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Abstract: PURPOSE OF REVIEW Optical coherence tomography (OCT) is a noninvasive in-vivo imaging tool that enables the quantification of the various retinal layer thicknesses. Given the frequent involvement of the visual pathway in multiple sclerosis, OCT has become an important tool in clinical practice, research and clinical trials. In this review, the role of OCT as a means to investigate visual pathway damage in multiple sclerosis is discussed. RECENT FINDINGS Evidence from recent OCT studies suggests that the peripapillary retinal nerve fibre layer (pRNFL) appears to be an ideal marker of axonal integrity, whereas the macular ganglion cell and inner plexiform layer (GCIP) thickness enables early detection of neuronal degeneration in multiple sclerosis. The thickness of the macular inner nuclear layer (INL) has been suggested as a biomarker for inflammatory disease activity and treatment response in multiple sclerosis. OCT parameters may also be used as an outcome measure in clinical trials evaluating the neuroprotective or regenerative potential of new treatments. SUMMARY OCT provides insights into multiple sclerosis beyond the visual pathway. It is capable of quantifying the major pathological hallmarks of the disease, specifically inflammation and neuroaxonal degeneration. OCT, therefore, has the potential to become another mainstay in the monitoring of multiple sclerosis patients.

DOI: https://doi.org/10.1097/WCO.0000000000000604

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Optical coherence tomography (OCT) is a noninvasive in-vivo imaging tool that enables the quantification of the various retinal layer thicknesses. Given the frequent involvement of the visual pathway in multiple sclerosis, OCT has become an important tool in clinical practice, research and clinical trials. In this review, the role of OCT as a means to investigate visual pathway damage in multiple sclerosis is discussed.

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Evidence from recent OCT studies suggests that the peripapillary retinal nerve fibre layer (pRNFL) appears to be an ideal marker of axonal integrity, whereas the macular ganglion cell and inner plexiform layer (GCIP) thickness enables early detection of neuronal degeneration in multiple sclerosis. The thickness of the macular inner nuclear layer (INL) has been suggested as a biomarker for inflammatory disease activity and treatment response in multiple sclerosis. OCT parameters may also be used as an outcome measure in clinical trials evaluating the neuroprotective or regenerative potential of new treatments.

Summary
OCT provides insights into multiple sclerosis beyond the visual pathway. It is capable of quantifying the major pathological hallmarks of the disease, specifically inflammation and neuroaxonal degeneration. OCT, therefore, has the potential to become another mainstay in the monitoring of multiple sclerosis patients.

Keywords
afferent visual pathway, low-contrast visual acuity, multiple sclerosis, optic neuritis, optical coherence tomography

INTRODUCTION

Multiple sclerosis is the most common chronic inflammatory demyelinating disorder of the central nervous system (CNS) and the main cause of non-traumatic neurological disability in young adults [1]. Inflammation, demyelination and neurodegeneration are key pathological features of multiple sclerosis [2]. Neuroaxonal damage occurs even in the earliest stages of the disease, as demonstrated in clinically isolated syndrome (CIS), and is responsible for persistent neurological disability [3–6]. Despite a heterogeneous clinical presentation, impaired vision is a frequent symptom and among the most common early manifestations of the disease [7,8], with 21% of CIS patients presenting with optic neuritis [7]. Optic neuritis represents the most frequent involvement of the afferent visual pathway (AVP) in multiple sclerosis, causing neuroaxonal damage of the optic nerves and retina leading to chronic functional impairment [9]. A recent study showed that visual function is rated by multiple sclerosis patients as their most important bodily function, independently of disease duration or disability [10]. However, involvement of the optic nerve even in the absence of a clinical history of optic neuritis has frequently been found in multiple sclerosis [11–13]. The AVP has been proposed as an ideal model to study both neurodegeneration and repair in multiple sclerosis, because of its retinotopic

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Curr Opin Neurol 2018, 31:000–000
DOI:10.1097/WCO.0000000000000604

