# Optical Coherence Tomography – A New Monitoring Tool for Multiple Sclerosis?

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## Abstract

Optical coherence tomography (OCT) is a simple office-based measure that can be used to quantify changes in the retina in patients with multiple sclerosis (MS). Such retinal changes in some MS patient subgroups, as assessed by OCT, are associated with brain atrophy as detected by magnetic resonance imaging (MRI). There is also some evidence that changes detected by OCT are correlated with increasing levels of cognitive impairment. OCT in MS patients introduces a new tool to characterise the disease process and could prove beneficial in the assessment of new therapies. It may provide information additional to that produced by MRI. For example, the use of OCT to quantify the retinal nerve fibre layer may offer some advantages by detecting neural degeneration in the MS disease process more quickly, cheaply and specifically than MRI. The latest OCT equipment and software offer high reproducibility and improve accuracy due to eye-tracking and follow-up scan capabilities.

## Keywords

Optical coherence tomography, retinal nerve fibre layer, multiple sclerosis, axonal loss, optic neuritis

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Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS) with inflammatory demyelinating lesions and neuronal loss that is clinically characterised by unpredictable clinical relapses, remissions and progression of disability over time.[1–3] Damage occurs to the myelin sheath that surrounds and protects nerve cells; this slows down or blocks messages between the brain and the body, leading to the symptoms of MS. The disease usually begins with one or more clinically isolated syndrome (CIS) leading to a relapsing–remitting phase (RRMS) that is accompanied by a varying degree of impairment.[2] After 10–15 years, approximately 50% of these patients advance to the secondary progressive form of the disease, which is characterised by a slow but progressive decline in performance with or without superimposed relapses.[4,5] Approximately 10–15% of MS patients show progression from the onset (primary progressive MS [PPMS]).[6,7] Symptoms are highly heterogeneous from one patient to another. More recently, our attention has been focused on the non-physical symptoms such as fatigue and cognitive symptoms.[8–11]

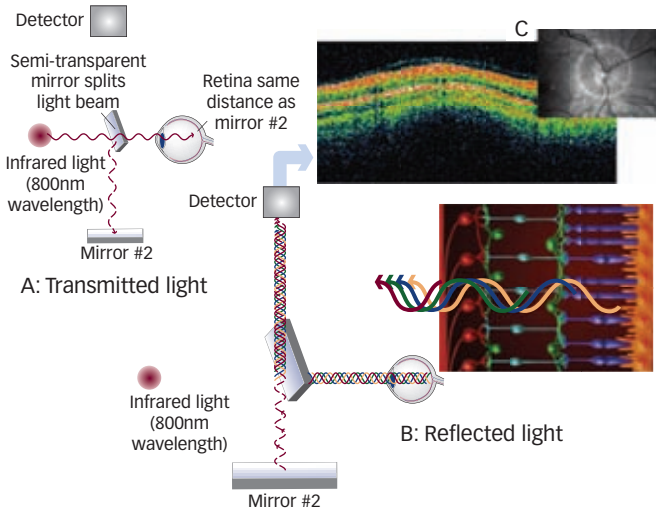
Despite significant advances in treatment, MS remains a highly disabling disease, and in many cases significantly reduces life expectancy.[12] Recent studies have shown that initiating treatment early with a disease-modifying drug, possibly during CIS, can provide significant advantages over delaying it until symptoms are more apparent. This has generated much interest and has modified treatment practices in MS.[13,14] However, some neurologists have questioned the long-term benefit of treating everyone with CIS, suggesting that in some cases the disease will not progress and that greater investigation of patients is warranted before starting more appropriately tailored therapies.[15]

Acute idiopathic demyelinating optic neuritis (ON) is a frequent early manifestation of MS that is often indicative of early disease and can be predictive of later progressive stages.[16] Optical coherence tomography (OCT) is an evolving technique that has the potential not only to diagnose ON but also to provide a valuable assessment of MS.[17] This review will consider the evidence for using OCT in patients with ON and its potential role as a tool for routinely monitoring MS.

