Optical Coherence Tomography in the Diagnosis and Management of Optic Neuritis and Multiple Sclerosis

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ABSTRACT

Optic neuritis (ON) is an inflammatory optic nerve injury, which is strongly associated with multiple sclerosis (MS). Optical coherence tomography (OCT) has the potential to provide a reliable means of capturing axonal deficits, which can be paired to tests of visual function to provide a structural–functional paradigm of brain injury. In this respect, the eye provides a unique view into the effects of central nervous system inflammation, which may enhance the understanding of disease mechanisms that contribute to neurological disability in MS. This review addresses the published experience with OCT in the diagnosis and treatment of patients with ON and MS, and discusses the applications of OCT in ongoing clinical trials. The potential gains and limitations of spectral-domain OCT as an evolving technology and surrogate marker of axonal brain injury are also discussed.

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system (CNS) that causes progressive neurodegeneration over time. Because it affects more than 2 million people worldwide, MS is one of the most common causes of acquired neurological disability in young adults. The pathogenesis of MS has long been ascribed to autoimmune mechanisms that target both white and gray matter elements, and is characterized by demyelination, gliosis, axonal damage, and neuronal loss in the brain and spinal cord. The phenotypic expression of MS is highly variable, both within and between patients, depending on the age and stage of the disease.

Initially, the majority (85%) of patients experience episodes of neurological dysfunction with clinical recovery in the relapsing-remitting phase (RRMS). Most patients transition to a secondary progressive course (SPMS) within two decades of their diagnosis, during which time they accumulate neurological disability with or without relapses. Approximately 15% of patients experience a
primary progressive course from onset, either without preceding relapses (PPMS) or with superimposed neurological events in what is known as progressive relapsing MS. These acronyms are embedded in the lexicon of neurologists and allow MS patients to be classified into clinical subsets based on their propensity for relapses, magnetic resonance imaging (MRI) features, and disease progression. Current disease-modifying therapies target inflammation and are most effective during the relapsing phase of the disease; yet, the factors that govern the transition from RRMS to the treatment-resistant progressive course of the disease are not well understood.

Eighty percent of MS patients present with an acute clinical episode affecting one or several neurological sites, which is known as the clinically isolated syndrome (CIS). Optic neuritis (ON) is the best studied CIS, and represents the first clinical manifestation of MS in approximately 20% of cases. In addition to being the clinical inception for many, an additional 30% to 70% of patients develop ON during the course of their disease, making the anterior visual pathway a frequent target in MS.

Much of our knowledge regarding the clinical presentation of ON has been gained from the Optic Neuritis Treatment Trial (ONTT). This randomized, multicenter study was initially designed to compare the visual benefits of treatment with either intravenous methylprednisolone (250 mg every 6 hours for 3 days followed by oral prednisone [1 mg/kg/day] for 11 days), oral prednisone (1 mg/kg/day), or oral placebo (for 14 days) in 457 patients with acute ON. From the ONTT, we learned that most ON patients are young (mean age: 32 years) white (85%) women (77%). Ninety percent of patients report pain at the onset of vision loss, which is often characterized as an “ache” made worse with eye movement. Vision loss is generally subacute in onset, progressing over hours to days. The severity of vision loss may range from mild to no light perception. Dyschromatopsia or decreased color vision is common, which is an invaluable clue to the diagnosis in patients presenting with relatively mild visual acuity deficits. Patients with unilateral ON often manifest a relative afferent pupil defect, unless there is coexisting optic nerve damage in the contralateral eye. Visual field defects in ON correspond to the topography of the retinal nerve fiber layer (RNFL) and may be arcuate, altitudinal, or cecocentral in shape. In cases of retrobulbar ON, the fundus examination is initially normal, whereas patients with anterior ON or “papillitis” may manifest optic disc swelling acutely (Case 1). Atypical features of ON such as bilateral involvement at presentation, optic disc hemorrhages, vitreous reaction, absence of pain, and poor clinical recovery should prompt investigations for possible clinical mimics.

Case 1. A 30-year-old woman presented with an isolated optic neuritis event in the left eye (OS). Visual acuity was 20/20 in the right eye (OD) and 20/100 in the left eye, and there was a left relative afferent pupil defect. Visual field testing was normal in the right eye and there was a central scotoma in the left eye. Fundus examination showed a normal-appearing optic nerve in the right eye (A) and optic disc edema in the left eye (B). At presentation, time-domain optical coherence tomography testing (C) showed an elevated mean retinal nerve fiber layer thickness in the left eye relative to the right eye.
Most ON patients recover vision over a period of weeks to months, during which time optic disc pallor may evolve as a “footprint” of the inflammatory injury, indicating axonal loss. Many patients report persistent visual problems including fatigue and heat-induced (Uthoff’s phenomenon) vision loss, altered motion and depth perception, and decreased spatial vision at low contrast levels after ON. ON patients may demonstrate evidence of disseminated CNS inflammation on MRI (50% to 70%) and harbor abnormal cerebrospinal fluid constituents (60% to 70%), which increase their future risk of MS.1,7,10,13-17

The long-term follow-up from the ONTT study showed that 72% of patients who have one or more white matter lesions on their baseline MRI scan developed clinically definite MS after 15 years compared to only 25% of ON patients with no baseline MRI lesions.16 Although MRI is useful in predicting the future risk and confirming the diagnosis of MS,7 there is an acknowledged dissociation between the lesion burden visualized on MRI and corresponding clinical deficits in MS patients, which is aptly referred to as “the clinical radiological paradox.”3 One potential reason for discord is that MRI is useful in detecting CNS inflammation in MS patients but the relative contributions of axonal damage and neuronal loss to disease progression are less ably captured with conventional imaging techniques. Moreover, although MRI shows focal or confluent abnormalities in more than 95% of MS patients, the presence of such lesions alone does not confirm the diagnosis of MS.1 Similar radiological lesions can be found in individuals without clinical manifestations of MS and many individuals older than 50 years have non-specific white matter brain lesions, which need to be interpreted with caution.1