KEY POINTS

- In recent years, OCT has become an important tool in both multiple sclerosis research and multiple sclerosis clinical practice.
- OCT enables the quantification of neuroaxonal damage and inflammatory disease activity within the retina of multiple sclerosis patients.
- Multiple sclerosis patients develop significant inner retinal atrophy during their disease course, regardless of whether they experience an episode of optic neuritis.
- OCT measurements show that neuroaxonal retinal damage develops rapidly in multiple sclerosis and correlates negatively with visual performance, disability and quality of life.
- Retinal OCT can assist in clinical multiple sclerosis management, specifically with diagnosis, monitoring and prognosis of individual multiple sclerosis patients.

organization throughout (ensuring that anatomical structure is linked to corresponding visual function) and anatomical discreteness [14]. Optical coherence tomography (OCT) permits the assessment and quantification of the retinal layers by generating a high-resolution cross-sectional view of the retina [15]. The use of OCT in both research and clinical practice, plays an important role in monitoring the integrity of the retinal architecture, and also in gaining a better understanding of the process of neuronal degeneration following optic neuritis.

OPTICAL COHERENCE TOMOGRAPHY

OCT generates tomographic, two-dimensional in-vivo images of the retina using low-coherent, near-infrared light. It is rapid, noninvasive, well tolerated, cost-effective and reproducible [15,16]. Contemporary spectral-domain OCT (SD-OCT) technology allows the visualization of the neural retina with an axial resolution in the range of 3–6 μm [17,18]. Two of the most common scan protocols are the optic nerve head (ONH) and macular volume scans. The ONH scan (also described as the peripapillary ring scan) generates circular two-dimensional B-scans centred on the optic disc. This protocol facilitates measurement of the thickness of the peripapillary retinal nerve fibre layer (pRNFL) around the ONH [19,20]. Scan quality control should be performed, for example, according to the OSCAR-IB consensus criteria [21,22]. As the pRNFL contains unmyelinated axons of the retinal ganglion cells (RGCs), a thickness reduction most likely reflects axonal thinning or loss rather than loss of myelin, rendering the pRNFL an ideal marker of axonal damage [23,24▪]. The macular volume scan consists of two-dimensional B-scans centred over the fovea from which a three-dimensional image of the central retina is extrapolated. For post-processing, the macula is divided into sectors according to the ETDRS (Early Treatment of Diabetic Retinopathy Study) grid [25]. Current SD-OCT devices typically ship with proprietary software, which delineates the borders of the retinal layers (a process known as 'automated segmentation') and calculates the thicknesses and volumes of the individual retinal layers (Fig. 1). Manual verification and, if necessary, correction of the automated segmentation is recommended in order to ensure accuracy [26]. As the boundary between the macular ganglion cell layer (GCL) and inner plexiform layer (IPL) is difficult to accurately distinguish, the two layers are often combined for analysis as the macular ganglion cell and inner plexiform layer (GCIP). pRNFL, total macular volume (TMV), and, more recently, GCIP and the inner nuclear layer (INL) appear to be the most widely studied retinal layers in multiple sclerosis research. Reductions in GCIP thickness are assumed to reflect primarily thinning of the GCL and, thus, atrophy of the cell bodies of the RGCs; GCIP thickness is, therefore, used as a biomarker for neurodegeneration within the retina [24▪,27]. The INL consists of the amacrine, bipolar and horizontal cells as well as the cell bodies of the Müller cells, the most abundant glial cell of the retina [28]. In recent years, researchers have proposed the INL as a biomarker for inflammation in multiple sclerosis [24▪,29▪▪]. Together, the peripapillary ring scan and the macular volume scan permit a comprehensive overview of the retina and retinal disease [30]. In recent years, crucial efforts were made to provide standardized acquisition protocols, guidance for quality control and recommendations for reporting, resulting in a substantial improvement of research [21,22,31].

CHARACTERIZING VISUAL PATHWAYWAY INVOLVEMENT WITH OPTICAL COHERENCE TOMOGRAPHY

Pathological OCT findings may be because of various underlying aetiologies. The following section summarizes the most important pathological OCT findings associated with multiple sclerosis.

