Optical Coherence Tomography in Multiple Sclerosis

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Abstract

Optical coherence tomography (OCT) grew out of a convergence of rapid advancements in femtoseconds optics research and fiber optic commercial technology. The basic concept of OCT is to "see" into tissues using light echoes, analogous to the sound echoes of ultrasonography. Multiple A-scans are assembled into a B-scan two-dimensional image of the tissue of interest. Retina is an ideal tissue for evaluation by OCT, since the eye is designed to minimize light scattering through the anterior chamber and vitreous. OCT has had a significant impact on the field of multiple sclerosis, where it has allowed direct imaging of the myelin-free segments of axons and cell bodies of retinal ganglion cells. Together with precise functional measurements of the afferent visual system, the addition of robust structural measurements of retinal injury has allowed for an unprecedented ability to correlate clinical effects with the degree of neuronal loss. In addition, OCT has proven helpful to distinguish different forms of demyelinating disease, such as multiple sclerosis (MS) and neuromyelitis optica, and has provided ideal outcome measures in remyelination and neuroprotection trials.

Keywords

- optical coherence tomography
- multiple sclerosis
- neuromyelitis optica

While it is now hard to imagine a multiple sclerosis (MS) center functioning without knowledge of optical coherence tomography (OCT), biomedical optics was a fringe topic in neurology just over a decade ago. Human research using OCT outcomes has exponentially increased since the first introduction of a commercial product in 1996. Ubiquitous in most ophthalmological practices, OCT has now also become a vital tool in many academic neurology departments, with applications in neuroinflammatory and neurodegenerative diseases, as well as in the monitoring of papilledema.

OCT applications in medicine first arose from a fortunate combination of femtosecond optics research and the advancement of commercial fiber optic communications.[1] The original concept to use light echoes as an optical ultrasound to visualize tissue structure predated OCT by 20 years.[2] Duguay and Mattick published work using photography of picosecond light pulses and echoes in 1971 and proposed that this approach could ultimately be employed to see inside biological tissues.[2] There was an immediate attraction to study retinal tissue in this manner because of the inherent advantages presented by the minimal scattering of light in the anterior chamber and vitreous. A series of key advances in technology and analytical approaches led to the development of femtosecond optics and ultrafast A-scans of bovine and rabbit retinal tissue.[1,3] While femtosecond optics was a promising step in the ultimate development of OCT, the subsequent development of low-coherence interferometry in the 1980's and early 1990's offered the promise of more feasible scalability and cost for clinical applications.[4] The first OCT B-scan images of the retina, false color scale representations of multiple A-scans, were published by Huang et al in 1991.[5] The first in vivo images of human retina followed shortly thereafter in 1993.[6]

As OCT technology rapidly improved and was introduced to the monitoring of ophthalmologic diseases, such as glaucoma,[7,8] an immediate relevance to neurology emerged. It became clear that this device could be applied to study other optic neuropathies and neurological conditions, such as MS. One of the first articles on OCT and MS, which appeared in 1999 by Parisi et al, demonstrated reduced retinal nerve fiber layer (RNFL) thickness in 14 patients with MS.[9] By 2005, there were still only a small number of articles using OCT to study multiple sclerosis or optic neuritis, but over 1,500 articles have now been published on these topics (PubMed). OCT measures have been included as endpoints in clinical trials of disease-modifying and remyelination agents,[10,11]

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and clinicians now incorporate structural visual outcomes into routine MS care.[12,13]

Modern spectral domain OCT allows visualization of not only the circumpapillary retinal axons but individual cell layers of the macula as well. This high-resolution imaging has provided many insights into the forms of retinal neurodegeneration that occur in MS. In both adults and children, OCT has demonstrated important differences between MS and its mimics, such as neuromyelitis optica (NMO). This review summarizes key examples of how the microstructural changes captured by OCT have been applied to improve understanding and optimize treatment in MS.