## The Role of Magnetic Resonance Imaging in Multiple Sclerosis

Magnetic resonance imaging (MRI) has revolutionised the diagnosis of MS and greatly facilitated our understanding of MS. Diagnostic criteria based on both clinical and MRI findings have been proposed and have been adopted by many treatment centres.[18] The presence of MRI lesions at symptom onset was found to be correlated with the development of clinically definite MS (CDMS). In patients with one or more $T_2$-weighted lesion at baseline, 56% developed MS within 10 years.[19] Neurological damage starts before symptoms become apparent. The presence of gadolinium (Gd)-enhancing lesions generally indicates current disease activity and is used as one of the key criteria for the assessment of the effectiveness of a new drug. Other key MRI variables include $T_2$ lesion load, indicating the global burden of the disease, and $T_1$ lesion load (black holes). The Gd-enhancing lesions and $T_2$ lesion load are considered to be related to the degree of inflammation and provide an approximation of the demyelinating component of the disease, whereas the black holes and brain and spinal cord atrophy are more related to the degenerative component of MS.[20] However, MRI is an imperfect tool that measures the results of many types of tissue loss rather than

**Figure 1: High-resolution Images of the Internal Retinal Structure Taken with Optical Coherence Tomography**




*A: Low-coherence infrared light is transmitted into the eye through use of an interoferometer. B: The infrared light is transmitted through the pupil and then penetrates through the nine transparent layers of the retina. C: A fundus image from the optical coherence tomography (OCT) device showing the optic disc appropriately centred and surrounded by the target image circumference marker for analysis of the retinal nerve fibre layer.*
*Source: Frohman et al., 2008.*[34]

specifically nerve damage itself. Furthermore, extensive lesions and brain shrinking occur relatively late in the progression of the disease and this can be confounded by inflammation in MS that may increase overall volume. MRI is therefore not a good tool for the detection of MS in its early stages. There is an urgent need for tools able to detect axonal loss early. In addition, MRI facilities are expensive and require expertise and considerable resources to operate, and are mostly confined to specialist centres. MRI investigation is thus not readily available to patients with MS in many locations, and for some people scanning can be an unpleasant procedure.

## Optic Neuritis in Multiple Sclerosis

The visual system is often affected in MS and, as the retina is an integral part of the central nervous system (CNS), examination of the eye enables unmyelinated axons of the CNS to be visualised directly. ON is inflammation with accompanying demyelination in the optic nerve that may cause complete or partial loss of vision. It is frequently the initial clinical manifestation of MS and is reported in 94–96% of MS autopsy cases.[21] Although there is a broad age range at onset, most patients with acute demyelinating ON are young (20–45 years of age).[22,23] There is a gender difference: women are three times as likely as men to develop ON.[22] A patient with typical demyelinating ON usually experiences a decline in vision over a seven- to 10-day period, often characterised by a decline in contrast sensitivity.[24] The progression of visual loss beyond two weeks is distinctly unusual and visual acuity usually recovers well.

In the Optic Neuritis Treatment Trial (ONTT),[25] which investigated the use of corticosteroids to treat a population of 448 patients with ON, the majority (92%) of patients had pain, particularly with eye movements. In a patient with typical ON, some recovery of vision should occur within 30 days of onset. Clinical features that suggest non-typical ON include the presence of retinal haemorrhages, a markedly swollen nerve, retinal exudates, the absence of pain and the presence of no light-perception vision at onset. These patients have a lower risk of developing MS, particularly when their baseline MRI scan is normal.[19] Approximately 50–80% of patients with ON have periventricular white-matter abnormalities consistent with demyelination on an initial MRI scan.[26]

In the ONTT, 10 years after acute ON the presence or absence of MRI lesions was the main factor in determining the risk of MS:[19] 56% of patients with one or more white-matter lesion on their baseline brain MRI scan developed MS, whereas 22% of patients with a normal baseline MRI developed MS at 10 years. The presence of oligoclonal bands in the CSF is also an independent risk factor for MS.[27] Subclinical or chronic forms of demyelinating ON in which the patient notices a gradual decline in vision instead of acute vision loss followed by improvement may also develop in MS. These patients may show abnormalities on neuro-ophthalmological examination, including field loss, pupillary abnormalities and disc pallor.[28] Subclinical ON can be sensitively detected using lower-contrast letter acuity testing.[29] ON and other visual defects contribute significantly to the reduction in quality of life of MS patients.[30]

