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Monitoring the Course of MS With Optical Coherence Tomography

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Opinion statement

Retinae of patients with multiple sclerosis (MS), as part of the central nervous system (CNS), display inflammatory and neurodegenerative changes. There is increasing evidence suggesting that retinal changes, and in particular neurodegeneration, mirror global CNS alterations in MS. Spectral domain optical coherence tomography (SD-OCT) is an inexpensive, rapid, non-invasive, and reproducible imaging technique that generates high-resolution images of tissues such as the retina. An advantage of SD-OCT over magnetic resonance imaging techniques in the assessment of neurodegeneration may be its sensitivity to capture changes at the individual patient level. Several studies demonstrate that changes within the inner retina (primarily as a reflection of optic neuropathy), as assessed by OCT, correlate with reduced quality of life, visual dysfunction, and global disability in MS. Moreover, longitudinal studies suggest that inner retinal thinning is an early phenomenon in MS and that retinal thinning may occur independent of previous symptomatic episodes of optic neuritis, significantly correlating with inflammatory disease. Preliminary studies suggest that MS disease-modifying therapies may have differential effects on OCT-determined rates of retinal atrophy, supporting a potential utility for OCT to investigate

the neuroprotective benefits of disease-modifying therapies in MS, as well as an outcome in trials of putatively neuroprotective strategies.

Introduction

Multiple sclerosis (MS) is regarded as an autoimmune, demyelinating disorder of the central nervous system (CNS) [1]. Neurodegeneration resulting from these processes is recognized as a principal substrate of long-term disability. Optical coherence tomography (OCT) is an inexpensive, rapid, well-tolerated, reproducible, non-invasive imaging technique that uses near-infrared light to generate cross-sectional or three-dimensional images of tissues, such as the retina [2–4] (Fig. 1). Research using OCT in MS was initially focused on evaluation of the peripapillary retinal nerve fiber layer (pRNFL). But modern high-definition spectral domain OCT, which renders 3- to 5-μm resolution images [5], has allowed detailed qualitative assessment of individual retinal layers by the application of OCT segmentation techniques able to quantify discrete macular retinal layers, including the macular ganglion cell layer + inner plexiform layer (GCIPL), inner nuclear layer (INL), outer nuclear layer (ONL), and photoreceptors [6•, 7, 8•, 9–11]. The advent of newer spectral domain optical coherence tomography (SD-OCT) devices and improved segmentation techniques allowing reliable GCIPL quantification represents a major advancement since GCIPL

thickness measures may have superior reliability, reproducibility, and structure–function relationships as compared to conventional pRNFL thickness measurements [6•, 7]. The histopathology of retinal tissue from MS patients demonstrates a multitude of pathologic changes, including axonal loss, neuronal soma shrinkage, synaptic loss, activation of microglia, and inflammation [12•]. Qualitative and quantitative assessment of all the discrete layers of the retina on SD-OCT allows us to potentially gain insight into these mechanisms in vivo in MS. For instance, GCIPL thinning has been reported to be a marker of neuroaxonal injury [13], INL thickening has been proposed as a marker of inflammation in patients with MS [14•, 15], and transient ONL thickening has been reported during the acute phase of optic neuritis (ON) [16•, 17]. Since 1999, when Parisi et al. reported the earliest description of pRNFL thickness reductions in MS patients as compared to healthy volunteers [18], numerous studies have investigated the role of OCT measurements in order to improve our understanding of MS pathobiology and identify novel biomarkers for monitoring neurodegeneration in MS and therapeutic response.
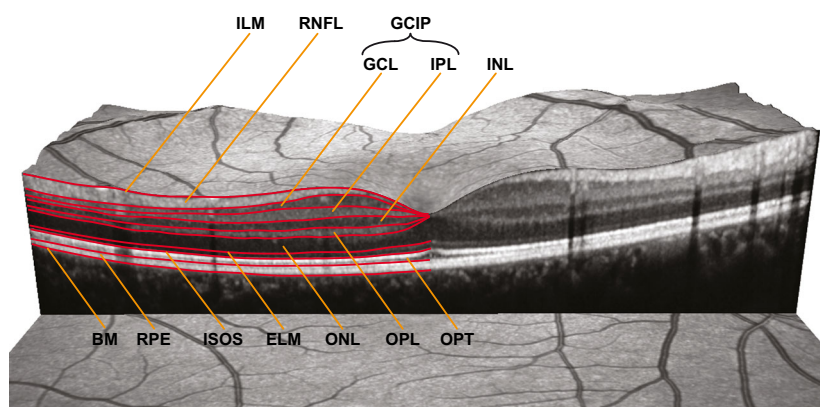