Measuring Axonal Loss in MS

Retinal ganglion cells (RGC) project axons to form the optic nerve. Just proximal to the formation of the optic nerve, the retinal nerve fiber layer (RNFL) consisting of these axons can be measured using the light echoes of OCT (►**Fig. 1**). The resulting metric is referred to as the peripapillary RNFL thickness (pRNFL, ►**Fig. 1**). Early studies of OCT in MS demonstrated that the pRNFL was reduced in eyes with a history of optic neuritis (ON) as expected but notably also reduced in eyes without prior optic neuritis.[14,15] One of the most important early contributions of this structural biomarker was the clear demonstration of subclinical retinal tissue loss between acute attacks.[16]

Correlation with Visual Function

Critical to the early adoption of OCT was establishing the associations between OCT structural outcomes and visual function, including low-contrast vision, visual field data, and electrophysiologic measures.[7,9,14,15,17,18] Associations were found to be robust for both cross-sectional and longitudinal studies. A critical concept, however, is that of a threshold of tissue loss that is associated with clinically relevant visual

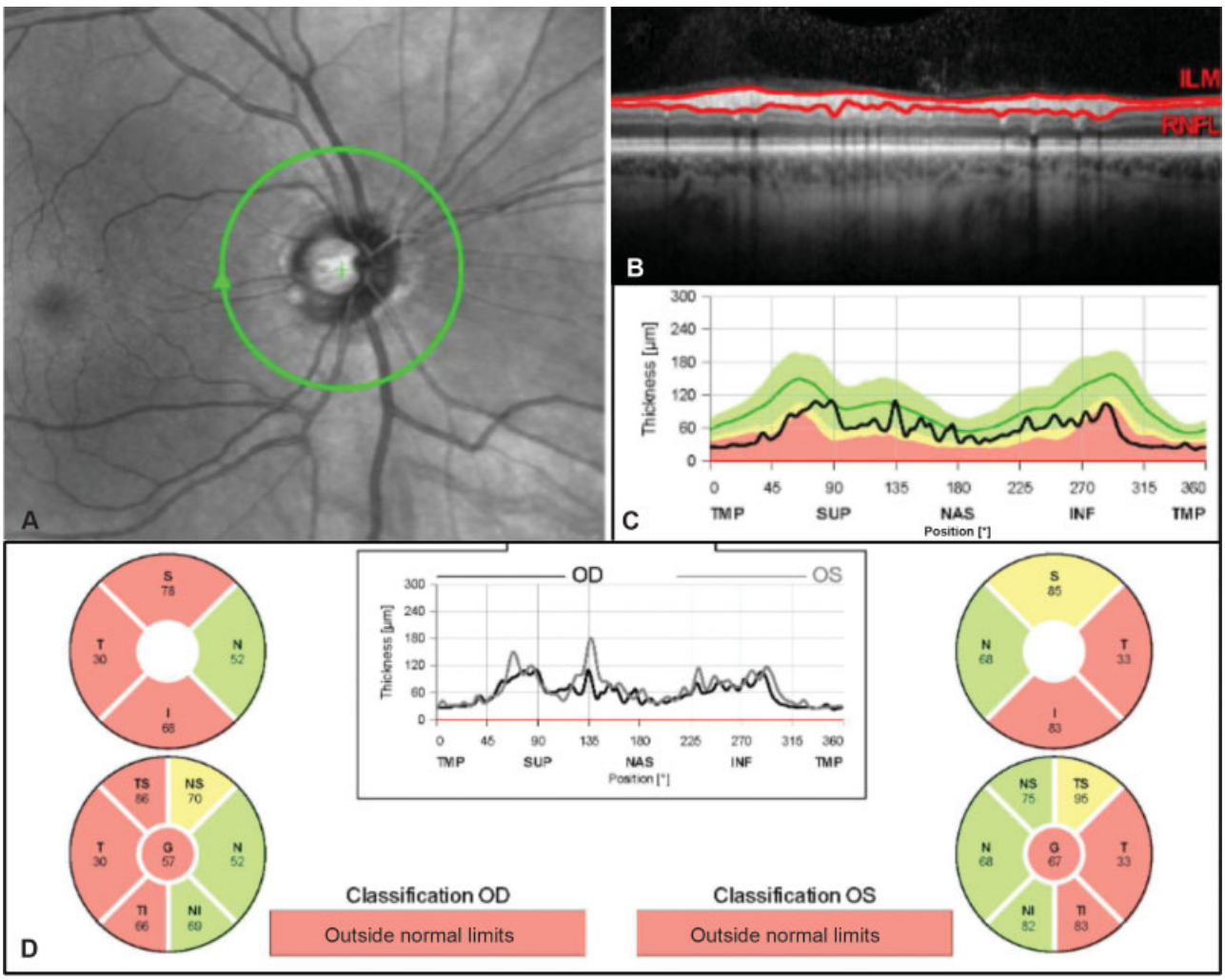

Fig. 1 OCT measurement of the peripapillary RNFL. Spectral domain OCT imaging (Heidelberg) demonstrates peripapillary retinal nerve fiber layer (RNFL) thinning in a patient with multiple sclerosis. (**A**) A 360-degree circumpapillary scan (green line) is performed around the optic nerve head (photographed is an image of the MS patient's right optic nerve head). (**B**) The OCT image with pRNFL layer highlighted in red. (**C**) The patient's data (black line) is compared with normal reference subjects. On the x-axis each quadrant of the circumpapillary scan is labeled. Red indicates a below-normal thickness compared with age-matched controls. (**D**) Mean global and quadrant pRNFL thicknesses (superior, inferior, temporal, and nasal) are depicted for both eyes and demonstrate bilateral thinning predominantly in the temporal quadrants in this MS patient. ILM, inner limiting membrane; INF, inferior; MS, multiple sclerosis; NAS, nasal; NI, nasal inferior; OCT, optical coherence tomography; OD, right eye; OS, left eye; pRNFL, peripapillary RNFL; SUP, superior; TI, temporal inferior; TMP, temporl.

dysfunction. Costello et al published in 2006 that pRNFL thinning was well tolerated until a cut-off of around 75 microns (normal, 100–110 microns); below this, there was a linear drop in visual function.[17]

Optic Neuritis

