS. The thickness of the retinal nerve fiber layer (RNFL) is significantly reduced in the clinically affected eyes of patients with MS and optic neuritis (ON), in the unaffected fellow eyes of patients with MS and ON, and in the eyes of patients with MS without ON. The RNFL thickness of eyes not affected by ON is inversely correlated with the patient's Expanded Disability Status Scale score. Atrophy of the RNFL is also correlated with brain atrophy and with disease activity. We investigated RNFL and macular volume measurements in a cohort of patients with CIS to determine whether OCT could reveal early retinal axonal loss.

METHODS

STUDY DESIGN AND PARTICIPANTS

This study is a prospective case series of 56 consecutive patients in the neurologic clinics at the university hospitals of Lille and Strasbourg (France). This study received approval from the ethical committee of Centre Hospitalier Régional Universitaire de Lille. All of the patients gave written informed consent.

We included only patients who had experienced a CIS in the previous 12 months. We excluded patients with ophthalmologic dis-
cases that might impair or bias OCT measurements (glaucoma, diabetes mellitus, retinal surgery, and retinal disease). All of the patients had an ametropia of less than 10 diopters. Patients with myelitis suggestive of neuromyelitis optica and those with antedated CIS sentinel events were excluded from the study. Patients were included before or 4 weeks after corticoid infusions independent of the time of the clinical event (within 12 months). In a few patients, OCT was performed during the clinical event but only on an asymptomatic eye with a normal ocular fundus.

A nonmatched healthy population was composed of 32 individuals evaluated using OCT. All of the control subjects gave written informed consent to participate in the study. Each of them had a healthy ocular fundus, and none had a history of retinal abnormality, diabetes mellitus, or glaucoma.

OPTICAL COHERENCE TOMOGRAPHY

The thickness of the RNFL and the macula was measured in each dilated eye by an experienced technician (P.D.), who was unaware of the results of other studies, using OCT (StratusOCT 3000 and OCT 4.0 software; Carl Zeiss, Dublin, Ireland) measuring RNFL or macular volume in MS or CIS cohorts. All of the scans met the signal strength requirement of greater than 7 (maximum of 10). The OCT system was used to obtain circular peripapillary scans (fast RNFL thickness protocol), which included three 3.4-mm-diameter retinal scans averaged to provide the RNFL thickness at 256 points along the circumference of the circular scan in each eye. Macular volume was measured once for each eye by means of 6 radial lines to compose a macular volume–volume map (fast macular volume map protocol). The OCT software used an automated computerized algorithm to calculate the overall thickness of the RNFL and to compare these measurements with a normative database of age-matched control individuals. The overall and sector (temporal, superior, nasal, and inferior quadrants) RNFL thickness measurements and the macular volume measurements were assigned a rank of normal (fifth percentile or higher) or below normal (lower than the fifth percentile) compared with the normative database of age-matched control individuals provided by the OCT 4.0 software.14 Because each individual has 2 RNFL measurements that might differ, we used the RNFL and macular volume showing the smaller value, except in patients with a history of ON, for whom we considered only the healthy fellow eye. Fisher et al13 showed that there was no difference in RNFL thickness between the unaffected fellow eyes of patients with MS and ON and the eyes of patients with MS without ON. For the CIS population (n=36), we pooled the data for unaffected fellow eyes of patients with CIS and ON and the data for eyes of patients with CIS without ON. For control groups, we also used the RNFL and macular volume showing the smaller values. In these 56 patients, we also considered the non–ON-CIS population (n=38) and the ON-CIS population (n=18). The ON eyes of the ON-CIS population (ON-eyes) were used as positive controls.

VISUAL EVOKED POTENTIALS

All visual evoked potentials were performed using the ophthalmologic monitor WIN8000D (Metrovision; Perenchies, Alsace, France). Mean (SD) P100 latency (118 [14] milliseconds) and visual evoked potentials were measured for all of the patients.

STATISTICAL ANALYSIS

The t test was used to compare the mean data of the CIS and control populations. The Fisher exact test was used to determine whether there was a link between the qualitative data of the present patients and RNFL or macula atrophy. All of the analyses were performed using a software program (SPSS version 12.0; SPSS Inc, Chicago, Illinois).