ON: A VIEW TO UNDERSTANDING DISEASE MECHANISMS IN MS

In 1998, Trapp et al.18 examined brain tissue obtained at autopsy in MS patients and noted that transected axons were a consistent feature of MS lesions and that the frequency of axonal transection was related to the degree of inflammation within lesions. These findings prompted a paradigm shift from viewing MS as a demyelinating disease to a more encompassing vantage point, in which axonal degeneration was recognized as an early pathological manifestation of MS; subsequently, the relative contributions of inflammation, acute and chronic axonal loss, and neurodegeneration were considered in the “gestalt” of disease pathogenesis. Trapp et al. proposed that axonal transection may be the pathologic correlate of the irreversible neurologic impairment in MS and suggested that a threshold of axonal loss is eventually reached, beyond which patients experience progressive neurologic deterioration.18 Moreover, they highlighted the need for improved noninvasive methods of monitoring and treating axonal pathologic changes in MS patients.

Understanding the pathological mechanisms that underpin disease progression is germane to identifying better biomarkers to capture pathological activity and, ultimately, to developing more effective regenerative and restorative treatments for MS patients. To this end, ON has emerged as a system model of CNS inflammation, which may provide unique insights regarding mechanisms of injury and repair in MS. The tenability of the model is bolstered by the fact that the functional consequences of ON can be quantified with reliable and validated measures of high and low contrast visual acuity, automated perimetry, and color vision testing.

Since the invention of the ophthalmoscope in 1851,19 the structural consequences of optic nerve injury have been visualized acutely as optic disc edema, followed by optic disc pallor and corresponding defects in the RNFL. The RNFL has the distinct feature of being an unmyelinated region of the CNS, and represents an isolated axonal sampling of the CNS. In 1974, Frisén and Hoyt interpreted RNFL defects as axonal attrition in MS patients,20 and recent work by Green et al.21 has provided post-mortem evidence for RNFL atrophy in this disease. Moreover, in the modern era, changes in retinal architecture can be quantified with optical coherence tomography (OCT),22-25 which provides a so-called in vivo “optical biopsy” of the RNFL,3 from which we can interpret the effects of more diffuse axonal damage in the CNS.

The advent of spectral-domain OCT (SD-OCT) and further technological advances in functional imaging of the visual system, including multifocal visual evoked potential (mfVEP), have enhanced our understanding regarding the effects of demyelination and remyelination on progressive axonal loss.3,26,27 Together, SD-OCT and mfVEP can be used to elucidate pathophysiological mechanisms of neurodegeneration in MS.26 For the ON model to be accepted as a structural-functional paradigm of CNS injury, however,
OCT must provide a reliable means of detecting RNFL changes representing anterior visual pathway injury, which can be distinguished from test–retest variability inherent to the technology or other causes of reduced thickness in the RNFL. As the data from OCT studies continue to mount, there is evidence to support the feasibility of the ON system model in clinical research and, potentially, to establish a role for OCT in the diagnosis and treatment of MS patients.

**EXAMINING THE EVIDENCE: OCT STUDIES IN ON AND MS**

The table (available at www.slackjournals.com/OSLI) summarizes the findings from some notable TD-OCT and SD-OCT studies in ON and MS patients to date.

**Interpreting RNFL Changes in ON as a CIS**

At the time of an acute isolated ON event, when vision loss is at its nadir, patients often manifest RNFL measurements that are either comparable to or increased in their affected eye (ON eye) relative to their fellow eye (non-ON eye).26,28-39 Correspondingly, the optic nerve in the ON eye may be mildly edematous or hyperemic secondary to axoplasmic flow stasis (Case 1). The degree of acute RNFL change has been shown to correlate with the length of the optic nerve lesion.32 In the ensuing 2 to 3 months, optic disc pallor and RNFL thinning evolve, with earliest signs of significant RNFL atrophy manifesting in the temporal RNFL region.30 Time-domain OCT (TD-OCT) studies have shown that RNFL values continue to decrease for 6 to 12 months after symptom onset, plateauing thereafter (Fig. 1).27,29-32 A year after an isolated ON event, RNFL measurements generally decrease by approximately 20% relative to the fellow eye.29,30,38

Studies have shown that visual recovery 12 months after ON is not related to the extent of RNFL swelling seen acutely, but ultimately is associated with the amount of RNFL thinning observed after 6 months.29,30 Lower RNFL values correlate with reduced visual acuity, visual field mean sensitivity, and color vision testing scores (Case 2).26-39 There are also strong correlations between the extent of RNFL thinning after ON, delayed mfVEP latencies, and reduced mfVEP amplitudes, which implicates a direct relationship between extent of acute inflammatory demyelination and consequent axonal loss.26 For patients selected without recruitment bias, 75 µm has been shown to represent a threshold of RNFL integrity that can predict the extent of visual recovery after ON (Fig. 2).34

**Interpreting RNFL Changes in ON Associated With MS**

For all intents and purposes, RNFL changes after ON in MS patients parallel those in patients with CIS because ON has a deleterious impact on RNFL integrity that is directly proportional to the severity of the event and is less dependent on the diagnosis of MS or MS subtype. Therefore, a patient with a CIS who has severe ON and poor clinical recovery may manifest worse RNFL atrophy than an MS patient with a relatively mild ON event. The key difference in distinguishing MS patients with ON from CIS patients is that the former are more likely to have reduced RNFL findings in both eyes.19

Numerous TD-OCT studies have been performed in MS patients,40-70 and a recent meta-analysis (14 studies [2,063 eyes]) demonstrated that RNFL values are reduced from 5 to 40 µm (averaging 10 to 20 µm) in eyes with MS and ON.19 Furthermore, comparing eyes with MS and ON with the eyes of healthy controls showed an estimated average RNFL loss of 20.4 µm (95% confidence interval [CI], -23 to -18).19 In 27 studies comparing RNFL values in eyes with MS and ON to the non-ON eyes of the same patients (4,199 eyes), there
Case 2. A 45-year-old woman presented with optic neuritis in the right eye (OD). Visual acuity was initially hand motions, but improved to 20/40 with a residual cecocentral scotoma (B). Visual acuity in the left eye (OS) was 20/20 and the visual field was normal in this eye (A). There was a right relative afferent pupillary defect. Fundus examination after 6 months showed right optic atrophy (C) and a normal optic disc appearance in the left eye (D). Time-domain optical coherence tomography testing 2 months after presentation (E) showed temporal retinal nerve fiber layer (RNFL) atrophy (arrow) in the right eye (mean RNFL = 110 µm). After 6 months, the patient had marked RNFL thinning in the right eye (mean = 73 µm) relative to the left eye (mean = 109 µm) (F).

