Optical Coherence Tomography Is Associated With Cognitive Impairment in Multiple Sclerosis

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Background: Optical coherence tomography (OCT) is a sensitive method for quantifying retinal neuronal and axonal structures. Reductions in retinal nerve fiber layer (RNFL) and ganglion cell inner plexiform layer (GCIPL) thicknesses have a reported association with white and grey matter atrophy in multiple sclerosis (MS). We hypothesized that the thinning of intraretinal layer measurements associates with cognitive decline in MS patients with no prior event of optic neuritis (ON).

Methods: OCT and NeuroTrax computerized cognitive assessments were performed in 204 relapsing remitting MS patients with no history of ON or other conditions affecting the eye. Data were collected between 2010 and 2020 and retrospectively analyzed. Correlations were examined between cognitive performance and a lower RNFL or GCIPL thickness. A multilinear regression model was generated to assess the significance of these correlations regarding the disability score and disease duration.

Results: The 204 study participants had a mean age of 40.52 ± 11.8 years (mean ± SD) and disease duration of 9.80 ± 9.40 years. The mean RNFL thickness in this whole cohort was 82.22 ± 10.85 μm and the global cognitive score was 95.32 ± 12.32. The mean GCIPL thickness measured in a subgroup of 104 patients was 74.27 ± 10.37 μm. The RNFL and GCIPL both correlated with the global cognitive score (r = 0.174, P = 0.013 and r = 0.29, P = 0.03, respectively), and with various cognitive domains. However, the GCIPL showed stronger correlations than RNFL, particularly with executive function (r = 0.29, P = 0.003), attention (r = 0.332, P = 0.001), and the information processing speed (r = 0.25, P = 0.012). These correlations remained significant after correcting for confounders.

Conclusion: OCT measurements correlate with cognitive performance in MS patients. OCT can thus be used to evaluate central nervous system neurodegeneration in MS, as reflected by cognitive decline.

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In the past decade, OCT has been thoroughly explored as a screening methodology in patients with mild cognitive impairment (MCI) and Alzheimer’s disease (AD) (10), and has revealed correlations between changes in RNFL thickness and/or volume, GCIPL degeneration, and cognitive decline. Moreover, GCIPL measurements were reported to be negatively correlated with disease duration in patients with mild AD (11), and an association between the RNFL thickness and continuous measures of cognitive ability has been described in various recent studies (12–14).

In accordance with the reported evidence to date, we speculated that OCT measurements would associate with cognitive decline in MS. We examined this possibility in our current study in MS patients with no evidence of past optic neuritis (ON) in either eye. These cases were chosen to avoid potentially misleading findings, because thinning of intraretinal layers could be the result of a previous event of ON, and not necessarily related to neurodegeneration in the entire brain. We aim to lay grounds for the possibility of using OCT as a biomarker of cognitive impairment in MS.

METHODS

Study Design and Patient Population

This was an observational study of patients diagnosed with MS that were followed between January 2010 and January 2020 in Sheba Multiple Sclerosis Center, Israel. Ethical approval to conduct the study was granted by the Sheba Medical Center Ethics Committee (IRB number 5596-08-SMC). All study subjects underwent spectral-domain OCT imaging with RNFL measurements for both eyes. A subgroup of patients underwent GCIPL measurements as well, and the eye yielding more prominent thinning was included in the statistical analysis, because it could better reflect the neurodegenerative process occurring in the brain. In addition, all study subjects completed a comprehensive cognitive assessment using the Neurotrax battery (15).

Inclusion criteria were as follows: (1) An MS diagnosis in accordance with the 2017 McDonald diagnostic criteria (16), including a brain MRI revealing typical demyelinating lesions; (2) a relapsing-remitting (RRMS) disease type; (3) normal visual acuity defined as a best-corrected visual acuity of ≥20/25 for both eyes, to avoid undocumented events of ON which affected visual acuity and could affect OCT measurements; and (4) cognitive and OCT assessments performed within 6 months of each other. Patients were excluded from the study if they satisfied any of the following: (1) a clinical history of ON, unilateral or bilateral; (2) known eye diseases for example, glaucoma, cataracts; or (3) the presence of any known systemic diseases that can affect the eye for example, diabetes, hypertension.