Optic neuritis

Acute optic neuritis is an inflammatory, demyelinating event affecting the optic nerve, and is frequently associated with multiple sclerosis [8].

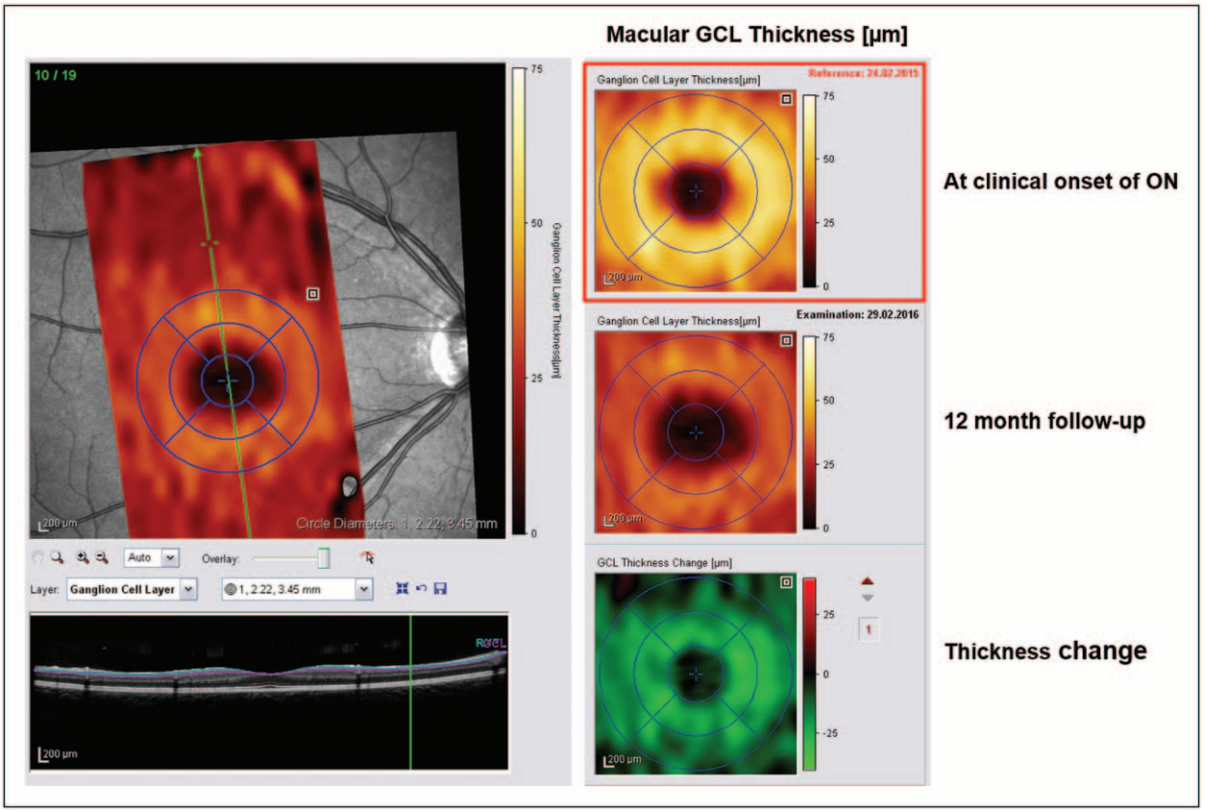

FIGURE 1. Optical coherence tomography-derived macular ganglion cell layer thickness (µm) for the right eye of a multiple sclerosis patient. Left: for postprocessing the macula is divided into sectors according to the ETDRS grid. Right: shown is a typical case of macular GCL atrophy following an episode of optic neuritis: Baseline macular GCL thickness is in a normal range at clinical presentation of optic neuritis, displayed on the thickness map by the yellowish colour, but shows an apparent decrease in its thickness at the 12-month follow-up examination, illustrated by the dark reddish colour. The bottom image shows the change of GCL thickness between the two examination timepoints. ETDRS, Early Treatment of Diabetic Retinopathy Study; GCL, ganglion cell layer; OCT, optical coherence tomography.