was an estimated RNFL loss of 14.6 µm (95% CI, -17 to -13) in ON eyes compared to a 7.1-µm reduction in RNFL thickness in non-ON eyes relative to control eyes. Thus, MS patients with ON are likely to manifest less inter-eye asymmetry with respect to RNFL thickness relative to CIS patients because changes in RNFL integ-
rity are more likely to be bilateral in the former. Similarly, corresponding VEP latencies may be prolonged and amplitudes reduced because MS patients have a predilection toward inflammation and axonal damage in the anterior visual pathway in the absence of clinically overt ON events. For eyes with MS and ON, visual function scores correlate with the extent of RNFL integrity after ON. Fisher et al.\textsuperscript{56} used TD-OCT to compare RNFL values between 90 MS patients and 36 control subjects, and reported that lower visual function scores were associated with reduced overall RNFL thickness in MS patients, such that for every 1-line decrease in low-contrast letter acuity or contrast sensitivity score, the mean RNFL thickness decreased by 4 µm.\textsuperscript{56}

**Interpreting RNFL Changes in Recurrent ON**

It can be difficult to detect RNFL changes in the setting of recurrent ON, because the extent of cumulative RNFL atrophy can be severe and the corresponding visual outcomes dire. In a recent TD-OCT study of 193 MS patients, RNFL values were compared between 29 eyes affected by two or more ON events, 125 eyes affected by a single ON event, and 232 eyes without ON. The mean RNFL values were significantly lower in recurrent ON eyes (64.2 µm) relative to single ON eyes (86.3 µm) ($P < .0001$) and eyes without ON (100.1 µm) ($P < .0001$).\textsuperscript{58} Yeh et al.\textsuperscript{60} noted that average RNFL thickness decreased with increasing number of ON episodes in pediatric patients, which supports the premise that recurrent inflammatory events have a cumulative impact in eroding axonal integrity in the anterior visual pathway. This creates a practical challenge to diagnosing ON in a patient with preexisting RNFL atrophy, because increments of change in RNFL thickness decrease over time and may be subtle in the context of a new ON event.

**Comparing RNFL Changes in ON Associated With Neuromyelitis Optica to RNFL Changes in ON Associated With MS**

Neuromyelitis optica (NMO) is a severe inflammatory process of the optic nerves and spinal cord that is generally associated with poor clinical recovery.\textsuperscript{62-64,71-73} Not surprisingly, RNFL atrophy tends to be extensive in eyes with NMO and ON (Case 3). Several studies have explored the role of OCT in distinguishing ON associated with NMO from that associated with MS.\textsuperscript{62-64} Naismith et al.\textsuperscript{62} reported lower RNFL values in ON eyes of 22 NMO patients compared to ON eyes of 47 MS patients and noted that the superior and inferior RNFL quadrants were more severely affected in the former. In this study, the odds of falling into the NMO group increased by 8% for every 1-µm decrease in RNFL thickness. Similarly, Ratchford et al.\textsuperscript{63} observed significant RNFL thinning in eyes with NMO and ON (63.6 µm) relative to eyes with RRMS and ON (88.3 µm) ($P < .0001$) and control eyes (102.4 µm) ($P < .0001$) and reported that a first episode of ON was estimated to cause 24 µm more RNFL loss in eyes with NMO and ON relative to eyes with RRMS and ON.\textsuperscript{63} Nakamura et al.\textsuperscript{64} described lower RNFL values in eyes with NMO and ON than eyes with MS and ON (64 versus 84 µm; $P = .0006$), and noted that the frequency of ON relapses and the time to initiate treatment with high-dose intravenous methylprednisolone significantly affected the preservation of RNFL thickness in NMO patients.

The importance of making the diagnosis on NMO cannot be overstated because the natural history of ON associated with this disorder is poor and long-term immunosuppressive therapy is needed, which further distinguishes NMO patients from MS patients. An auto-antibody (anti-NMO IgG) has been identified, which targets aquaporin-4,\textsuperscript{71} a water channel protein, and facilitates the diagnosis of NMO with a specificity and sensitivity of 94% to 100% and 76% to 91%, respectively.\textsuperscript{62-64,71-73} Therefore, a patient with ON and a baseline cranial MRI scan that does not show disseminated white matter lesions and clinical characteristics such as bilateral presentation, recurrent ON,

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**Figure 2.** One regression line (dotted line) shows the relation between retinal nerve fiber layer (RNFL) values less than 75 µm and visual field mean deviation (VFMD); the other regression line (solid line) shows the relation between RNFL values of 75 µm or greater and VFMD. Among patients with average RNFL measurements less than 75 µm, the slope of change in VFMD (dB) was 0.646 ($P = .0002$).
and/or poor visual recovery may harbor the diagnosis of NMO. It is noteworthy that patients who manifest an inter-eye asymmetry in RNFL thickness of 15 µm or greater have been deemed more likely to have the diagnosis of NMO (75%) than RRMS (24%). Yet, in studies showing significantly more RNFL thinning in NMO eyes affected by ON relative to ON eyes in MS patients, there has been considerable overlap in the distribution of RNFL values. Hence, in using OCT to differentiate ON associated with NMO from ON associated with MS, it is important to be mindful of issues that could affect RNFL values in either group, including recurrent ON in the same eye and bilateral optic nerve involvement.