Although there is some variability across studies, eyes of MS patients with a remote history of ON typically have mean global pRNFL that is at least 20 microns thinner than healthy control eyes (►**Fig. 1**).[14,17,19] Measurements of the temporal quadrant of the pRNFL are even more sensitive in identifying axonal loss in MS ON and may help distinguish MS-related ON from other etiologies (►**Fig. 1**).[9,20,21]

Timing is important in measuring atrophy related to ON. In the acute phase, there may be optic disc swelling, confounding measurement of axonal damage. Such swelling may be subtle, not visible on fundus exam but often can be detected with OCT.[20] The degree of swelling in the acute phase has been associated with the extent of atrophy observed several months later.[22] While pRNFL thinning may be evident as early as 2 months after acute ON,[20] most of the thinning occurs between 3 and 6 months post-ON and then stabilizes.[17] Thus, to assess the extent of axonal damage from a single episode of ON, it is best to perform OCT at least 6 months after the acute episode.

Subclinical Axonal Loss

From the earliest cross-sectional studies of OCT in MS eyes, there has been evidence of thinner pRNFL even in the absence of a clinical history of optic neuritis compared with healthy controls.[14,23] These differences are indicative of subclinical axonal loss. This thinning has been associated with brain parenchymal volume in MS patients, suggesting a pathological link between subclinical retinal and brain tissue atrophy.[24] In most cases, retinal injury is initiated at the level of the RGC, but some studies have suggested that higher lesion loads in the posterior visual pathways (e.g., the optic radiations) are associated with this subclinical pRNFL thinning, implying a potential mechanism of retrograde transsynaptic neuronal loss.[25–27] As a less expensive, more convenient, and more accessible tool than magnetic resonance imaging (MRI) to measure axonal injury, these results have motivated pursuit of OCT as an alternative clinical trial outcome.[10,11]

Important to establishing the concept of subclinical axonal injury were the longitudinal OCT studies that followed the initial cross-sectional observations. These studies have consistently demonstrated a loss of approximately 2 microns per year in mean global pRNFL in MS non-ON eyes, in comparison to 0.25 microns per year from aging alone in healthy controls.[16,28] This loss occurs even in very early MS and in patients with lower disability scores.[29,30] Evidence of subclinical RGC axon injury has provided an intriguing new treatment target for studies of neuroprotection and repair.