Demographic and clinical data were collected for all of the study subjects and included age, gender, years of education, disease duration, and disability status as measured by the Expanded Disability Status Scale (EDSS) (17). All subjects underwent comprehensive ophthalmologic tests including best-corrected visual acuity, intraocular pressure, color perception, pupillary light reflex, and a slit lamp examination of the anterior and posterior segments of both eyes.

Optical Coherence Tomography Measurements

Spectral-domain optical coherence tomography (SD-OCT) examinations were conducted using a Cirrus HD-OCT, model 4000 device, with version 6.0 software (Carl Zeiss Meditec, Jena, Germany) in all subjects to measure RNFL thickness, and GCIPL thickness in a subgroup of patients. The optic disc RNFL thickness was measured as an average thickness across 4 segments as follows: superior (120°), temporal (50°), inferior (120°), and nasal (70°). The average RNFL thickness was calculated also for the papillomacular bundle. The software for the Cirrus HD-OCT device maps all layers, including the 2 borders of the RNFL, and automatically calculates the thickness of the layers. The normal mean RNFL and GCIPL thicknesses are 100.6 ± 11.6 μm and 82.1 ± 6.2 μm, respectively, based on previous large-scale studies (18,19). We defined mild-to-moderate thinning as values at 1 SD below these normal levels, and severe thinning as values at 2 SD below these normal levels.

Cognitive Assessments

Cognitive performance in the study subjects was evaluated using a computerized cognitive test battery (Mindstreams; NeuroTrax Corp, New York, NY), designed to evaluate multiple cognitive domains including verbal and nonverbal memory, executive function, visual–spatial perception, verbal function, attention, information processing speed, and motor skills (15). A detailed description of this test battery, and explanation of the index scores used to designate the cognitive domains we tested, are available at http://www1.mindstreamhealth.com. The global cognitive score and each cognitive domain score for the study patients were standardized relative to age and education, stratified by cognitively intact norms, and scaled to an IQ-style scale (mean: 100, SD: 15). A value of 85 that is, 1 SD below normal, was designated as the cutoff for mild–moderate cognitive impairment, and a value of 70 that is, 2 SD below normal, as the cutoff for severe cognitive impairment.

Statistical Analysis

Statistical analyses were performed using IBM SPSS, version 25. Categorical variables were expressed as numbers and percentages and continuous variables as mean values with
Correlation Between Optical Coherence Tomography Measurements and Cognitive Performance

OCT parameters significantly correlated with components of the cognitive assessment used in this present study. The RNFL thickness correlated with the global cognitive score, verbal function, attention, and motor skills. The GCIPL thickness correlated with the global cognitive score, executive function, attention, information processing speed, and motor skills. These results are detailed in Table 2 and demonstrated in Figure 1.

A multivariate linear regression model was used to examine whether the correlations found between OCT measures and cognition remained significant in the presence of the additional disease-related factors, EDSS, and disease duration. The results are detailed in Table 3, and the full models can be found in Supplemental Digital Content 1 (Table 1a–e, http://links.lww.com/WNO/A485).

The R^2 of the model for global cognitive score was 0.187, demonstrating that 18.7% of the variance in the score could be explained, in descending order of influence, by the EDSS and the GCIPL thickness, as reflected by their standardized beta coefficients (Std β). Similarly, 28.2% of the variance in executive function could be explained by the EDSS and GCIPL measures, with 21.9% of the variance in attention attributable to these 2 variables. Regarding the information processing speed, 6.3% of the variance was explained by the GCIPL thickness alone.