Using RNFL Values to Predict Risk of Converting to MS After ON

Few studies have explored the association between RNFL atrophy and future risk of MS in ON patients. In a prospective study of 50 CIS patients with isolated ON, there were no significant differences in RNFL thickness in either ON eyes or non-ON eyes between patients who developed clinically definite MS (42%) and those who did not develop MS (58%) during the 2-year study period.

Outteryck et al. performed OCT testing on 56 CIS patients and 32 control subjects to investigate whether measures of RNFL thickness and macular volume revealed early retinal axonal loss. In this prospective case series, there was no link between RNFL and (1) MRI evidence of CNS inflammation at baseline; (2) disseminated CNS inflammation according to the revised McDonald criteria; (3) gadolinium enhancement on initial MRI; (4) multifocal CIS presentation; (5) altered VEPs; or (6) development of “McDonald” proven MS at 6 months. These investigators concluded that OCT does not predict conversion to MS at 6 months in CIS patients and postulated that conversion to MS after ON is more likely influenced by inflammatory events than axonal degeneration.

Interestingly, mfVEP latency delays in ON patients have been shown to predict an increased risk (36%) of developing MS. Hence, the hypothesis that CNS in-

Case 3. A 30-year-old woman with neuromyelitis optica experienced optic neuritis in the right eye (OD) with poor visual recovery. Visual acuity was 20/200 in the right eye and 20/20 in the left eye (OS). There was a right relative afferent pupil defect. Fundus examination showed right optic atrophy (A) and a normal-appearing optic disc in the left eye (B). Spectral-domain optical coherence tomography showed reduced mean retinal nerve fiber layer (RNFL) thickness in the right eye (61 µm) relative to the left eye (84 µm) (C). ONH = optic nerve head.
flammation occurs independent of axonal loss in early phases of MS seems tenable and may suggest a role for mVEP in identifying CIS patients at higher risk of developing future MS.

**Interpreting RNFL Changes in MS Independent of ON Events**

For most MS patients, the hallmark of the diagnosis is change, both in terms of neurological disability and the MRI measured burden of disease over time. At this point, the role of OCT in complementing conventional tools used to diagnose MS is not known. According to the revised McDonald criteria, a delayed but well-preserved conventional VEP waveform can be used to show dissemination of inflammatory CNS lesions and thus confirm the diagnosis of MS. As previously mentioned, a recently published meta-analyses showed an average RNFL thinning of approximately 7 µm in non-ON eyes of MS patients. Thus, it is conceivable that RNFL values could eventually be used to capture clinically silent disease activity, providing there is consensus regarding the amount of progressive RNFL thinning that constitutes paraclinical evidence of anterior visual pathway pathology and assurance that the deduction in RNFL thickness can be distinguished from the test–retest variability of the technology. Newer OCT technology now available, including eye tracking and repeat measurement software, helps to stabilize the scan on the retina in the same location and reduces retest measurement variability, which may facilitate this task.

To date, TD-OCT studies have shown correlations between RNFL thickness and MRI measures of brain atrophy, but there is currently no consensus regarding what brain atrophy measure is optimal. Furthermore, although correlations may be statistically significant, they are not predictive. Lower RNFL values have been associated with worse clinical scores of neurological disability and longer disease duration in MS patients, albeit the results of published reports have been inconsistent. The disparities are in part due to the inherent heterogeneity of MS cohorts, and the fact that the most widely used clinical trial measure of neurological disability (Expanded Disability Status Scale [EDSS]) is heavily weighted toward motor dysfunction.

In a prior 2-year prospective study, Sepulcre et al. reported that RNFL atrophy correlated with greater disability ($r = -0.348, P = .003$) in a heterogeneous MS cohort. Baseline temporal RNFL atrophy was associated with the presence of new relapses and EDSS changes ($P < .05$) at the completion of the study. RNFL measurements correlated with white ($r = 0.291, P = .005$) and gray ($r = 0.239, P = .021$) matter MRI volumes. Similarly, in a cross-sectional study, Fisher et al. reported that RNFL values declined with increasing neurological impairment in an MS cohort consisting largely of RRMS patients (84%). Yet, in a subsequent study of progressive MS patients, changes in RNFL thickness were not significantly different for patients or healthy controls, prompting the investigators to conclude that TD-OCT detects little disease-related loss of retinal axons in progressive forms of MS and has limited use for monitoring candidate neuroprotective therapies at this stage of disease.

A recent cross-sectional study demonstrated significant correlations between RNFL thickness and the extent of neurological disability for RRMS and CIS patients, but this relationship did not hold true for progressive MS subtypes. These data suggest that there may be concordance between the extent of axonal damage in the anterior visual pathway and measures of neurological impairment for MS patients with mild to moderate neurological disability, but not for patients with either mild or advanced disease (Fig. 3). Patients with progressive MS may have more extensive axonal damage in a functionally eloquent region such as the spinal cord, with relative sparing of other CNS systems, including the anterior visual pathway. This may account for the lack of correlation in structure and function between imaging modalities such as OCT and global measures of neurological disability in these patients.

A recent longitudinal TD-OCT study of 299 MS patients (84% RRMS) who underwent RNFL measurements at “baseline” and 6 or more months later demonstrated that in pooled analysis for eyes with MS and ON and non-ON eyes each year of follow-up was associated with an average 2-µm decrease in RNFL integrity ($P < .001$). In contrast, control subjects showed an average RNFL thinning of 0.5% over a 3-year period. The investigators concluded that RNFL thinning occurs as a consequence of subclinical axonal loss in the anterior visual pathway in MS, and suggested that OCT and low-contrast acuity could be used to potentially evaluate the effectiveness of neuroprotection protocols in MS.

However, as Petzold et al. have rightly noted,
caution is needed in generalizing the time course of RNFL loss to a given individual from cross-sectional data. The estimated yearly thinning of overall RNFL (2 µm) is below the detection limit of TD-OCT, which creates further challenges. Ideally, future longitudinal studies with SD-OCT and associated hardware and software improvements that minimize repeat measurement variability may enable resolution at this level, but this has yet to be determined. To this end, a follow-up period of at least 2 years will likely be needed to determine whether clinically significant changes in RNFL integrity secondary to subclinical disease activity can be captured in MS patients. It will be technically difficult to achieve longitudinal monitoring of RNFL changes in MS patients, but two clinically validated methods include topographical change analysis and statistical image mapping, which may prove useful.