Macular Volumes and Retinal Layer Segmentation

The introduction of spectral domain models of OCT, which leverage high-speed data acquisition and the fast Fourier transform methods, allowed measurement of precise macular volumes, as well as the thickness, of the individual retinal layers.[31] A key advance in structural imaging in MS and other neuroophthalmic disorders has been the ability to measure the retinal ganglion cell layer (GCL), which refers to the cell bodies from which the axons in the retinal nerve fiber layer arise. Even with high-resolution OCT imaging, however, this layer is hard to discern from the adjacent inner plexiform layer (IPL), so these layers are typically segmented together and reported as a combined GCL/IPL thickness. Other layers have also been of interest, including the inner nuclear layer (INL), the thickness of which has been associated with other MS outcomes.

Total Macular Volumes

Most software in clinical use for OCT will report a total macular volume (►**Fig. 2**). The values may differ based on the sampling approach. The software typically will use either a 3.45 or 6 mm circle of the macular region to generate a volume estimate. Most of the ganglion cells are concentrated within the 3.45 mm circle. Macular volume loss has been observed in both ON and non-ON MS eyes.[18,31] Macular volumes may be reduced by approximately 5 to 6% after an acute episode of ON.[32] In a large dataset of 712 patients from a baseline analysis of a phase-3 trial of fingolimod, Winges et al reported that 25% of MS patients had at least one eye with abnormally reduced total macular volume.[33] Most of these patients also had reduced pRNFL. A rare 7% of these patients had reduced macular volume with normal pRNFL.[33] While this trial used the older time-domain version of OCT, other studies with spectral domain OCT have also reported approximately 10% of subjects having isolated macular thinning.[31,33] Another research group from Germany could not identify a similar phenotype in their cohort, however.[34]

Decreased macular volumes are associated with decreased visual function, reduced brain volumes, and disability scores in patients with MS.[35] Baseline macular volume has been shown to predict 10-year disability in MS patients, demonstrating significant relevance for prognosis.[36] Macular volume, both absolute reduction in volume, as well as asymmetry between eyes, can be used as an additional clinical tool to identify evidence of demyelinating disease in the anterior-visual pathway. Clinically, total macular volume measurement is readily available (►**Fig. 2**), while more sophisticated segmentation algorithms used for research allow the study of more specific macular markers of retinal injury in MS.

Segmentation and the Retinal Ganglion Cell Layer

Early retinal segmentation studies involved manual alignments of boundaries of the tissue layers by different optical density margins.[37] Currently, several automated algorithms are in use. The advantages and disadvantages of these approaches have been described elsewhere.[38–40] Some of the main technical challenges in these algorithms have been managing corrections for blood vessels within the layers and irregular boundaries across the quadrants sampled in the macular tissue.[40]

