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EDITORIAL

OCT as a window to the MS brain

The view becomes slightly clearer

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Optical coherence tomography (OCT) has been applied to multiple sclerosis (MS) to investigate retinal neuroaxonal loss. Reductions in peripapillary retinal nerve fiber layer (pRNFL) thickness have been reported in different MS-related subtypes from clinically isolated syndromes[1] to secondary progressive MS.[2] A recent meta-analysis additionally confirmed atrophy of the ganglion cell–inner plexiform (GCIP) layer in MS.[3] Associations between OCT-derived retinal thicknesses (pRNFL and GCIP) and cerebral atrophy quantified by MRI have also been reported,[4,5] leading to the suggestion of using OCT as a biomarker of MS disease progression in the clinic. Despite challenges and lingering questions, several recent studies suggest potential for clinical value. For example, a recent retrospective study provided evidence for differential rates of GCIP atrophy according to DMT usage. Natalizumab-treated patients with MS exhibited the lowest atrophy rates (−0.16 μm/y), similar to healthy controls (−0.14 μm/y), whereas those treated with interferon-β and glatiramer acetate had more atrophy (−0.28 to −0.54 μm/y).[6] An earlier study found faster GCIP annualized thinning rates associated with clinical or radiologic MS activity in 161 patients.[7] In addition, a recent cohort study identified a cutoff of 88 μm for the pRNFL to predict twice the risk of disability worsening at 2 years and 4 times higher risk at 5 years for the patients (many being treated) below this cutoff.[8] This literature implies a potential role for OCT in the clinical monitoring of MS in the future.

In this issue of *Neurology*®, Pisa et al.[9] extend this work by determining OCT associations with no evidence of disease activity (NEDA) in MS. NEDA has been suggested as a long-term treatment goal in MS. Conventionally applied to active MS amenable to disease-modifying treatments (DMTs), it relies upon 3 criteria being concurrently met: no clinical relapse, no disability worsening, and no new MRI activity (no new/enlarging T2 lesions and no gadolinium-enhancing lesions). Pisa et al. performed a longitudinal investigation of 72 patients with MS, performing MRI, OCT, visual evoked potentials, and Expanded Disability Status Scale (EDSS) assessments, 2 years apart. Patients with MS with NEDA at follow-up (31.7%) had mean binocular RNFL thinning of −0.93 μm ± 1.35 SD, whereas patients with evidence of disease activity (EDA) demonstrated greater RNFL thinning at −2.83 μm ± 2 SD (t test $p <$ 0.001). There was no interaction between NEDA/EDA and disease subtype (relapsing vs progressive). Further analyses showed RNFL loss when MRI activity or relapse activity were considered separately. Greater RNFL loss over 2 years was also associated with worsening EDSS scores. After receiver operating characteristic curve calculation, a value of −1.25 μm was obtained as the optimal cutoff value associated with NEDA status, with specificity 81.4% and sensitivity 80%. A history of optic neuritis did not appear to alter the longitudinal changes in RNFL thinning.

In the clinic, how would recording serial changes in OCT add value to clinical assessment and MRI? Certain challenges remain for OCT (e.g., determining its contribution to clinical monitoring over a realistic time frame, its value in the presence of optic nerve or radiation lesions). Therefore, large prospective studies are required, in which OCT metrics are used as risk factors for disease worsening. For example, the Rio criteria established that in the first year of starting a new therapy, a higher composite score, which includes relapses, disability worsening, and >2 T2 lesions, is associated with higher risk of disability worsening over the next 2 years.[10] Analogously, OCT could be validated within a composite score of several predictors of MS clinical progression. However, we first need to understand the critical threshold for OCT metrics, and how this interacts with our other markers for disability worsening. Multicenter, international clinical repositories with long-term follow-up could be leveraged to derive and validate thresholds and interactions for OCT and other early disease markers. Once we understand how OCT fits with our established predictors, one would next need to know the effectiveness of treatment escalation upon long-term MS outcomes for disability. As an example, if a patient was stable from

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a clinical and imaging perspective, what would be the long-term benefit of a more effective therapy if the patient demonstrated a sustained annual retinal thinning of some validated threshold?

Overall, this study provides interesting insights into the potential utility of OCT for monitoring MS disease activity. Some limitations to this study exist, such as the requirement to validate in an independent cohort, the limited sample size and follow-up, and lack of a normative reference population for defining the spontaneous decline of retinal thickness with age. Moreover, the cutoff proposed is based on the change in RNFL and not on a specific absolute value such as in previous studies and for this reason these results cannot be considered a validation of previous biomarkers. Nevertheless, the findings of this study lend support to the notion that OCT is related to inflammatory activity, presumably through an indirect mechanism that affects neuroaxonal loss. Future studies should be able to address the outstanding issues related to its potential utility in MS for monitoring disease progression and even, perhaps, guide therapy decision-making. However, these studies will require multicenter collaborations with large enough patient numbers and data of sufficient duration to inform long-term, accurate predictions. This will be a large research endeavor; nevertheless, the findings from this current study provide us with impetus and encouragement to pursue this goal.

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REFERENCES

1. Oberwahrenbrock T, Ringelstein M, Jentschke S, et al. Retinal ganglion cell and inner plexiform layer thinning in clinically isolated syndrome. Mult Scler 2013;19:1887–1895.
2. Henderson APD, Trip SA, Schlottmann PG, et al. An investigation of the retinal nerve fibre layer in progressive multiple sclerosis using optical coherence tomography. Brain 2007;131:277–287.
3. Petzold A, Balcer LJ, Calabresi PA, et al. Retinal layer segmentation in multiple sclerosis: a systematic review and meta-analysis. Lancet Neurol 2017;16:797–812.
4. Sepulcre J, Murie-Fernandez M, Salinas-Alaman A, Garcia-Layana A, Bejarano B, Villoslada P. Diagnostic accuracy of retinal abnormalities in predicting disease activity in MS. Neurology 2007;68:1488–1494.
5. Saidha S, Al-Louzi O, Ratchford JN, et al. Optical coherence tomography reflects brain atrophy in multiple sclerosis: a four-year study. Ann Neurol 2015;78:801–813.
6. Button J, Al-Louzi O, Lang A, et al. Disease-modifying therapies modulate retinal atrophy in multiple sclerosis: a retrospective study. Neurology 2017;88:525–532.
7. Ratchford JN, Saidha S, Sotirchos ES, et al. Active MS is associated with accelerated retinal ganglion cell/inner plexiform layer thinning. Neurology 2013;80:47–54.
8. Martinez-Lapiscina EH, Arnow S, Wilson JA, et al. Retinal thickness measured with optical coherence tomography and risk of disability worsening in multiple sclerosis: a cohort study. Lancet Neurol 2016;15:574–584.
9. Pisa M, Guerrieri S, Di Maggio G, et al. No evidence of disease activity is associated with reduced rate of axonal retinal atrophy in MS. Neurology 2017;89:2469–2475.
10. Río J, Castilló J, Rovira A, et al. Measures in the first year of therapy predict the response to interferon β in MS. Mult Scler J 2009;15:848–853.