Recent publications have highlighted the importance of distinguishing the effects of subclinical axonal attrition in MS patients from mild ON events and diffuse inflammatory lesions along the entire afferent visual pathway, which may result in retrograde degeneration and RNFL atrophy in MS patients. Clinically silent demyelinating lesions are frequent in the optic nerves, chiasm, optic tracts, and radiations of MS patients. Loss of RNFL following axonal transection beyond the lateral geniculate body, however, requires trans-synaptic degeneration. The phenomenon of trans-synaptic degeneration in the optic pathway was described by Matthews et al. as early as 1960 and compelling evidence of retrograde trans-synaptic degeneration (although age and species specific) has emerged from several animal studies. A recent pathophysiological study of retinal pathology in MS patients by Green et al. also lends support to the mechanism of trans-synaptic degeneration as a likely basis of producing retinal atrophy.

Mehta and Plant reported topographically accurate reduction of OCT-measured RNFL thickness in patients with long-standing occipital lesions. Jindahra et al. recently demonstrated trans-synaptic retrograde degeneration in the visual system not only in congenital homonymous hemianopia, but also in acquired lesions of the occipital cortex. Moreover, Bridge et al. showed that RNFL thinning presents 18 months after post-V1 lesion. Also noteworthy was a recent report demonstrating a moderate but significant correlation between RNFL thickness and MRI indexes of abnormality along the optic radiation, indicating that trans-synaptic retrograde degeneration is a plausible mechanism of axonal loss in MS. However, this finding needs to be scrutinized carefully because it is often difficult to reliably localize the initial site of damage to only the post-geniculate pathway in MS.

The potential impact of trans-synaptic generation on RNFL thickness indicates that more frequent imaging and vigilant clinical surveillance may be needed to determine the full extent of afferent visual pathway involvement in MS patients. Only then will it be possible to discern whether structural RNFL changes and alterations in visual function evolve as a consequence of mild ON events, trans-synaptic degeneration from posterior visual pathway lesions, or insidious axonal attrition in the anterior visual pathway.

**Using RNFL to Assess Therapeutic Benefits for ON and MS Patients: Ongoing Clinical Trials**

Despite a paucity of reproducible longitudinal data and prevailing uncertainty regarding the time course of

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**Figure 3.** Mean retinal nerve fiber layer (RNFL) thickness in eyes with optic neuritis across categories (tertiles) for patients with multiple sclerosis who underwent neurological testing with the Expanded Disability Status Scale (EDSS). Tertile ranges represent minimal abnormalities on neurological examination: a score of 0 to 1.5 represents no disability, 2.0 to 2.5 mild disability, and 3.0 to 7.0 moderate to severe disability. EDSS scores of 6.0, 6.5, and 7.0 are assigned if a patient requires unilateral assistance (cane), bilateral assistance (walker), or a wheelchair, respectively, for ambulation. CIS = clinically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; PPMS = primary progressive multiple sclerosis. (Reprinted with permission from Costello F, Hodge W, Pan YI, Eggenberger E, Freedman MS. Using retinal architecture to characterize multiple sclerosis patients. Can J Ophthalmol. 2010;45:520-526.)
RNFL loss in MS, OCT is being employed as an outcome measure in several ongoing observational studies and interventional trials. A phase II study entitled Neuroprotection and Repair in Optic Neuritis (Mino in ON) will estimate the treatment effect of 100 mg of oral minocycline, taken twice daily (over 90 days), versus no treatment in patients with acute ON. The primary outcome measure is mean RNFL thickness measured by TD-OCT. Biogen Idec is sponsoring an interventional study that will evaluate the role of natalizumab on MRI, RNFL, and cognitive outcomes in RRMS patients over 2 years. A phase II, multi-center, prospective, double blind, placebo-controlled study (Flupirtine as Oral Treatment in Multiple Sclerosis [FLORIMS]) aims to evaluate the efficacy and safety of flupirtine add-on therapy to interferon beta-1b on neurodegeneration in RRMS patients. In this study, OCT-measured RNFL thickness has been designated a secondary outcome.

The University of Cambridge has sponsored a safety/efficacy study in which RNFL measures at 12 and 52 weeks post-infusion will be determined for MS patients undergoing treatment with autologous adult mesenchymal stem cells in the Mesenchymal Stem Cells in Multiple Sclerosis (MSCIMS) study. The Visual Reconstitution Therapy After Optic Neuritis (VISION) phase II study is using OCT to determine whether the effects of software-based visual reconstitution therapy are superior to active comparator treatment in improving visual field function after ON. The OCTAGON study (a randomized double-blind, placebo-controlled multi-center phase 3 study of the effects of glatiramer acetate on the RNFL and visual function in patients with a first episode of acute optic neuritis) is currently underway, and RNFL thickness in ON eyes (from 0 to 6 months) is the primary outcome comparison between patients treated with glatiramer acetate versus placebo. The safety and efficacy of erythropoietin as add-on therapy to methylprednisolone in the treatment of acute ON is being evaluated in an ongoing phase II study, and RNFL loss at weeks 4, 8, and 16 compared to baseline represents the primary outcome measure. OCT is also being implemented to determine patient eligibility in a phase II study sponsored by Sanofi-Aventis evaluating the effect of nerispidine (50 to 400 mg given orally) versus placebo in MS patients with prior ON. Thus, there is already considerable momentum behind using OCT as a surrogate measure of axonal damage in MS, and through an ongoing process of “trial by fire” we will learn much about the utility of the OCT in monitoring the effects of emerging therapies in the years to come.