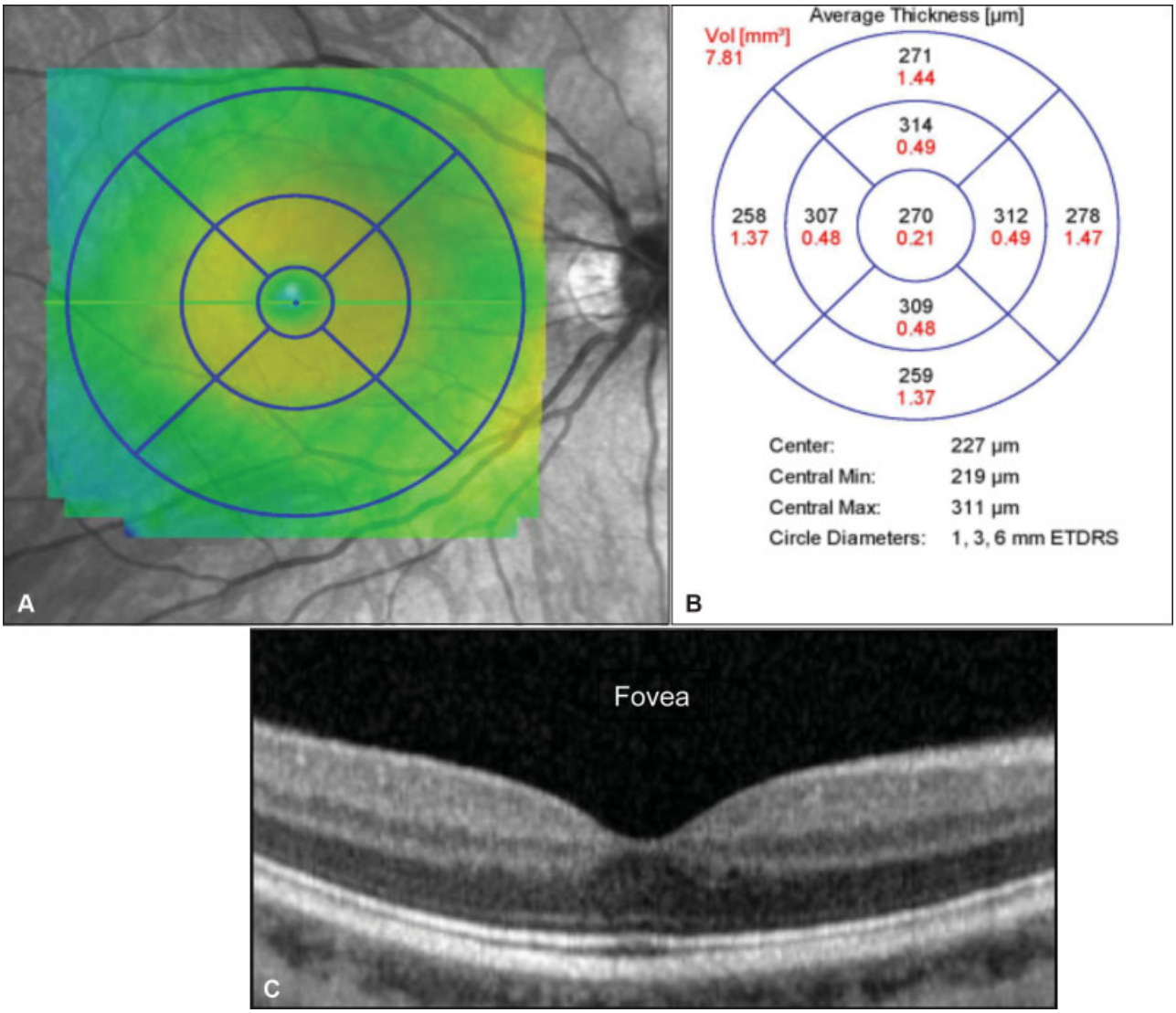

Fig. 2 Visualization of the Macula by OCT. Visualization of the right macula in a patient with MS. (**A**) Grid for macular thickness measurements overlaid on photograph of the posterior pole with fovea in the center. Green line indicates location of image in C. (**B**) Macular thickness and volumes estimates. (**C**) Cross-sectional view of the macula through the fovea.