Fig. 1. The different layers of the retina. The different layers of the retina are illustrated in a central vertical scan through the middle of the foveolar. *ILM* inner limiting membrane, *RNFL* retinal nerve fiber layer, *GCL* ganglion cell layer, *IPL* inner plexiform layer, *GCIP* ganglion cell and inner plexiform layer, *INL* inner nuclear layer, *BM* Bruch membrane, *RPE* retinal pigment epithelium, *ISOS* inner and outer segments, *ELM* external limiting membrane, *ONL* outer nuclear layer, *OPL* outer plexiform layer, *OPT* outer photoreceptor tips.

Retinal changes mirror global central nervous system burden in MS

Magnetic resonance imaging (MRI) is the most widely used imaging method for quantifying neurodegeneration and neuroinflammation in MS. The diagnostic guidelines for MS rely on MRI-derived lesion load for establishing a diagnosis of MS [19]. Moreover, MRI-derived measures of brain atrophy are increasingly used to monitor neurodegeneration [20].

An association between neuroaxonal damage in the retina, as determined by pRNFL thickness, and measures of brain volume was reported almost 10 years ago [21, 22] and subsequently confirmed in numerous studies since [23], including a longitudinal study [24•]. The association between retinal thickness and brain volume in MS raises questions regarding the mechanisms and pathobiology underpinning these associations, as well as the translation of these findings in terms of potential clinical utility.

ON occurs frequently in MS, leads to optic nerve damage, and results in retrograde neuroaxonal damage within the retina, which can be detected and quantified by OCT measurements such as pRNFL and GCIPL thicknesses [16•, 17, 25•]. Non-conventional MRI of the optic nerve, such as diffusion tensor imaging (DTI) [26, 27] and magnetization transfer imaging [28], similarly reflects this damage. Optic nerve damage in MS may lead to anterograde trans-synaptic neurodegeneration via the lateral geniculate nucleus within weeks to several months [29•], as insinuated by a decrease of N-acetyl aspartate (a marker of neurodegeneration) in magnetic resonance spectroscopy of the primary visual cortex [30•].

Likewise, optic radiation lesions in MS are associated with visual dysfunction and potentially lead to retrograde trans-synaptic degeneration, as suggested by pRNFL and GCIP thickness reductions in OCT [31–33]. The functionally anatomic association of damage in different parts of the visual pathway intervened between the retina and visual cortices in MS is further supported by the relationship between DTI-derived fractional anisotropy (FA) measures (thought to primarily reflect axonal integrity) in the optic radiation and retinal OCT [34].

However, the noted associations between retinal neurodegeneration (estimated by OCT) and global neurodegeneration (as estimated by MRI volumetric assessments primarily of whole brain, gray matter, and white matter volumes) in MS seem to extend beyond OCT and MRI simply reflecting functional anatomic damage isolated to the visual pathways. pRNFL thickness correlates not only with FA of the optic radiation but also with the combined FA of all white matter tracts [34]. Likewise, a relationship between retinal neuroaxonal damage and cortical gray matter, as well as caudate volume, has been reported [35]. This association between MRI and OCT is upheld in eyes without a history of ON, supporting the possibility of an underlying disease activity similarly affecting more global regions of the CNS in MS [35, 36]. This is furthermore supported by a surprisingly strong association between spinal cord damage measured by MRI and retinal atrophy measured by OCT [37]. In this regard, ON may cause disproportionate localized retinal tissue injury, thereby masking retinal–global CNS relationships [38•].

An interesting OCT parameter for reflecting MS disease activity may be INL thickness. Increased INL thickness was reported to be associated with a moderately

increased odds ratio to develop new T2 lesions or contrast-enhancing lesions [14•, 15]. A similar connection seems to exist in patients with radiologically isolated syndrome, in which an increased INL thickness was indicative of future MS-related disease activity [39].