In patients with acute ON, treatment with a three-day course of high-dose (1g/day) intravenous corticosteroids is usually recommended. The ONTT used three treatment groups: intravenous methylprednisolone for three days followed by an oral prednisone taper; oral prednisone; and oral placebo.[31] The use of oral corticosteroids was associated with an increased risk of recurrent ON five years after an initial bout of ON; patients who received oral prednisone (1mg/kg) had the highest rate of recurrence (41%) compared with those who received methyl-prednisolone or placebo (25% for both groups). However, there was no significant difference in the long-term risk of MS.

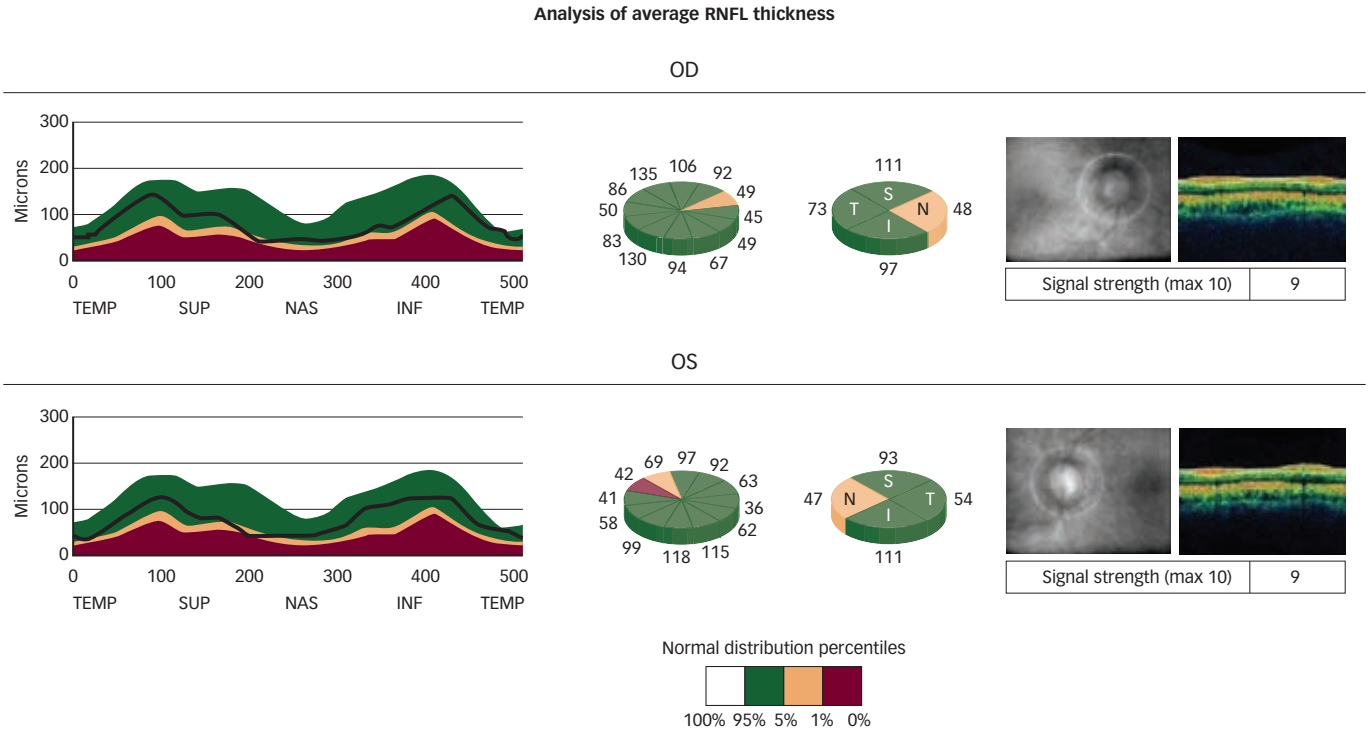
## Optical Coherence Tomography

One of the most exciting developments in ophthalmic imaging is arguably OCT, which was introduced in 1991[32] and has been a part of clinical practice since 1995.[33] OCT is widely used to obtain high-resolution images of the retina and the anterior segment of the eye. *Figure 1* provides a summary of the operation of OCT. OCT creates images by reflecting laser light on the retina to generate a cross-sectional image. The extent of the reflectivity differs between cell types in retinal layers. OCT measures retinal nerve fibre layer (RNFL) thickness utilising interferometry – the technique of determining the properties of two waves by analysing the pattern of interference created by their superposition.[34] The light source is a super-luminescent diode. OCT captures cross-sectional images from a series of lateral adjacent depth-scans. OCT therefore determines overall thickness and quadrant thicknesses in different pathological conditions including ON or MS and compared with normative values (see *Figure 2*). OCT has the advantages of being non-invasive, easy to use and quantitative. Its sensitivity allows direct visualisation and measurement of RNFL thickness and macular volume with micron-scale resolution (see *Figure 3*).[35,36] The latest technical improvements, such as higher resolution (between 2 and 3µm) and dual laser beams to overcome eye movements, have enabled these instruments to gain a high clinical utility in predicting MS disease course and determining treatment response.[33,37]