Twenty to 25% of all multiple sclerosis patients manifest with acute optic neuritis as their clinical index event, whereas up to 70% of patients are affected at some point during their disease course [8,32]. Acute onset of unilateral retrobulbar pain upon eye movement, reduced vision, colour desaturation and visual field defects are typical symptoms suggestive of optic neuritis [33]. Symptoms worsen over days or weeks, followed by partial recovery over a period of months. A recent study suggests that patients are frequently left with persistent visual impairment, in particular, affecting low-contrast visual acuity (LCVA), colour vision and visual quality of life [National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25)] [34▪▪]. The pathophysiology of acute optic nerve lesions resembles that of multiple sclerosis brain lesions, where inflammatory demyelination is predominantly mediated by autoreactive T cells, with involvement from B cells, microglia and antibodies [35]. In approximately one-third of optic neuritis patients, acute inflammation is also present in the retina around the ONH, as evidenced by an initial increase in pRNFL thickness, most likely reflecting inflammatory oedema [36]. Resolution of this oedema over time may mask concurrent pRNFL thinning. The current mechanistic understanding is that alongside inflammatory demyelination, the optic nerve suffers from axonal damage. This results in retrograde degeneration from the retrobulbar optic nerve towards the ganglion cell bodies of the retina [37]. Using OCT, retrograde degeneration can be visualized in a reduction of pRNFL and GCIP thickness [23,27]. Two important prospective longitudinal studies found a progressive decline of pRNFL thickness over 12 months following optic neuritis, with most of the reduction occurring within the first 3 months post-onset [38,39]. Similar results were found for the macular GCIP thickness [39]. Importantly, as opposed to pRNFL, measures of macular GCIP are usually uncontaminated by inflammatory oedema and degeneration of retinal neurons is detectable as early as 1 month after optic neuritis onset [39]. The rate of atrophy becomes lower with

longer disease duration, suggestive of a plateau effect [40]. Optic neuritis also appears to affect outer retinal layers, namely the INL, outer plexiform layer (OPL), outer nuclear layer (ONL) and photoreceptor complex, suggesting trans-synaptic alterations [41]. These outer retinal layers exhibit thickening rather than thinning, which may indicate outer retinal inflammation [41].

Although optic neuritis is frequently associated with multiple sclerosis, there are many other possible causes of optic neuritis. Among the various differential diagnoses, neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein (MOG)-antibody-associated optic neuritis are of particular importance [42]. Signs suggestive of atypical non multiple sclerosis-related optic neuritis include painless or very painful onset, simultaneous bilateral involvement, severe or complete visual loss with poor recovery, or haemorrhages and exudates detectable on fundoscopy [42].

Microcystic macular oedema

Microcystic macular oedema (MME) can be observed in around 5% of patients with multiple sclerosis and present as discrete, cyst-like spaces restricted to the INL [43,44]. Various causes have been proposed, including a disruption of the blood–retinal barrier [44]. The prevalence of MME is higher in eyes with, but can also be found in eyes without, a history of optic neuritis [43].

Primary retinal pathology

Saidha *et al.* [45] described a subset of multiple sclerosis patients with a novel OCT-defined phenotype characterized by normal pRNFL thickness but reduced macular thickness (with disproportionate thinning of the INL and ONL) when compared with other multiple sclerosis patients and healthy controls, unattributable to retrograde degeneration, and interpreted as evidencing primary retinal disease. Using electroretinography (ERG) and OCT, we recently showed evidence of bipolar cell and photoreceptor dysfunction (located in the INL and ONL, respectively) in the absence of corresponding structural changes and independent of optic neuritis [46▪]. The ERG findings are corroborated by You *et al.* [47] in a cohort without previous optic neuritis. Together, these findings support the idea of primary retinal abnormalities in multiple sclerosis patients.