Against this background, the clinical utility of OCT to complement MRI measures of disease activity still needs to be further defined. The first large longitudinal study of the relationships between OCT parameters and brain atrophy was recently published. The rates of GCIP and whole-brain atrophy were associated across the cohort ($r = 0.45$, $p < 0.001$), with the relationship primarily driven by the association between the rates of GCIP and gray matter (as opposed to white matter) atrophy [24•].

Neuroaxonal injury on OCT correlates with reduced quality of life and visual and global disability in MS

Since the extent of axonal loss increases with disease progression, the greatest retinal atrophy has been described in secondary progressive MS, followed by relapsing–remitting MS and then clinically isolated syndrome [40–42, 43•, 44], particularly in eyes previously affected by ON as compared to eyes without a history of clinical ON (non-ON eyes) [40–42]. Even amongst patients with purported benign MS, without prior ON [45], and patients with primary progressive MS [41, 46] who typically do not manifest overt episodes of ON, studies using OCT have shown pRNFL thickness reductions in these patient cohorts as compared to healthy volunteers.

Microcystic macular edema (MME) is characterized by cystic areas of hyporeflectivity in the INL on OCT. Even though MME is not specific to MS [47], the presence of MME in MS has been associated with a more severe disease phenotype. In a study of 318 MS patients, 15 patients were found to have MME. MME was particularly frequent in ON eyes, and subjects with MME were generally older, had longer disease duration, and had worse global and visual disability scores as compared to patients without MME [48•]. In a longitudinal study, MME was associated with INL thickening. Moreover, independent of MME, INL thickening at baseline was predictive of clinical relapses, the formation of new T2 lesions and contrast-enhancing lesions on MRI, as well as disability progression during follow-up [14•]. It is worth noting that MME may be a misnomer since the "cystic" areas are actually unlikely to be true cysts. Therefore, macular microcystoid changes might be a more appropriate term to describe the OCT appearances that have been described as MME.

Visual dysfunction is a common finding in MS, with 50% of patients presenting with visual disturbance as their first symptom of MS and 80% reporting visual disturbances throughout the course of the disease [49–51]. Deficits in vision are strongly correlated to worse quality of life (QOL) in patients with MS [52, 53]. GCIPL thickness is an important structural marker of visual disability in MS [6•, 54, 55]. Low-contrast letter acuity (LCLA) has emerged as the leading outcome measure for visual function in MS clinical trials. LCLA captures visual loss not measured by high-contrast visual acuity (HCVA) [50, 56•]. Even when HCVA has recovered to 20/40 or better, deficits in LCLA and vision-specific quality of life are seen, revealing dysfunction

commonly reported by patients, but not measured by standard HCVA testing [57]. Several studies have shown correlations between RNFL and GCIPL thicknesses, HCVA, and, in particular, LCLA scores [9, 54, 58, 59•]. Patients with dyschromatopsia in non-ON eyes have been found to have worse global disability and cognitive scores as well as reduced pRNFL thicknesses and lower normalized brain parenchymal volume. Patients developing incident dyschromatopsia after 1 year of follow-up had greater disability worsening than those who remained with normal color vision [60•]. Visual field (VF) deficits (measured by mean deviation, MD) have been associated with disability and brain and retinal markers of neuroaxonal injury [61]. MS patients with baseline impaired VFs have been shown to have a threefold risk of disability progression during follow-up [61]. Another study also found a linear relationship between pRNFL thickness and MD in ON eyes, but not in non-ON eyes [62].

The 25-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-25) is a valid and useful tool in assessing visual dysfunction in MS patients [63, 64]. Complementing the NEI-VFQ-25, the ten-item Neuro-Ophthalmic Supplement (NOS) was developed in MS cohorts and captures patient-reported visual disability [65]. Longitudinal studies have shown that reductions of pRNFL and GCIPL thicknesses, even in the absence of ON, correlate with clinically meaningful reductions in NEI-VFQ-25 and NOS scores [53, 54, 57, 65, 66]. Deficits in LCLA and vision-specific QOL are found many years after ON, even when HCVA has recovered [63]. Patients with MS-related ON report poor QOL even with "good" visual recovery to 20/40 or better at high contrast. Such self-reported deficits may reflect underlying axonal and neuronal loss and visual dysfunction, potentially highlighting an unmet therapeutic need [57].