CONCLUSIONS

The evidence supporting the role of OCT in the diagnosis and management of ON and MS patients continues to mount. OCT may complement our existing arsenal of tools, including tests of visual function, neuroimaging techniques, and electrophysiological studies in developing a structural-functional paradigm of CNS inflammation. Furthermore, OCT may be used in the ON “system model” to capture structural changes in the anterior visual pathway, which will provide unique insights regarding pathogenic mechanisms of CNS injury and, in turn, to develop more effective therapeutic strategies for MS patients.

The feasibility of the ON model will rely on its ability to capture the full spectrum of pathogenic mechanisms that govern disability in MS patients. Previous studies have suggested that chronic demyelination in the absence of active inflammation may contribute to progressive axonal degeneration by making axons more vulnerable to physiological stress. Alterations in neurofilament spacing, lack of trophic support from myelin or myelin-forming cells, disruption of normal axon-myelin interaction, and functional oligodendrocyte pathology are factors that may cause degeneration of chronically demyelinated axons. By measuring optic nerve conductivity with mfVEPs and axonal damage with SD-OCT, it may be possible to further interrogate the relationship between chronic demyelination and neurodegeneration in MS. Moreover, prospective studies will make it possible to ascertain to what extent patients maintain intact axonal integrity despite persistent demyelination after ON.

Recent OCT studies have measured changes in macular volume, raising intriguing questions regarding the potential for this imaging technique to capture neurodegenerative consequences of chronic CNS inflammation. Burkholder et al. reported that lower macular volumes were associated with RNFL thinning in MS eyes, such that a 10-μm difference in RNFL thickness corresponded to a 0.20 mm³ reduction in total macular volume. Because the ganglion cell layer comprises 34% of the total average macular thickness, tracking macular volume changes may help determine the temporal relationship between primary neuronal cell death and axonal loss after a
CNS inflammatory event. With advanced image analysis software currently being developed, it will be possible to routinely segment the inner layers of the macula containing the ganglion cells, which will allow the macular OCT scan to be a more sensitive measurement of ganglion cell loss. This may help overcome the problem encountered with RNFL measurements in following the course of ON; namely, subclinical RNFL edema during the acute episode may confound efforts to determine whether a reduction in RNFL thickness is due to a decrease in edema, atrophy of axons, or both. The inner layers of the retina in the macular scan do not manifest acute edema, which will help obviate this issue.

Evolutions in OCT technology have done much to improve the ease, speed, and reproducibility of retinal measurements in MS patients. The introduction of SD-OCT will hopefully strengthen the structural-functional paradigm of CNS injury, and validate the role of ON as a system model for MS. Yet, challenges remain. RNFL measurements in MS patients differ considerably between TD-OCT and SD-OCT devices, partly due to differences in software layer segmentation algorithms, with excellent correlations between values obtained from both imaging techniques. Recently, Bock et al. compared SD-OCT and TD-OCT imaging techniques in 55 MS patients and reported a strong correlation (Pearson’s $r = 0.926, P < .001$) between the two technologies. However, there were significant differences in the absolute RNFL measurements (mean ± standard deviation 8.1 ± 6.2 µm; range: -12 to 23 µm), and therefore the results from the two devices were not interchangeable. The findings of this study were similar to those reported by Knight et al., who compared SD-OCT and TD-OCT RNFL values in glaucomatous patients. In both studies, SD-OCT tended to measure “more thinly” than TD-OCT at higher RNFL values; whereas, for thinner RNFL values, SD-OCT measured “more thickly” than TD-OCT.

Although recent innovations in OCT techniques offer obvious advantages, including minimizing error and improving test–retest reliability, changes in technology disrupt the collection of longitudinal data, which is vital in the management of a chronic disease. Going forward, the goal remains to define the amount of RNFL change measured by SD-OCT that represents pathology related to MS and to distinguish this “signal” from the “noise” of the technology. This repeat measurement variability may be determined by testing normal eyes and those with a range of RNFL thinning repeatedly on different days, but over a short enough time period where the actual disease is not changing. This would allow a determination of the combined instrument and biologic measurement variability, which can then be used as criteria for determining what amount of change represents true disease progression, outside the range of repeat measurability defined. With current technology combining eye tracking, averaging of multiple B-scans together, and repeat scan functions, it appears that detecting small changes in the RNFL (< 2 µm) annually may soon be possible.

That said, the task of determining whether different subtypes of MS behaved differently with respect to how RNFL change manifests over time may be onerous because MS cohorts are heterogeneous by nature and prone to subclinical disease activity, which means that interpreting clinical outcome measures is hampered by a “shifting baseline” in the clinical expression of the disease, both within and between patients. On a practical level, MS patients may develop other occult ocular conditions (ie, age-related macular degeneration and glaucoma) that damage the retinal architecture, making the interpretation of RNFL atrophy difficult, particularly when OCT testing is done in the absence of a detailed ophthalmic examination. Furthermore, it may be necessary to interrogate the entire afferent visual pathway to distinguish the effects of post-geniculate lesions, axonal attrition in the anterior visual pathway, and mild ON events when interpreting RNFL values.

On a practical level, the most important task on the horizon will be to determine whether longitudinal measurements of OCT in an individual MS patient is helpful in capturing disease activity and, potentially, in directing management. As our knowledge regarding the strengths and limitations of SD-OCT grows and the results of ongoing OCT studies become available, our understanding regarding the role of OCT in the treatment of ON and MS patients will continue to evolve.