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE POPULATIONS

Details of the patients’ demographic and clinical characteristics are summarized in Table 1. Two-thirds of the patients had dissemination in space according to the Barkhof criteria.16 One-third of the patients had a unilateral acute ON. Only 4 patients had a subclinical visual evoked potential alteration (latency prolongation or alteration of amplitudes on the fellow eye or the non–ON-CIS eye) but always without RNFL atrophy. The control population comprised 32 individuals with a mean (SD) age of 30.03 (8.3) years.

RNFL THICKNESS

CIS Population vs Controls

The RNFL thickness findings are summarized in Table 2. All patients underwent RNFL study by OCT. There were no significant differences in RNFL thickness measurements (overall and in the temporal, superior, nasal, and inferior quadrants) between the CIS population and control groups. All of the patients had a normal overall RNFL thickness (the fifth percentile or higher according to the Zeiss normative database). However, when we consid-

| Table 1. Demographic and Clinical Characteristics of the 56 Study Patients |
|------------------|------------------|
| Characteristic | Value |
| Age, mean (SD), y | 31.9 (10.2) |
| Sex, F/M, No. (ratio) | 40/16 (2.5) |
| Disease duration before OCT evaluation, mean (SD), mo | 4.33 (3.32) |
| Clinical presentation, No. (%) | | |
| Monofocal (82%) | | |
| ON | 11 (20) |
| Hemispheric | 6 (11) |
| Infratemporal | 11 (20) |
| Spinal cord | 18 (32) |
| Multifocal (18%) | | |
| With ON | 7 (13) |
| Without ON | 3 (5) |
| Dissemination in space according to the Barkhof criteria, No. (%) | | |
| Without ON | 35 (63) |
| to the revised McDonald criteria, No. (%) | | |
| With ON | 40 (71) |
| Gadolinium enhancement, No. (%) | | |
| Oligoclonal IgG bands, No. (%) | | |
| Clinically definite MS at 6 mo, No. (%) | | |
| MS according to the revised McDonald criteria at 6 mo, No. (%) | | |

Abbreviations: MS, multiple sclerosis; OCT, optical coherence tomography; ON, optic neuritis.
ere the 4 RNFL quadrants individually, 9% of patients (vs 6% of controls) had atrophy (lower than the fifth percentile) in the temporal quadrant, 7% (vs 9%) in the superior quadrant, 5% (vs 6%) in the nasal quadrant, and 7% (vs 3%) in the inferior quadrant. Fourteen patients (25%) and 7 controls (22%) had atrophy in at least 1 quadrant. Four patients but no controls had atrophy in 2 quadrants. There was no link between atrophy in 1 or more quadrants of the RNFL and dissemination in space according to the Barkhof criteria at initial magnetic resonance imaging (MRI),\textsuperscript{16} dissemination in space according to the revised McDonald criteria,\textsuperscript{17} gadolinium enhancement at initial MRI, multifocal presentation, alteration of visual evoked potentials, or development of MS at 6 months according to the 2005 revised McDonald criteria. Moreover, patients who, at 6 months, had developed clinically definite MS (CDMS) (n=13) or MS according to the revised McDonald criteria (n=23) did not have significantly more severe RNFL atrophy (Table 3). Of the 14 patients with atrophy in at least 1 RNFL quadrant, 44% had an infratentorial presentation, 31% had myelitis, 21% had ON, and 6% had a supratentorial presentation. These percentages were different from those of the cohort as a whole, but \( \chi^2 \) analysis could not be performed because of the few patients involved.

Table 2. RNFL Thickness Findings in the CIS, Non–ON-CIS, ON-CIS, and Control Groups