Several cross-sectional studies have reported correlations between pRNFL thickness reductions and higher (worse) Expanded Disability Status Scale (EDSS) scores [21, 22, 67–70]. A recent multicenter study of 879 MS patients showed that pRNFL at baseline thickness is predictive of disability course over time. Subjects with pRNFL thicknesses lower or equal to 87 μm measured by Cirrus SD-OCT or 88 μm measured by Spectralis SD-OCT had double the risk of disability worsening by EDSS progression any time after the first and up to the third year of follow-up (Fig. 2). After the third and up to the fifth year of follow-up, this risk increased nearly fourfold, indicating that measuring pRNFL thickness is useful in determining risk of disability worsening over time in MS [71•]. One of the limitations of EDSS is that it includes mainly physical neurological impairment. For this reason, some authors have specifically investigated the relationship between OCT parameters and cognitive outcomes, but results have been inconclusive since some studies have found correlations between pRNFL thickness and Symbol Digit Modalities Test [67, 72] while others have reported that there is no correlation between these outcomes [73, 74]. Nevertheless, assessments of the relationships between OCT and comprehensive neuro-psychological assessments in MS are generally lacking. Finally, Garcia-Martin et al. analyzed the relationship of pRNFL thickness with overall QOL (measured by the MSQOL-54 questionnaire). Reductions in pRNFL thickness were associated with worse QOL and EDSS scores. Questions on the MSQOL-54 relating to the patients' perception of their physical condition correlated in particular with pRNFL thickness. Baseline pRNFL thickness predicted decreases in QOL [75].
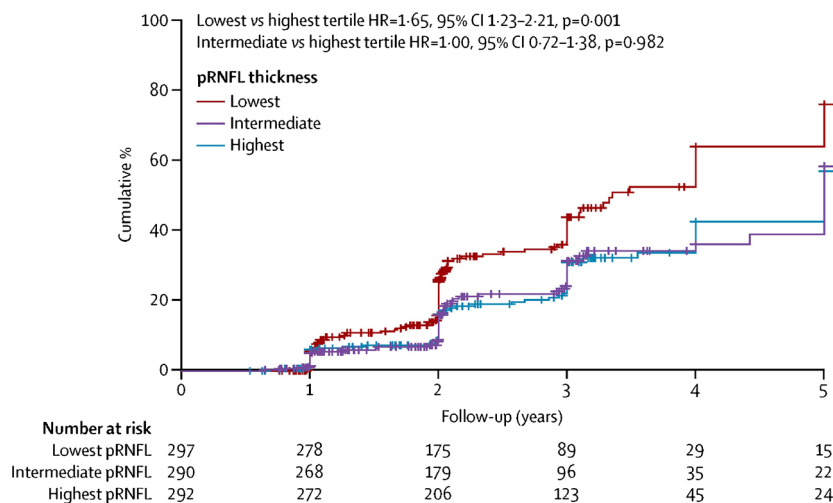
Fig. 2. Cumulative percentage of disability worsening in a cohort of patients with multiple sclerosis according to pRNFL thickness in eyes without optic neuritis. *Number at risk*: number of patients at risk of disability worsening just before the selected time points. The difference in the number of patients between one time point and the next is the sum of the number of events and number of censored patients. *HR* hazard ratio, *pRNFL* peripapillary retinal nerve fiber layer. pRNFL thicknesses are lowest (≤87 µm), intermediate (>87–97 µm [Spectralis OCT] and >87–98 µm [Cirrus OCT]), and highest tertiles (>97 µm [Spectralis OCT] and >98 µm [Cirrus OCT]). This figure was reprinted from [71], Copyright (2016), with permission from Elsevier.