REFERENCES


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<td><strong>Parisi</strong></td>
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<td>14 MS patients and 14 HCs</td>
<td>MSON eyes = 60μm (11); MS non-ON eyes = 83μm (11); HC eyes = 111μm (11)</td>
<td>RNFL thickness was significantly reduced in MSON eyes compared with HC eyes (p&lt;0.01) and MS non-ON eyes (p&lt;0.01). RNFL values were thinner in MS non-ON eyes relative to HC eyes (p&lt;0.01).</td>
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<td><em>(1999)</em></td>
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<td><strong>Trip</strong></td>
<td>OCT3</td>
<td>Cross sectional study</td>
<td>25 ON patients and 15 HCs</td>
<td>ON eyes = 69μm (19); non-ON eyes = 95μm (15); HC eyes = 103μm (15)</td>
<td>RNFL values were 33% lower in ON eyes compared to HC eyes (p &lt; 0.001). Macular volumes were 11% lower in ON eyes (p &lt; 0.001) compared to HC eyes.</td>
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<td><em>(2005)</em></td>
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<td><strong>Costello</strong></td>
<td>OCT3</td>
<td>Prospective case series</td>
<td>54 ON patients</td>
<td>ON eyes = 78μm (30); non-ON eyes = 100μm (33)</td>
<td>Mean RNFL was thinner (p &lt; 0.0001) in ON eyes compared to non-ON eyes. Regression analyses demonstrated a threshold of RNFL thickness (75μm) predicted visual recovery after ON.</td>
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<td><em>(2006)</em></td>
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<td><strong>Klistorner</strong></td>
<td>OCT3</td>
<td>Prospective cross sectional study</td>
<td>32 ON patients and 25 HCs</td>
<td>ON eyes = 85μm (15); HC eyes = 104 (9); Non-ON eyes = 104 (11)</td>
<td>There was a reduction (18.7%) in RNFL thickness and mfVEP amplitudes (39.8%) in ON eyes relative to HC eyes.</td>
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<td><em>(2008)</em></td>
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<td><strong>Henderson</strong></td>
<td>OCT3</td>
<td>Prospective cohort study</td>
<td>23 ON patients</td>
<td>ON eyes = 82μm (19); non-ON eyes = 101μm (12)</td>
<td>RNFL in ON eyes was increased at presentation and reduced at all later time points.</td>
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<td><em>(2010)</em></td>
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<tr>
<td>Study</td>
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<td>Outteryck</td>
<td>OCT3</td>
<td>Prospective case series</td>
<td>56 CIS patients</td>
<td>CIS eyes = 99µm</td>
<td>Mean RNFL thickness and MVs in CIS eyes were not different from HC eyes. No relationship was found between RNFL thickness or MV and conversion to MS at 6 months</td>
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<td></td>
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<td>and 32 HCs</td>
<td>(9); CDMS eyes = 102µm</td>
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<td>and MMS 98µm (12)</td>
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<tr>
<td>Fisher</td>
<td>OCT3</td>
<td>Cross Sectional Study</td>
<td>90 MS patients</td>
<td>MS eyes = 92µm</td>
<td>RNFL values were lower in MS eyes versus HC eyes ($p &lt; 0.001$). For every 1-line decrease in low-contrast letter acuity or contrast sensitivity score, RNFL values decreased by 4µm.</td>
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<td></td>
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<td>and 36 HCs</td>
<td>(16); MSON eyes = 85 (17)</td>
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<td>MS non-ON eyes = 96 (14);</td>
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<td>HC eyes = 105µm (12)</td>
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<td>Sepulcre</td>
<td>OCT3</td>
<td>2-year prospective study</td>
<td>61 MS patients</td>
<td>MS eyes = 86µm</td>
<td>Baseline temporal RNFL atrophy was associated with new relapses and changes in EDSS ($p &lt; 0.05$).</td>
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<td></td>
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<td>and 29 HCs</td>
<td>(14); HC eyes = 92µm</td>
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<td>Pulicken</td>
<td>OCT3</td>
<td>Cross sectional study</td>
<td>163 MS and 47 HCs</td>
<td>MS ON eyes = 84µm (15);</td>
<td>There were significant differences in RNFL thickness within quadrants of the peri-papillary retina comparing relapsing to progressive MS subtypes.</td>
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<td>HC eyes = 103µm (12);</td>
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<td>RRMS eyes = 94µm (15);</td>
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<td>PPMS eye = 89µm (13);</td>
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<tr>
<td>Henderson</td>
<td>OCT3</td>
<td>Cross sectional study</td>
<td>23 PPMS patients</td>
<td>PPMS eyes = 94µm (14);</td>
<td>In non-ON eyes, mean RNFL and macular volumes were significantly reduced in SPMS but not PPMS eyes compared to HC eyes. RNFL loss was most evident in the temporal sector, where significant decreases were observed in PPMS versus HCs and in SPMS versus PPMS patients.</td>
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<td>27 SPMS patients</td>
<td>SPMS eyes = 88µm (11);</td>
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<td></td>
<td>and 22 HCs</td>
<td>HC eyes = 98µm (11)</td>
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<tr>
<td>Costello (2009)</td>
<td>Prospective Cohort</td>
<td>35 CIS patients, 39 RRMS patients, and 7 SPMS patients</td>
<td>Mean RNFL values in non-ON eyes better distinguished MS subtypes than ON eyes. RNFL values did not change significantly for any MS subtype during the study.</td>
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<tr>
<td>Burkholder (2009)</td>
<td>Cross sectional</td>
<td>530 MS eyes and 111 HCs</td>
<td>In MS eyes lower MVs were associated with reduced RNFL values, such that a 10-µm difference in RNFL corresponded to a 0.20 decrease in MV.</td>
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<td>Siepman (2010)</td>
<td>Cross sectional</td>
<td>65 MS patients</td>
<td>RNFL values were lower in MS ON eyes relative to non-ON eyes (p &lt; 0.001). No RNFL differences were found between PPMS and “relapse-onset” MS.</td>
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<td>Talman (2010)</td>
<td>Prospective Study</td>
<td>299 MS patients</td>
<td>MS eyes with visual loss had greater RNFL loss than eyes without visual loss. RNFL thinning increased over time, with average losses of 2.9 µm at 2 to 3 years and 6.1 µm at 3 to 4.5 years (p &lt; 0.001 versus 0.5–1-year follow-up interval). Proportions of eyes with RNFL loss greater than test-retest variability (&gt;6.6 µm) increased from 11% at 0 to 1 year, to 44% at 3 to 4.5 years (p &lt; 0.001).</td>
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<td>Henderson (2010)</td>
<td>Prospective study</td>
<td>34 progressive MS patients and 18 HCs</td>
<td>No significant decrease in RNFL thickness was observed between baseline and follow-up in patients or HCs.</td>
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<td>Kitsos (2010)</td>
<td>Cross sectional</td>
<td>56 MS patients and 56 HCs</td>
<td>RNFL and perimetric scores were lower in non-ON eyes compared with HCs.</td>
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**Neuromyelitis Optica Studies**
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<td>Naismith (2009)</td>
<td>OCT3</td>
<td>Cross sectional study</td>
<td>22 NMO spectrum patients and 47 MS patients</td>
<td>MS eyes = 81 µm (19) and NMO eyes = 71 µm (26); MS ON eyes = 77 µm (2.4) and NMO ON eyes = 55 µm (3.7) After ON, NMO was associated with a thinner mean RNFL compared to MS. The superior and inferior quadrants were more severely affected in NMO than MS.</td>
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<tr>
<td>Nakamura (2010)</td>
<td>OCT3</td>
<td>Cross sectional study</td>
<td>18 NMO patients 14 MS patients</td>
<td>NMO ON eyes = 64 µm ; MSON eyes = 84 µm; NMO non-ON eyes = 106 µm (15); MS non-ON eyes = 110 µm (13) Mean RNFL was thinner in the NMO-ON group than in the MS-ON group (p=0.0006). The number of ON relapses and the time for beginning the treatment with high-dose IVMP significantly affected the preservation of the RNFL. A first episode of ON was estimated to cause 24 µm more loss of RNFL thickness in NMO than RRMS.</td>
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<tr>
<td>Ratchford (2009)</td>
<td>OCT3</td>
<td>Cross sectional study</td>
<td>26 NMO spectrum patients with ON, 17 patients with TM, 378 RRMS patients, and 77 HCs</td>
<td>NMO ON eyes = 64µm (20); RRMS ON eyes = 88µm (17); HC eyes = 102 µm (11.0)</td>
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**Spectral Domain OCT Studies**