Of all the retinal layers, the combined GCL/IPL has had overall strongest performance for identifying pathology of interest in MS.[38,41] These OCT observations of the GCL/IPL are consistent with postmortem analysis of RGC loss in the retinal tissue of MS patients.[42] Eyes with a history of ON demonstrate approximately 16 to 17 microns thinner GCL/ICL compared with controls.[38] As with the pRNFL, there is evidence of subclinical loss of GCL/IPL thickness even without optic neuritis (approximately 6.5 microns in cross-sectional studies).[38,43] Importantly, the GCL/IPL is less prone to the confounding by optic disc swelling in acute optic neuritis[22,44] and can detect damage prior to pRNFL thinning.[44] Correlations with both visual function and overall disability scores are stronger for GCL/IPL than for pRNFL.[45,46] GCL/IPL measurements are associated with cortical gray matter volumes.[47] Lastly, changes in the GCL/IPL layer over time are sensitive to treatment effects. For example, patients treated with natalizumab exhibit lower rates of GCL/IPL thinning compared with those on platform injectable therapies.[48]

Inner Nuclear Layer

In addition to the GCL/IPL, there have been other findings of interest in studying macular retinal layers in MS patients. Gelfand et al demonstrated that microcystic macular edema (MME) was observed in the INL of 5% of participants with MS.[49] MME was associated with higher disability scores, lower visual acuity, and history of optic neuritis.[49] Saidha et al found similar results, with MME causing thicker INL that was associated with greater disability progression and more active disease.[50] INL MME has also been observed in other forms of severe optic neuropathy.[51,52]

In the absence of MME, INL thinning has been reported in all subtypes of MS, including 13% of MS participants in one study.[45,53] Saidha et al reported a possible unique microstructural phenotype of reduction of the inner and outer

nuclear layers, without significant GCL/IPL or pRNFL thinning.[31] More recently, additional studies have identified changes in the inner nuclear layer (INL) associated with markers of overall MS severity.[49,50] INL thinning, however, has not been as well correlated with visual function.[45] In animal model studies, use of a putative neuroprotective agent, α-lipoic acid, reduced the loss of INL thickness over time.[54] Unfortunately, this apparent protection was not associated with better visual outcomes.

Treatment Monitoring in Fingolimod Use

The MS disease modifying therapy fingolimod can cause increased macular thickness and macular edema because of its effect on specific sphingosine receptor subtypes in the retina.[55] OCT scans are typically performed at baseline before drug initiation and 3 to 6 months after drug start date. Structural analysis with OCT allows for detection of early changes, ideally before clinically apparent edema or visual loss. While some thickening is common after fingolimod use,[55] edema, large thickness changes, or microcystic changes should prompt very close monitoring and consideration of medication cessation.

Asymmetry in OCT Outcomes and Diagnosis of MS and Optic Neuritis

Evidence of a missed event of optic neuritis could be helpful in making a diagnosis of MS. A recent international study of OCT outcomes in MS patients found that intereye differences of 5 microns for pRNFL and 4 microns of GCL/IPL thickness were robust thresholds for identifying prior unilateral optic neuritis.[56] In these patients, observing a similar asymmetry in total macular volume would also increase suspicion of a pathologically relevant difference. As visual evoked potentials do not consistently show delays in all patients that have had remote optic neuritis, particularly in young or early stage patients, these OCT parameters of relevant asymmetry can be helpful in the clinical setting of suspected ON or MS.

Distinguishing MS from NMO using OCT

The increased severity of optic neuritis episodes in neuromyelitis optica compared with MS is well recognized. The use of OCT has allowed for quantification of differences in structural damage, and in some ways can aid in distinguishing the two diseases.[21,57–59] There tends to be greater mean global pRNFL loss and GCL/IPL thinning after an episode of NMO-related ON. In addition, the pattern of atrophy differs in NMO compared with MS. Specifically, there is a global pattern of pRNFL loss in NMO, with less predilection for the temporal quadrant.[21,57] Subclinical changes in pRNFL are less common between episodes of ON from NMO compared with MS.[57,58] These observed differences not only serve as useful diagnostic biomarkers to distinguish these types of demyelinating disease but also offer insights into the distinct pathogenetic mechanisms and consequences of these disorders.