Posterior visual pathway pathology

In multiple sclerosis patients without prior optic neuritis, pRNFL thinning is associated with atrophy of the optic radiations and primary visual cortex as assessed by MRI. Authors have interpreted that lesions in the posterior visual pathway may result in a thinning of the pRNFL by trans-synaptic (via the lateral geniculate nucleus of the thalamus) retrograde axonal degeneration, however, this needs to be verified by more mechanistic studies [48–50]. In eyes without prior optic neuritis, it has been proposed that posterior visual pathway pathology accounts for as much as 35–40% of pRNFL thinning [50,51]. Conversely, optic nerve disease may also result in trans-synaptic anterograde degeneration, affecting parts of the posterior visual pathway, as indicated by more severe visual cortex atrophy in multiple sclerosis patients with a previous history of optic neuritis [48,52].

CLINICAL RELEVANCE OF OPTICAL COHERENCE TOMOGRAPHY FINDINGS IN MULTIPLE SCLEROSIS

In order to validate the utility of OCT as a clinical and research tool in multiple sclerosis, the functional relevance and implications of the structural retinal changes discussed above is of critical importance. There is a significant body of evidence showing that OCT outcomes are associated with both visual and overall disability, disease activity, and, increasingly, response to treatment in multiple sclerosis [29▪▪,53,54].

Firstly, measures of visual performance including visual acuity, colour vision and perimetry have been shown to correlate with the thicknesses of the pRNFL and even more strongly with the thickness of the macular GCIP [53,55–58]. In particular, LCVA has been shown to strongly correlate with OCT outcomes, and is probably the most sensitive measure to capture visual dysfunction following optic neuritis [59▪]. The importance of LCVA monitoring becomes obvious when considering the higher prevalence of residual low contrast as opposed to high-contrast visual functional impairment following optic neuritis [59▪]. Moreover, a study with optic neuritis patients demonstrated that the GCIP and pRNFL thickness changes within the first month following optic neuritis onset could predict visual recovery, measured by LCVA and colour vision, at month 6 [34▪▪]. Visual recovery after optic neuritis tends to be better in women than men and may also be associated with serum vitamin D levels [38,60].

A significant relationship between OCT parameters and electrophysiological tests such as the visual evoked potential (VEP) and ERG has been observed in multiple sclerosis [61]. VEP and ERG examinations are performed in order to quantify the cortical (VEP) and retinal (ERG) response to precisely defined visual stimuli [62].

The Expanded Disability Status Scale (EDSS), widely used to assess multiple sclerosis-related disability, is weighted towards motor impairment and problems with gait, whereas visual functional deficits are highly underrepresented [63]. Despite this, studies of multiple sclerosis patients without previous optic neuritis have found that a pRNFL thickness value below a certain threshold (varying by OCT device), measured at any given timepoint in the disease, was predictive of a more severe disability progression (as measured by EDSS) relative to those patients with greater pRNFL thickness [54]. Further, a strong relationship between cognitive impairment and atrophy of the pRNFL and macular GCIP has been found [64]. Additionally, a reduction in quality of life is associated with a reduction in the thickness of the pRNFL [65].

Likewise, the presence of MME has been associated with disease severity in multiple sclerosis patients [43,44]. It has been suggested that an increase in INL thickness, with or without visible MME, may be reflective of inflammatory disease activity in multiple sclerosis [44]. Patients with relapsing–remitting multiple sclerosis, who had relapses or new gadolinium-enhancing lesions during a 3-year follow-up period, had higher baseline INL thicknesses compared with patients who did not have relapses [44]. Knier *et al.* [29▪▪] recently reported that INL thickness was greater in untreated multiple sclerosis patients than healthy controls, and that patients responding to immune therapies show a normalization of INL thickness, indicating a reduction in inflammatory disease activity. As a result, the INL has gained significant interest as a possible biomarker for treatment response [29▪▪]. Subsequent findings from the same centre show an association between INL volume and prospective MRI activity (T2 lesion load and number of gadolinium-enhancing lesions) [66▪], providing further evidence for the emerging importance of the INL in multiple sclerosis.