## Optical Coherence Tomography Studies in Optic Neuritis and Multiple Sclerosis

Among patients with ON, optic nerve atrophy has often been detected by MRI.[38–40] In a study in the UK including 10 patients with a history of ON, a correlation was found between the mean loss of

**Figure 2: Example of a Patient with a History of Left Optic Neuritis with Complete Recovery**



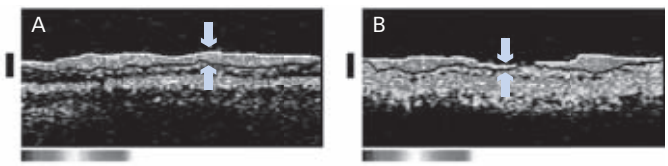

| | OD (n=1) | OS (n=1) | OD – OS |
|---|---|---|---|
| $I_{max}/S_{max}$ | 0.98 | 1.00 | -0.02 |
| $S_{max}/I_{max}$ | 1.02 | 1.00 | 0.02 |
| $S_{max}/T_{avg}$ | 1.97 | 2.26 | -0.29 |
| $I_{max}/T_{avg}$ | 1.93 | 2.26 | -0.32 |
| $S_{max}/N_{avg}$ | 3.02 | 2.59 | 0.42 |
| Max – min | 104.00 | 90.00 | 14.00 |
| $S_{max}$ | 144.00 | 122.00 | 22.00 |
| $I_{max}$ | 141.00 | 122.00 | 19.00 |
| $S_{avg}$ | 111.00 | 93.00 | 18.00 |
| $I_{avg}$ | 97.00 | 111.00 | -14.00 |
| Avg. thickness | 82.16 | 76.19 | 5.97 |

*Circle with different quadrants next to the picture of the optic disc of the left eye shows one quadrant (nasal–superior) with retinal nerve fibre layer (RNFL) thicknesses in the lowest first percentile for age (red). The nasal quadrant of the right quadrant (N, yellow) is slightly but significantly thicker compared with controls. Normal values are expressed in green. The table gives the quantitative values of all quadrants. The last column of the table gives the difference between the eyes. N = nasal quadrant; OD = right eye; OS = left eye; S = superior quadrant; T = temporal quadrant.*
*Source: Carl Zeiss, Stratus.*

cross-sectional area of the optic nerve and changes in the amplitude of visual-evoked potential (VEP), implicating axonal loss in this progressive atrophy.[39] In ON and MS, axonal loss is an early pathological feature despite clinical recovery and lack of clinical symptoms. Even in the absence of a history of ON, the eyes of patients with MS have reduced numbers of retinal ganglion cell axons in pathological studies.[21]