<table>
<thead>
<tr>
<th>RNFL Sector</th>
<th>CIS (n=56)</th>
<th>Non–ON-CIS (n=38)</th>
<th>ON-Eyes (n=18)</th>
<th>Controls (n=32)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>98.98 (10.26) [84-122]</td>
<td>98.03 (10.73) [84-117]</td>
<td>92.27 (12.82) [62-109]</td>
<td>98.71 (9.08) [83-113]</td>
<td>.90 .87 .02 ( ^2 )</td>
</tr>
<tr>
<td>Temporal</td>
<td>66.44 (11.95) [39-97]</td>
<td>66.02 (11.31) [39-93]</td>
<td>59.38 (15.9) [38-70]</td>
<td>70.21 (12.54) [47-102]</td>
<td>.17 .14 .06 ( ^2 )</td>
</tr>
<tr>
<td>Superior</td>
<td>124.5 (15.90) [96-162]</td>
<td>123.18 (13.99) [96-147]</td>
<td>118.84 (22.19) [75-149]</td>
<td>124.16 (16.38) [95-168]</td>
<td>.92 .79 .30</td>
</tr>
<tr>
<td>Nasal</td>
<td>75.46 (14.71) [45-120]</td>
<td>74.67 (14.82) [45-96]</td>
<td>74.30 (14.43) [54-98]</td>
<td>73.31 (15.61) [50-108]</td>
<td>.52 .71 .82</td>
</tr>
<tr>
<td>Inferior</td>
<td>125.54 (16.82) [91-163]</td>
<td>124.69 (18.25) [91-158]</td>
<td>116.61 (18.36) [86-149]</td>
<td>126.69 (14.35) [105-157]</td>
<td>.75 .62 .03 ( ^2 )</td>
</tr>
</tbody>
</table>

Abbreviations: CIS, clinically isolated syndrome; ON, optic neuritis; RNFL, retinal nerve fiber layer.

\( ^2 \)Statistically significant.

Table 3. Comparison of RNFL Thickness After 6-Month Follow-up Between CIS Remaining as Such and CIS Becoming CDMS or MS According to the Revised McDonald Criteria

<table>
<thead>
<tr>
<th>RNFL Sector</th>
<th>CIS vs Controls</th>
<th>CIS vs Non–ON-CIS</th>
<th>ON-Eyes vs Controls</th>
<th>CDMS vs Controls</th>
<th>MS (McDonald 2005) vs CDMS</th>
<th>MS (McDonald 2005) vs ON-Eyes</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>99.36 (9.11) [84-118]</td>
<td>101.20 (13.48) [85-123]</td>
<td>98.43 (11.95) [84-123]</td>
<td>.39 .74 .03 ( ^2 )</td>
<td>.89 .85 .82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior</td>
<td>125.70 (13.36) [96-153]</td>
<td>128.70 (19.68) [99-162]</td>
<td>122.80 (18.02) [99-162]</td>
<td>.26 .71 .98</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasal</td>
<td>75.42 (14.31) [45-111]</td>
<td>75.46 (14.71) [45-120]</td>
<td>75.52 (15.59) [55-120]</td>
<td>.26 .71 .98</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior</td>
<td>125.90 (15.76) [91-158]</td>
<td>127.20 (18.25) [91-163]</td>
<td>125.10 (18.58) [91-163]</td>
<td>.26 .71 .98</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CDMS, clinically definite multiple sclerosis; CIS, clinically isolated syndrome; MS, multiple sclerosis; RNFL, retinal nerve fiber layer.

Non–ON-CIS Population vs Controls

There were no significant differences in RNFL thickness measurements (overall and in the temporal, superior, nasal, and inferior quadrants) between the non–ON-CIS population and controls (Table 2).

ON Eyes vs Controls

There were significant differences in RNFL thickness measurements (overall and in the temporal and inferior quadrants) between the ON-eyes and control eyes. No significant differences were observed on the superior and nasal quadrants (Table 2).

MACULAR VOLUME

CIS Population vs Controls

Forty-nine patients underwent macular study by OCT. Macular volume of patients with CIS (mean [SD], 6.86 [0.32]; range, 6.17-7.41 mm\(^3\)) was not significantly reduced compared with control values (mean [SD], 6.92 [0.38]; range, 6.22-7.41 mm\(^3\); \( P = .49 \)). All but 1 patient had a normal macular volume (the fifth percentile or higher according to the Zeiss normative database). No control individuals showed atrophy on macular volume. There was no link between atrophy of the macula (lower than the fifth percentile) and dissemination in space according to the Barkhof criteria at initial MRI, dissemination in space according to the revised McDonald criteria, gadolinium enhancement at initial MRI, multifocal presentation, alteration of visual evoked potentials, or development of MS at 6 months according to the 2005 revised McDonald criteria. Moreover, macular volume of patients who at 6 months had developed CDMS (mean [SD], 6.81 [0.35]; range, 6.36-7.41 mm\(^3\)) or MS according to 2005 McDonald criteria (mean [SD], 6.83 [1.16]; range, 6.17-7.41 mm\(^3\)) was not significantly different from...
that of patients who continued to have CIS (mean [SD], 6.9 [0.29]; 6.25-7.48 µm³; P=.33 and .69).