Motor skills was the only domain in which the OCT data did not show a significant association. The model showed that 23.6% of the variance in that domain could be attributed solely to the EDSS. All of the beta coefficients showed significance of below 0.05. Finally, although the disease duration was found to be significantly associated with 3 different cognitive domains, this relationship did not prove to be significant in the presence of OCT measures and the EDSS value.

DISCUSSION

We have here analyzed a large cohort of RRMS patients for the correlation between OCT measures and cognitive performance. Because we aimed to isolate and explore the damage to the retina that could reflect the overall neurodegeneration in the brain, we applied strict criteria to include only patients with no previous history of ON or other eye disorders that could affect the thickness of either the RNFL or GCIPL. In spite of exclusion of this subgroup of patients, the cohort is characteristic of RRMS, showing episodes of inflammation excluding the eye. For cognitive assessments, we used an advanced comprehensive cognitive battery that enabled the evaluation of a wide range of cognitive domains, correcting for age and level of education, and including the response time into the calculated scores.
This provided an advantage over the manual cognitive assessments used in previous studies, which are less precise because they do not measure response time, and do not include all cognitive domains (2,20).

As expected, our current MS patients demonstrated reduced RNFL and GCIPL thicknesses than a previously reported age-matched healthy population, a recurrent finding in studies exploring MS subjects (21,22). Moreover, and similarly to our OCT findings, the cognitive performance of our MS cohort was below that expected for an age- and education-matched healthy population, thus demonstrating a mild decrease in cognitive functions. The most

### TABLE 1. Demographic and clinical characteristics of the study subjects

|                          | All Subjects (N = 204) | Disease Duration ≤ 10 (N = 128) | Disease Duration >10 (N = 76) | P       |
|--------------------------|------------------------|---------------------------------|------------------------------|---------|
| Age, yrs                 | 40.52 (11.8)           | 36.46 (10.91)                   | 47.35 (9.98)                 | P < 0.001 |
| Gender (%)               |                        |                                 |                              |         |
| Male                     | 59 (28.9%)             | 41 (32.0%)                      | 18 (23.7%)                   | 0.207   |
| Female                   | 145 (71.1%)            | 87 (68.0%)                      | 58 (76.3%)                   |         |
| Disease duration, yrs    | 9.80 (9.40)            | 4.03 (3.02)                     | 19.53 (8.43)                 | P < 0.001 |
| Education, yrs           | 14.41 (2.5)            | 14.08 (2.51)                    | 14.99 (2.39)                 | 0.013   |
| Expanded disability status scale | 2.527 (1.81)     | 2.14 (1.55)                     | 3.17 (2.03)                  | P < 0.001 |
| Median (IQR)             | 2 (2)                  | 2.1 (1.5)                       | 2.5 (3.5)                    | P < 0.001 |
| Retinal nerve fiber layer, μm | 82.22 (10.85)    | 84.98 (10.06)                   | 77.58 (10.62)                | P < 0.001 |
| Ganglion cell inner plexiform layer, μm | 74.27 (10.37) | 76.93 (10.01)                  | 68.79 (8.95)                 | P < 0.001 |
| Global cognitive score   | 95.32 (12.32)          | 96.49 (11.44)                   | 93.36 (13.52)                | 0.079   |
| Memory                   | 96.20 (13.5)           | 96.4 (12.74)                    | 95.87 (14.77)                | 0.787   |
| Executive function       | 95.61 (13.87)          | 97.4 (12.73)                    | 92.59 (15.21)                | 0.016   |
| Visual spatial           | 100.32 (16.31)         | 100.77 (15.31)                  | 99.56 (17.95)                | 0.612   |
| Verbal function          | 93.84 (20.22)          | 93.92 (19.82)                   | 93.68 (21.03)                | 0.937   |
| Attention                | 94.66 (15.29)          | 96.64 (12.27)                   | 91.36 (18.96)                | 0.032   |
| Information processing speed | 94.67 (17.07)     | 95.72 (17.15)                   | 92.85 (16.89)                | 0.259   |
| Motor skills             | 93.15 (19.66)          | 95.47 (18.45)                   | 89.17 (21.12)                | 0.030   |
| Immunomodulatory treatment |                      |                                 |                              |         |
| Treated (%)              | 104 (50.9%)            | 68 (53.1%)                      | 36 (47.4%)                   | 0.432   |
| Treatment duration, months | 31.31 (44.97)    | 18.37 (21.35)                   | 55.74 (64.34)                | P < 0.001 |
| Treatment type (% of patients treated) |           |                                 |                              |         |
| Dimethyl fumarate        | 26 (25%)               | 22 (32.3%)                      | 4 (11.1%)                    | 0.018   |
| Interferon beta          | 25 (24%)               | 16 (23.5%)                      | 9 (25%)                      | 0.865   |
| Fingolimod              | 20 (19.2%)             | 9 (13.2%)                       | 11 (30.5%)                   | 0.522   |
| Natalizumab             | 14 (13.5%)             | 10 (14.7%)                      | 4 (11.1%)                    | 0.034   |
| Teriflunomide            | 12 (11.5%)             | 11 (16.2%)                      | 1 (2.7%)                     | 0.041   |
| Intravenous immunoglobulin | 5 (4.8%)             | 3 (4.4%)                        | 2 (5.5%)                     | 0.803   |
| Ocrelizumab             | 2 (1.9%)               | 0 (0%)                          | 2 (5.5%)                     | 0.052   |