Axonal degeneration in the RNFL of patients with MS, as observed in ophthalmoscopic studies, is detectable in some patients before any visual signs or symptoms of ON have appeared, and has been associated with electrophysiological abnormalities as measured with visual-evoked response testing.[41] More recent evidence also supports axonal loss as an early event in the clinical course of MS,[42] and optic nerve atrophy is detectable with MRI within months after a single episode of ON. Recent studies using OCT provide direct evidence that patients with only partial recovery from a single ON episode were found to have significantly reduced RNFL thickness compared with healthy controls. This reduction correlated with the loss of visual acuity. Thinning of the RNFL in these patients was also shown to be significantly correlated with optic nerve atrophy, detected by MRI as reduced optic nerve cross-sectional area.[40,43] Even patients with MS but without a history of ON have been shown to have reduced RNFL thickness compared with healthy controls.[44] Visual function correlated

**Figure 3: Representative Optical Coherence Tomography Retinal Nerve Fibre Layer Scan Results from a Normal Subject (A) and a Patient with Band Atrophy (B)**




*The arrows delineate the retinal nerve fibre layer.*
*Source: Monteiro et al., 2004.*[35]

well with RNFL thickness in patients with MS: every one-line decrease in low-contrast letter acuity and contrast sensitivity test score was associated with an average 4µm thinning of the RNFL.[44]

Some correlations have been shown between RNLF thickness and disease characteristics. In one study RRMS patients who experienced relapses or a disability progression had a significantly thinner average RNLF compared with patients who remained relapse-free over a two-year period.[45] Lower average RNFL thickness was correlated with patients with more active disease and greater Expanded Disability Status Scale (EDSS) at baseline and greater increase of EDSS over two years. The correlations are better in the temporal quadrant.[46] Correlations have also been found between RNFL thickness and performance on some tests of cognitive function in MS patients, particularly the symbol digit modality test.[45] Despite some conflicting results, longitudinal studies have shown a progressive thinning of RNLF thickness over time, with lower values in progressive MS than in RRMS.[47] In patients with CIS who had no history of ON, our group in Lille failed to find significant differences in RNLF thickness, and changes did not increase the risk of conversion to MS after a six-month period of follow-up.[48] However, our analysis was not performed using the latest technical methods. Since RNLF thickness may be associated with the degenerative component of MS, OCT measurements and atrophy of the brain, assessed using the brain parenchymal fraction (BPF), were compared. This identified a partial but significant correlation between BPF and minimum RNLF thickness, and the correlation was stronger in RRMS than in PPMS patients.[49,50] Determination of axonal thickness in the retina by OCT can therefore provide concurrent information about MRI brain abnormality in MS.

The reliability of OCT in MS was demonstrated in a study in the US. A total of 396 patients with MS and 153 healthy controls were assessed using OCT at three different medical centres; the results showed excellent inter- and intra-rater reproducibility (intra-class correlation [ICC] 0.89 and 0.98, respectively).[51] In addition, there was excellent inter-visit correlation (ICC 0.91). These results indicated that OCT can be reliably performed at different centres to assess MS patients and can be performed by different operators at different times, with the results remaining comparable.

The feasibility of using OCT as an alternative to MRI scanning for monitoring the effects of glatiramer acetate versus placebo treatment on the condition of the optic nerve is being assessed in a study in The Netherlands.[52] This study will involve a target 60 patients with clinically diagnosed MS with or without ON, and will also determine the mean change in RNFL in both eyes and other ophthalmological parameters. Another study is investigating the correlation between cognition and RNFL thickness determined by OCT in a group of 20 patients with MS who are receiving either natalizumab or an active comparator.[53] These small studies may provide additional evidence justifying the use of OCT as a lower-cost alternative for monitoring MS patients in both clinical trials and clinical practice.

## Future Perspectives

Data from longitudinal and multicentre studies comparing OCT scans in patients with different MS subtypes and treatment regimens are limited. In addition, correlations of up-to-date OCT measurements with MRI and other clinical tests (physical evaluations, cognitive tests) have been mostly obtained in small patient populations assessed during short follow-up periods and correlated with single parameters.[54] There is consequently a need for more extensive studies that demonstrate the value of OCT in MS in larger populations than used to date. Future perspectives should therefore include: prospective and long-term studies including patients with different types of MS; confirmation of the relationship between MRI markers of disease activity, including RNLF, and clinical outcomes; and assessment of RNLF thickness in response to treatment. These studies need to be performed with the more advanced OCT instruments with facilities that include a realtime eye-tracking system. ■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