Retinal thinning in patients with MS is prominent early in the disease

Understanding the dynamics of neuroaxonal injury throughout the MS course and its relationship with inflammatory activity is crucial in order to define the best therapeutic strategy for MS. If the rate of neuroaxonal injury was fastest early in the disease course and in relation with inflammation, neuroprotection in MS would mean early and active anti-inflammatory treatment. Conversely, if the rate of neuroaxonal injury was greatest later in the MS disease course and therefore less related to inflammatory activity, primary neuroprotective therapies would be necessary.

In addition to other imaging modalities such as MRI, SD-OCT may be useful for assessing the dynamics of retinal neuroaxonal injury throughout the course of MS. Most individual axons have 1 µm diameter on average. Even though brain tracts comprise numerous axons, tract diameters are still usually measured in micrometers [76]. Changes in MRI outcomes are quantified in cubic millimeters, while changes in SD-OCT outcomes are measured in micrometers, suggesting SD-OCT may have an advantage over MRI, at least in terms of resolution.

Previous studies have quantified retinal neuroaxonal loss in patients with MS [13, 24•, 77–80]. All studies found significant retinal neuroaxonal injury by means of pRNFL and GCIPL thinning during the follow-up, except for the study published by Serbecic et al. which evaluated retinal atrophy in a group of 37 patients followed over nearly 2 years [77]. The rate of pRNFL thinning ranged from −1.49 µm/year [78] to −0.21 µm/year [13], whereas the rate of GCIPL thinning ranged from −0.55 µm/year [80] to −0.30 µm/year [79]. Three out of

these six studies specifically addressed whether the rates of retinal atrophy were different between eyes with and without a history of ON and did not find significant difference between these groups [78–80]. Ratchford et al. found that the rate of retinal thinning was faster for patients with disease duration lower than 5 years than for those with a longer disease duration. Interestingly, these authors found no differences when they repeated these analyses using 10 years as a cutoff instead of 5 years [13]. Similarly, Balk et al. assessed the rates of retinal neuroaxonal injury and found that the rates of retinal atrophy were fastest in the early period of MS and described a plateau effect for patients with disease duration longer than 20 years [80]. Both studies suggest that the rate of neuroaxonal loss may be highest early in the MS disease course. Finally, Ratchford et al. found that the rates of retinal GCIPL atrophy were faster in patients with relapses (42% faster), patients with new gadolinium-enhancing lesions (54% faster), and patients with new T2 lesions (36% faster) than in patients without these clinico-radiological features [13]. Therefore, the rate of retinal neuroaxonal loss may be partially related to the degree of ongoing inflammatory activity.

OCT measurements as promising markers of therapeutic response in MS

Collectively, the above findings provide ample support for the proposed utility of OCT measures, and in particular GCIPL thickness, as outcomes for objectively assessing and monitoring neurodegeneration and, accordingly, neuroprotection. Yet, there has been a paucity of such investigations to date. The currently available disease-modifying therapies (DMTs) for relapsing–remitting multiple sclerosis (RRMS) modulate or suppress the immune system, reducing the risk of future inflammation and associated neurodegeneration. Accordingly, the effect of DMTs on MRI-derived estimates of brain atrophy has become a common outcome in MS trials. However, unlike MRI volumetry which lacks sensitivity and requires large numbers of patients to detect significant differences, due to being highly reliable, sensitive, and objective outcomes for assessing neuroprotection, OCT measures may be able to detect significant differences between small cohorts of patients.

In the 2016 American Academy of Neurology annual meeting, authors from the University of British Columbia reported an improvement in retinal measurements (pRNFL thickening of over 1.5 μm) over 2 years in a small cohort of 26 RRMS patients who were treated with alemtuzumab. The authors reported a significant inverse correlation between pRNFL global changes and EDSS ($r = -0.42$, $p = 0.047$) [81]. Although promising, the findings need validation in future studies as well as further explanation of the mechanisms behind these results. In a recent retrospective and preliminary assessment of the effects of glatiramer acetate (GA, $n = 48$), natalizumab (NTZ, $n = 46$), and interferon beta-1a subcutaneously ($IFNB_{SC}$, $n = 35$) and intramuscularly ($IFNB_{IM}$, $n = 28$) in RRMS patients monitored over a mean follow-up period of 3 years, relative to NTZ-treated patients, $IFNB_{SC}$- and GA-treated patients exhibited 0.37 μm/year ($p < 0.001$) and 0.14 μm/year ($p = 0.035$) faster rates of GCIPL thinning, respectively. Despite the small treatment cohort sizes, the findings were strikingly