Also of interest in distinguishing the two diseases are microstructural changes in the fovea region in patients with NMO.[25,59,60] The Müller glial cells in the fovea are rich in aquaporin-4 channels, and several groups have reported foveal and parafoveal morphological changes in patients with NMO even in the absence of pRNFL or GCL loss.[25,60] Shen et al found evidence of functional changes on multifocal VEP associated with this pitted appearance of the fovea in NMO,[25] and You et al reported abnormal Müller's cell function on ERG associated with the same structural phenotype.[61] In contrast, macular atrophy in MS patients is not characterized by these specific foveal changes.

Pediatric MS and Optic Neuritis

Structural findings by OCT in pediatric patients are largely similar to those found in adults.[62] As in adults, children exhibit temporal-predominant pRNFL atrophy both with and without a history of clinical optic neuritis.[32,63] Pediatric MS eyes also demonstrate macular volume loss and thinning of the GCL/IPL.[32,62] Unaffected MS eyes also seem to demonstrate thinner pRNFL and reduced macular volumes compared with control eyes.[32] More studies are needed to assess longitudinal subclinical axonal or cell soma loss in this population.

Sex Differences and Other Risk Factors for Worse Retinal Degeneration

In both adults and children, male sex appears to be associated with worse OCT outcomes among MS patients.[22,32] After an episode of acute optic neuritis, men experience greater thinning of both the pRNFL and GCL/IPL.[22] Even in young boys, there is evidence of worse temporal quadrant atrophy in eyes with a remote history of ON.[32]

Genetic ancestry may also be important in structural outcomes. Caldito et al recently published that African Americans experience more rapid thinning of the pRNFL and the GCL/IPL than Caucasian Americans.[64] They also experienced a larger frequency of developing MME. These results correlated with greater loss of cortical gray matter, white matter, and thalamic volume in the same African American participants.

OCT studies have shown that vitamin D insufficiency, a well-established risk factor for MS, is associated with increased optic nerve head edema acutely and greater retinal tissue injury following optic neuritis.[22] Although cigarette smoking is associated with an increased risk of MS and with worse outcomes in those who have the disease, a recent study by Rosso et al did not demonstrate an association of smoking with any of the above OCT outcome measures.[65]

Does the Hardware Matter?

Following an individual patient on different types of OCT machines or combining different models in multisite trials raises critical albeit surmountable analytical issues. As an example, Stratus (Zeiss), Cirrus (Zeiss), and Spectralis (Heidelberg) OCT models measure similar longitudinal changes in MS patients but baseline and normative pRNFL values are shifted by several microns among devices.[66] When using

multiple model types in a single study, *z*-scores or other adjustments may be required to make OCT data compatible.

OCT as a Biomarker in Clinical Trials

Given the potential of the above microstructural neuronal outcome measures, OCT measures have been incorporated into multiple MS clinical trials. Novartis is completing a 3-year multisite study in Germany on OCT outcomes in patients treated with fingolimod (NCT01705236). OCT pRNFL thickness was a secondary outcome in the phase-2 trial of ibudilast in primary and secondary progressive MS (NCT01982942). In a trial of neuroprotection in acute optic neuritis with erythropoietin (NCT00355095), OCT pRNFL was the primary outcome, with a reported positive treatment effect.[67] OCT outcomes were also included in a neuroprotection study with phenytoin (NCT01451593), demonstrating a 30% reduction in pRNFL loss.[68] The ReCOVER trial (NCT02521311), studying the potential remyelinating effects of clemastine after acute ON, is ongoing. Chronic optic neuropathy studies have also used OCT as either inclusion criteria or outcome measures (REBUILD NCT02040298; VISIONARY-MS NCT03536559).

Conclusion

OCT has allowed unprecedented studies of microstructure in MS. Both acute and chronic injury can be measured directly. OCT outcomes can be used to aid diagnosis and are sensitive enough to detect treatment effects. The tool can be used in MS patients of all ages and all disease stages. Future work will help to clarify the extent to which there is primary neurodegeneration in the retina and whether OCT will be an outcome that allows more rapid development of neuroprotective therapies.

Conflict of Interest
None.

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