In addition, several studies have shown that injury in the AVP reflects global CNS damage in multiple sclerosis that can be quantified using MRI [67–69]. Currently, MRI is the mainstay of diagnosis and monitoring of multiple sclerosis and the most accepted surrogate marker of disease progression. pRNFL thinning has been shown to be associated with whole-brain atrophy [67,68]. Furthermore, Saidha and colleagues have found that GCIP atrophy reflects grey matter atrophy over time, an important measure of disease progression [69–71]. However, MRI is expensive and time-consuming. As a sensitive, accurate, rapid and cost-effective tool, OCT provides an excellent complement to MRI for monitoring CNS integrity in patients with multiple sclerosis.

Consequent to the remarkable development of OCT technology over recent years, particularly with regard to retinal layer segmentation, OCT may be helpful in the characterization of pathologically distinct multiple sclerosis phenotypes. For example, patients exhibiting primary retinal pathology have been proposed to have an aggressive form of multiple sclerosis, characterized by more rapid disability progression [45], as have patients with MME [43]. Consideration of disease phenotype, stage, activity and progression of individual patients is important for optimal disease management and OCT will increasingly play a vital role in the assessment and management of these patients.

Inner retinal layer (RNFL; GCIP) changes are already detectable in CIS patients not yet diagnosed with multiple sclerosis but presenting with a first clinical event suggestive of multiple sclerosis [6]. Hence, OCT may potentially aid the early detection of at-risk patients and facilitate early diagnosis of multiple sclerosis. As irreversible axonal and neuronal injury can occur even in the earliest stages of multiple sclerosis, early detection and treatment is a high priority [72].

Moreover, differential diagnosis is of great importance; for instance, the prognosis and treatment of optic neuritis depends strongly on the underlying cause [8]. Optic neuritis associated with AQP4-seropositivity has been associated with a more severe clinical outcome, as have some (but not all) cases of MOG-seropositive optic neuritis [73]. Early diagnosis and appropriate treatment are paramount to avoid severe functional sequelae, including blindness, which further emphasizes the utility of OCT in patients with acute optic neuritis [74–76].

During recent years, OCT measures have been proven as appropriate outcome measures in multiple sclerosis clinical trials, often in combination with LCVA and other clinical measures [77]. In particular, optic neuritis has been proposed as a unique clinical model to study the potential of neuroprotective and neurodegenerative therapies. The thickness of the pRNFL may serve as a robust long-term axonal outcome measure, whilst the thickness of the macular GCIP is considered an early measure of neuronal integrity [24▪,78▪,79]. Results from recent longitudinal OCT studies focusing on the timing of neuroaxonal loss in multiple sclerosis may have important implications for future clinical trial planning, in particular, with regards to the timing of treatment intervention. As atrophy is most pronounced at early stages of the disease course, early or even hyperacute intervention may be the most promising strategy to prevent irreversible neuroaxonal degeneration [40,78▪].

CONCLUSION

OCT has been validated as a reliable tool for quantifying the major pathological hallmarks of multiple sclerosis disease: inflammation, axonal loss and neuronal degeneration [8,24▪,28,80]. OCT has the potential to become a mainstay in the monitoring of multiple sclerosis patients as it may provide important complementary information to MRI, thereby assisting in the clinical decision-making process. OCT may also be used as an outcome measure in clinical trials of new compounds with neuroprotective and neuroregenerative potential.

Acknowledgements

None.

Financial support and sponsorship

C.A.W. has received a travel grant from Teva. J.V.M.H. is supported by the Clinical Research Priority Program of the University of Zurich and has previously received travel support and speaker fees from Biogen. S.S. is supported by the Swiss National Science Foundation (S-86012-01-01), the Myelin Repair Foundation, the Clinical Research Priority Program of the University of Zurich and the Swiss multiple sclerosis Society.

Conflicts of interest

There are no conflicts of interest.

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- ▪▪ of outstanding interest

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