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<td>Watson (2010)</td>
<td>OCT3; 3D OCT 1000; Cirrus OCT; RTVue-100, Heidelberg Spectralis</td>
<td>Cross sectional Study</td>
<td>46 ON/MS patients</td>
<td>Stratus: OD = 94µm (13); OS = 88 µm (15); 3D OCT 1000: OD = 96 µm (11); OS = 92 µm (12). Cirrus: OD = 86 µm (13); OS = 83 µm (14). RTVue 100: OD = 97 µm (13); OS = 92 µm (15). Spectralis: OD = 91 µm (15); OS = 85 µm (18). There were significant differences in RNFL thickness across instruments (p &lt; 0.001) for both eyes with different OCT techniques.</td>
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<td>Rebolleda (2010)</td>
<td>Cirrus OCT</td>
<td>Cross sectional study</td>
<td>18 ON patients</td>
<td>For TD-OCT median RNFL in ON eyes = 86 µm; non-ON eyes = 102 µm. For SD-OCT, ON eyes = 81 µm; non-ON eyes = 93 µm. The median signal strength was significantly higher with SD-OCT. TD-OCT RNFL measurements were larger than SD-OCT, but smaller when average RNFL thickness was very thin (&lt;56 µm).</td>
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<tr>
<td>Bock (2010)</td>
<td>OCT3 and Cirrus OCT</td>
<td>Cross sectional study</td>
<td>55 RRMS patients and 62 HCs</td>
<td>MS eyes = 93 µm (16) with TD-OCT and 85 µm (13) with SD-OCT. HC eyes = 103 µm (9) with TD-OCT and 95 µm (9) with SD-OCT. ON eyes = 86 µm MS eyes had lower RNFL values relative to HC eyes with both TD-OCT and SD-OCT (p &lt; 0.001). SD-OCT measured thinner than TD-OC, but correlation between the devices was strong (Pearson r = 0.93, p &lt; 0.001). However, owing to...</td>
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considerable differences in absolute RNFL measurements results from the two devices were not interchangeable.

Syc (2010)  Cirrus OCT  Prospective study  58 MS patients and 32 HCs  MS eyes = 82µm (14) ; HC eyes = 95 (11)  Excellent reproducibility of RNFL values, AMT, and MV was found for MS patients and HCs.

Khanifar (2010)  Heidelberg Spectralis  Retrospective case series  94 MS eyes  MS eyes = 89 µm ; ON eyes = 83 µm; non-ON eyes = 91µm  Decreased RNFL was associated with increased risk of ON. RNFL thickness was decreased in patients with a duration of MS greater than five years compared with those with a duration less than or equal to one year (p=0.008).

**Table legend:** OCT = “Generation” of optical coherence tomography used; Design = study design; Pt Pop = patient population; RNFL = mean retinal nerve fiber layer measurement in microns (µm); MV = macular volumes (mm³); ON eyes = optic neuritis affected eyes; non-ON eyes = the fellow eye of a patient with optic neuritis; CIS = clinically isolated syndrome patients; MS = multiple sclerosis; HC = healthy controls; VEP = visual evoked potentials; (SD) = standard deviation; CDMS = clinically definite MS; MMS = McDonald criteria proven MS; NMO = Neuro-myelitis optica; BCVA = best –corrected visual acuity; TD-OCT = time domain OCT; SD-OCT = spectral domain OCT; IVMP = intravenous methyl-prednisolone; TM = transverse myelitis; AMT = average macular thickness;
References:


fibre layer in progressive multiple sclerosis using optical coherence tomography. 

11. Costello F, Hodge W, Pan YI, Freedman M, and DeMeulemeester C. Differences in 
retinal nerve fiber layer atrophy between multiple sclerosis subtypes. J Neurol Sci. 
2009; 281:74–79.

optical coherence tomography as a measure of neuronal loss in multiple sclerosis. 

13. Siepman TA, Bettink-Remeijer MW, Hintzen RQ. Retinal nerve fiber layer thickness 
in subgroups of multiple sclerosis, measured by optical coherence tomography and 


the retinal nerve fiber layer in progressive multiple sclerosis. J Neurol. 2010; 16: 46 – 
52.

and peri-papillary nerve fiber layer thickness findings in multiple sclerosis. Eur J 