in accordance with the effects of these DMTs upon brain atrophy observed in large-scale studies. The $IFNB_{SC}$ cohort had a 0.14-μm/year ($p = 0.001$), 0.11-μm/year ($p = 0.011$), and 0.12-μm/year ($p = 0.023$) faster rate of INL thinning compared to the NTZ, GA, and $IFNB_{IM}$ cohorts, respectively. Moreover, the GA, IFN_{SC}, and IFN_{IM} cohorts exhibited 0.18 μm/year ($p = 0.014$), 0.38 μm/year ($p < 0.001$), and 0.22 μm/year ($p = 0.013$) faster rates of ONL thinning relative to NTZ-treated patients, respectively. The rate of GCIPL thinning in the healthy control (HC) cohort was 0.14 μm/year, adjusting for baseline GCIPL thickness, age, and sex. The GA-, $IFNB_{SC}$-, and $IFNB_{IM}$-treated patients exhibited 0.16 μm/year ($p = 0.010$), 0.40 μm/year ($p < 0.001$), and 0.14 μm/year ($p = 0.08$) greater rates of GCIPL thinning compared to HCs, respectively. On the other hand, NTZ-treated patients and HCs did not differ in their rates of GCIPL loss ($p = 0.720$) [82•]. This study, however, did not assess the effects of oral DMTs or monoclonal antibodies other than NTZ on retinal atrophy or include patients with PMS, limitations that need to be addressed in future, larger prospective studies.

Conclusions

There is increasing evidence that retinal changes mirror global central nervous system aberrations in MS. Current evidence provides strong support that OCT measures of pRNFL and GCIPL thicknesses reflect global neurodegeneration in MS, with numerous studies finding consistent correlations between brain volumes and retinal thickness measures. Moreover, over time, the rates of GCIPL thinning and brain atrophy have been shown to mirror one another in MS. In addition, studies raise the possibility that INL thickness may have utility in predicting and/or monitoring inflammatory activity in MS. Thinning of axonal and neuronal layers on OCT correlates with reduced quality of life, vision, and disability in MS. Patients with MS display significant retinal thinning during their disease course, regardless of whether or not they have a history of ON. Retinal neuroaxonal loss seems to be greatest during the early phases of the disease and particularly prominent for patients with active MS. While few studies have investigated the role of OCT measurements in assessing the neuroprotective effects of DMTs in MS, emerging preliminary data do strongly support the feasibility of OCT to investigate differences in the neuroprotective benefits of various DMTs.

Compliance with Ethical Standards

Conflict of Interest

Alexander U. Brandt has received travel reimbursement from Bayer, Biogen, Teva, and Novartis and consulting or speaker honoraria from Biogen, Teva, Heidelberg Engineering, Motognosis, and Nexus. He is a member of the working committee of International Multiple Sclerosis Visual System (IMSVISUAL) Consortium.

Elena H. Martinez-Lapiscina is a researcher in the OCTIMS Study, an observational study (which involves no specific drugs) to validate SD-OCT as a biomarker for multiple sclerosis, sponsored by Novartis. She has received speaking honoraria from Biogen and Genzyme and travel reimbursement from Genzyme, Roche, for international and national meetings over the last 3 years. She is a member of the working committee of the International Multiple Sclerosis Visual System (IMSVISUAL) Consortium.

Rachel Nolan is a member of the working committee of the International Multiple Sclerosis Visual System (IMSVISUAL) Consortium.

Shiv Saidha has received consulting fees from Medical Logix for the development of CME programs in neurology, consulting fees from Axon Advisors LLC, speaking honoraria from the National Association of Managed Care Physicians, Family Medicine Foundation of West Virginia, and Advanced Studies in Medicine, and served on scientific advisory boards for Biogen-Idec, Genzyme, Genentech Corporation, and Novartis. He received research support from the Race to Erase MS and Genentech Corporation. He is a member of the working committee of the International Multiple Sclerosis Visual System (IMSVISUAL) Consortium.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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