Data are presented as a mean (SD) unless otherwise specified.

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### TABLE 2. Correlations between optical coherence tomography parameters and cognitive performance

|                  | RNFL | GCIPL |
|------------------|------|-------|
|                  |      |       |
| Global cognitive score | 0.174 | 0.29 |
| Executive function  | 0.133 | 0.35 |
| Visual spatial     | 0.114 | 0.14 |
| Verbal function    | 0.169 | 0.332 |
| Attention          | 0.164 | 0.025 |
| Information processing speed | 0.116 | 0.258 |
| Motor skills       | 0.218 | 0.01 |
| Memory             | 0.044 | 0.109 |

*r*, correlation coefficient.

†P < 0.05 was considered significant.

GCIPL, ganglion cell inner plexiform layer; RNFL, retinal nerve fiber layer.
The most notable findings of our current study were the correlations between OCT measures and various cognitive domains. Both the RNFL and GCIPL thicknesses measured...
in our present MS series significantly correlated with the global cognitive score, attention, and motor skills of these patients. The RNFL values additionally correlated with verbal function, whereas those for the GCIPL correlated with executive function and information processing speed. Significantly, these correlations remained after correcting for disease-related confounders including neurological disability and disease duration. Although the correlation coefficients were relatively low, especially for the RNFL relationship with the global cognitive score, albeit better for GCIPL thickness, we assume that decrease in intraretinal layer thickness may in part suggest a cognitive decline. Our findings are therefore in agreement with our suggested hypothesis that is, that the ongoing neurodegenerative process observed in the retina through OCT analysis in MS reflects that occurring in the brain. Hence, we suggest that axonal loss in the retina may be indicative also of cognitive decline and therefore possibly serve as an early biomarker for cognitive impairment in MS patients.

Consistent with our present findings, Toledo et al (24), Sadighi et al (25), and Ashtari et al (26), who studied MS cohorts of 52, 60, and 100 patients, respectively, found that the RNFL thickness correlated with either executive function or verbal function. A further prior study has evaluated the association between the GCIPL and cognition in 56 RRMS patients with no history of ON, and assessed cognition in these cases using the manual BRB-N examination (27). The authors demonstrated that the GCIPL measurements better correlated with cognitive domains than those for RNFL, particularly regarding executive function and visuospatial memory.