Non–ON-CIS Population vs Controls

There was no significant difference in macular volume between the non–ON-CIS population (mean [SD], 6.85 [0.31] µm³; range, 6.17-7.41 µm³) and controls (mean [SD], 6.92 [0.38] µm³; range, 6.22-7.41 µm³; P=.37). Macular volume was significantly reduced in the ON-CIS population (mean [SD], 6.65 [0.53] µm³; range, 5.74-7.36 µm³) compared with controls (mean [SD], 6.92 [0.38] µm³; range, 6.22-7.41 µm³; P=.03).

ON-Eyes Population vs Controls

Macular volume of the ON-eyes population was significantly reduced compared to HC.

As in previous study findings,¹⁸,¹⁹ the present study shows that atrophy of the RNFL and macula is observed after an episode of ON, but it did not find evidence of RNFL or macula atrophy in patients with CIS other than ON or in nonaffected eyes of patients with CIS and ON. We found no link between atrophy of the RNFL or macula and the development of CDMS and MRI inflammatory markers. Based on this evidence, OCT does not reveal subclinical retinal axonal loss at the earliest clinical stage of MS.

There were no significant differences in RNFL thickness between the CIS population and controls. Thus, RNFL atrophy, which has been shown to be correlated with Expanded Disability Status Scale score and cerebral atrophy in an MS cohort, is not observed at the earliest clinical stage of the disease. These results agree with those of a study¹⁸ of a cohort of patients with CIS and MS and ON that found no differences in RNFL thickness between clinically unaffected eyes and control eyes. In the present study, only the temporal quadrant appeared to be thinner in the CIS group than in the control group, but the difference did not reach statistical significance. Temporal atrophy of the RNFL has already been shown to be correlated with disease activity, the number of relapses, and a change in Expanded Disability Status Scale score.¹⁵ No link was found between RNFL atrophy in 1 or more quadrants (less than the fifth percentile according to the Zeiss normative database), MRI inflammatory markers (Barkhof criteria and gadolinium enhancement), and development of MS at 6 months according to 2005 revised McDonald criteria. In the same way, axonal injury demonstrated by means of H-MRS studies in CIS is irreversible and independent of the short-term disease evolution.³ Brain volume measurements and H-MRS studies that might have confirmed these data were unavailable.

We did not observe a significant reduction in macular volume in the CIS group compared with the controls. This result agrees with that of the previously mentioned study¹⁸ of a cohort of CIS and MS patients with ON, which found no differences in macular volume between clinically unaffected eyes and control eyes.

At 6 months, patients who developed CDMS or MS according to the revised McDonald criteria did not have significantly more RNFL or macular atrophy. Six months may not be a sufficiently long follow-up period to declare whether OCT predicts conversion to MS. Long-term follow-up is warranted. Although follow-up remains short, the findings from this study are consistent with a recent work published by Costello et al²⁰ about 2-year follow-up of an ON-CIS cohort with OCT. The researchers did not find significant differences in RNFL values of unaffected eyes between patients who, 2 years after an ON-CIS, developed CDMS and those who did not. The present study indicates that RNFL thickness does not reliably distinguish patients at higher risk for converting to CDMS at 6 months. Conversion to MS is weighted to inflammatory events and not to axonal degeneration. Thus, it is comprehensive to state that a measure of axonal damage does not predict inflammatory events.

There were no significant differences in RNFL measurements (overall, temporal, superior, nasal, and inferior) between the non–ON-CIS population and controls or between the CIS population and controls. These data are in accord with those of Fishers et al¹⁵ that showed there were no differences in RNFL thickness between the unaffected fellow eyes of patients with MS and ON and the eyes of patients with MS without ON. An episode of ON is not accompanied by subclinical axonal damage in the fellow eye.

Whereas OCT has emerged as a new tool enabling axonal loss to be quantified in MS, this study indicates that OCT does not reveal subclinical retinal axonal loss at the earliest clinical stage of MS. Extended follow-up of these patients, an increase in the cohort size, and an MRI study remain necessary.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES


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