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pRNFL as a marker of disability worsening in the medium/long term in patients with MS

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MS is an inflammatory and neurodegenerative disease of the CNS (including the retina) that leads to progressive neurologic disability. Disability correlates with the degree of axonal pathology in the disease.[1,2] The clinical course of MS is unpredictable, making the search for biomarkers associated with enhanced risk of disease progression a major unmet need. Spectral domain optical coherence tomography (SD-OCT) is a potential predictor of disability worsening up to 5 years of follow-up after a single evaluation of the peripapillary retinal nerve fiber layer (pRNFL).[3] Time domain OCT (TD-OCT) is an older technology, characterized by lower axial resolution and slower acquisition speed (400 axial scans per second) resulting in lower resolution images and more frequent motion artifacts compared with SD-OCT.[4] TD-OCT was used over 10 years ago to assess retinal neurodegeneration in patients with MS but only now has enough time passed to assess its actual predictive potential for clinical progression.

To investigate the capacity of TD-OCT measures to predict disability worsening in patients with MS, we performed a retrospective evaluation of 305 patients with MS (228 relapsing-remitting, 29 secondary progressive, 32 clinically isolated syndrome, 10 primary progressive MS according to 2005 McDonald criteria,[5] and 6 with MS but unclear disease course) who had undergone Stratus TD-OCT (Carl Zeiss Meditec AG, Jena, Germany) from January 2006 to December 2008, collecting the values of the pRNFL and macular volume (MV). The Committee on Human Research at UCSF approved the study. All participants provided written informed consent. The baseline cohort characteristics are presented in the table. All patients had at least 1 measurement of the Expanded Disability Status Scale (EDSS) during the subsequent follow-up period. In our analyses, we used the most recent available EDSS. The median follow-up duration from the time of OCT to the most recent EDSS evaluation was 7.9 years (interquartile range 6.4–8.9 years, range 0.04–9.5 years); 91% of the cohort had >5 years of follow-up. The association between the baseline pRNFL and the subsequent EDSS was investigated using multivariable linear regression, adjusted for age and sex, taking into account the correlation of pRNFL thickness in the patient's 2 eyes (figure). For each 1-μm decrease in the pRNFL, there was a 0.024 increase in EDSS (95% CI: 0.011–0.037; $p < 0.001$). In a sensitivity analysis, the results were similar (0.022 increase in the EDSS, 95% CI 0.035–0.01, $p = 0.001$) when analyzing only patients with >5 years of follow-up. A model adjusted for the presence of previous episodes of optic neuritis yielded similar results (a 1-μm decrease in the RNFL was associated with a 0.024 increase in the EDSS; $p < 0.001$). There was no association with MV. The lack of consistent association of MV with disability worsening has previously been reported[3] and may relate to the lack of segmentation from whole macular thickness where some layers increase volume and others lose volume during the course of disease. In addition, TD-OCT had poorer reproducibility for volume scans because of the low speed of image acquisition. These results show that TD-OCT and a single evaluation of pRNFL atrophy is

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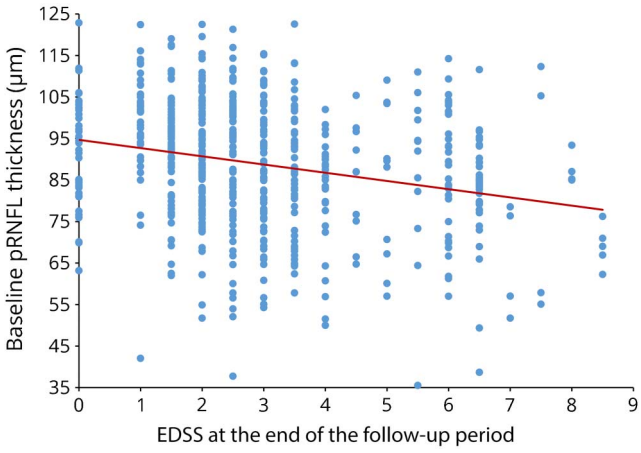
Table Demographic and baseline characteristics and the follow-up data of the study population (number of patients = 305)

Female	65.7
Average age (SD), y	42.7 (11.8)
Average disease duration in years (SD)	10 (9.2)
Average most recent EDSS (SD)	2.9 (1.9)
Average days from OCT to EDSS (SD)	2,696.4 (655.0)
Median years from OCT to EDSS (IQR, range)	7.9 (6.4–8.9, 0.04 to 9.5)
Average RNFL thickness (SD)	88.9 (15.2)
Average ON-positive RNFL (SD) (N = 193)[a]	82 (16.4)
Average ON-negative RNFL (SD) (N = 410)[a]	91.9 (13.5)
% of patients using DMT at OCT visit	68.7
Average duration of DMT use at EDSS visit in years (SD)	10.3 (5.3)

Abbreviations: DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; IQR = interquartile range; ON = optic neuritis; RNFL = retinal nerve fiber layer.
[a] Seven eyes were excluded from the analysis because of poor quality (total number of eyes = 603).

useful in predicting disability up to 6–9 years later in MS—significantly longer than has been previously reported. A limitation of the study is the absence of the baseline EDSS in the entire cohort, which limited our ability to consider its influence as a confounder in the estimate of association between the baseline RNFL and subsequent EDSS. Recent meta-analyses show that the mean RNFL loss in a population of patients with optic neuritis is similar between TD-OCT and SD-OCT.[6,7] However, despite the similarity in means at an individual level, SD-OCT is known to be more accurate. Stratus TD-OCT is no longer used in MS research because of the availability of more sophisticated OCT machines being able to quantify retinal measures with a much lower level of noise.[8] Nevertheless, despite the effect on SDs, this noise does not affect the mean, and data from earlier iterations of the technology can be useful to indicate the association between retinal thinning and future disability.

Figure Association of baseline RNFL with EDSS at the end of the follow-up period



RNFL = retinal nerve fiber layer.

Author contributions

C. Cordano: study concept and design, interpretation of data, and composition of the manuscript. B. Nourbakhsh: analysis and interpretation of data. M. Devereux and V. Damotte: acquisition of data and composition of the manuscript. D. Bennett: acquisition of data and supervision of the manuscript. S.L. Hauser and B.A.C. Cree: study supervision and composition of the manuscript. J.M. Gelfand: analysis and interpretation of data and composition of the manuscript. A.J. Green: study concept and design, analysis and interpretation of data, and composition of the manuscript.

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