In our present analyses, we also found that the GCIPL thickness showed stronger correlations than that of the RNFL across various cognitive domains in MS patients. This was not a surprising finding, however, because the GCIPL includes the ganglion cell layer and its thinning signifies axonal loss, whereas the RNFL is formed by the expansion of the fibers of the optic nerve. As opposed to the optic nerve axonal counts, which are an accurate measure of the total number of ganglion cells in the retina, the RNFL thickness provides data on focal RNFL loss, and hence on focal ganglion cell loss. Hence, GCIPL measurements are a better biomarker for cognitive performance and are more specific than RNFL in assessing neurodegeneration in MS patients (22).

When examining the effect of MS disease duration on both OCT measures and cognitive function, it was unsurprising that the patients with the longer duration had a significantly thinner RNFL and GCIPL, reflecting a progressive neurodegeneration with the disease course. Cognitive function was found in our present observations to be partially associated with MS duration, showing significance in executive function, attention, and motor skills. However, when inserted into the multilinear regression model alongside OCT measures and the EDSS, the association between disease duration and cognition was not significant compared with other factors.

In our current model, the GCIPL thickness maintained its significant effect on the global cognitive score, executive function, attention, and information processing speed in the MS subjects. The OCT measures did not show a significant effect on motor skills when a correction for the EDSS was done, an unsurprising finding as this variable is a measure of disability and relates particularly to motor function. This provides further confirmation that OCT measures have a substantial relationship with cognitive function in MS, independent of the effect of disease duration, and that these associations are significant even in the presence of important predictors such as the EDSS.

The strength of our current study relates to the large cohort we enrolled and our strict exclusion criteria that were designed to avoid confounding factors, particularly those that could impair OCT measurements such as prior ON. Hence, we believe that the reductions we observed in both the RNFL and GCIPL thickness in MS are attributable solely to the neurodegenerative processes in this disease occurring at the retina, which parallel those manifesting in the brain.

The most significant drawback of our study was the relatively preserved cognitive performance of many of the subjects, which could have biased the findings. Only 19.1% of our study patients showed cognitive impairment, probably because of the relatively short disease duration in

**TABLE 3. Multivariate model for cognitive score and its components**

|                     | RNFL | GCIPL | EDSS | Disease Duration |
|---------------------|------|-------|------|------------------|
| Global cognitive score | $R^2 = 0.187$ | 0.216 | 0.258 | $-0.329$ | 0.001 | — |
| Executive function   | $R^2 = 0.282$ | 0.258 | 0.001 | $-0.41$ | $P < 0.001$ | — |
| Attention            | $R^2 = 0.219$ | 0.242 | 0.009 | $-0.342$ | $P < 0.001$ | — |
| Information processing speed | $R^2 = 0.063$ | 0.25 | 0.012 | — | — | — |
| Motor skills         | $R^2 = 0.236$ | — | — | $-0.485$ | $P < 0.001$ | — |

Results are presented as standardized beta coefficient and $P$ value.

— The variable did not significantly influence the model and therefore was excluded.

EDSS, expanded disability status scale; GCIPL, ganglion cell inner plexiform layer; RNFL, retinal nerve fiber layer.

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this cohort, and thus only a minor proportion of our cohort contributed to the analysis. Despite this limitation however, the retinal thinning we observed in our MS patients, which appeared even in the cases with a short disease duration and preserved cognitive function, may suggest that this phenomenon, and especially GCIPL thinning, is an early biomarker of future cognitive decline in MS. Future studies that conduct a longitudinal assessment of these associations are warranted. Another potential limitation of our current analyses is the possibility that immunomodulatory treatment in most study cases had a beneficial effect in preventing cognitive decline, but with a lesser effect on retinal thinning.

To summarize, a decrease in RNFL and GCIPL thickness is associated with a decline in cognitive performance in MS patients. Although these OCT parameters do not fully explain the variations in cognitive performance in MS, they may serve as early biomarkers of cognitive decline and neurodegeneration in patients with this disease.

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