Review article

Optical coherence tomography in diagnosis and monitoring multiple sclerosis

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ARTICLE INFO

Article history:
Received 3 August 2015
Accepted 17 October 2017
Available online 31 October 2017

Keywords:
Multiple sclerosis
Optical coherence tomography
Retinal nerve fiber layer
Ganglion cell layer

ABSTRACT

This paper presents application of optical coherence tomography (OCT) for diagnosis and monitoring of multiple sclerosis (MS). The peripapillary retinal nerve fibre layer thinning and the reduced total macular volume analysis are shown. With the course of the MS, the severity of these abnormalities increases which reflects the progressive degeneration of retinal ganglion cells and nerve fibres. The OCT parameters are sensitive, non-invasive indicators useful in assessing the progression of inflammation and neurodegeneration in MS.

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1. Introduction

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disorder of the central nervous system (CNS). The disease involves the presence of demyelinating lesions and axonal loss associated with the demise of oligodendrocytes and astrogliotic proliferation, as well as neurodegeneration. As a result, multifocal CNS damage occurs disseminated in space and time, leading to severe neurological deficits and disability. Although both inflammation and neurodegeneration play a role in MS, the dynamics of the two processes differs. In the early stages of the disease the inflammatory processes predominate. With disease progression, they slow down whereas the axonal degeneration, which is the main cause of MS-related disability, accelerates [1–3]. Neurological symptoms of MS are not pathognomonic for the final diagnosis. The main diagnostics criteria include the confirmed multifocal lesions and the onset of individual symptoms at different points in time and space [4]. The presentation of cerebrospinal fluid oligoclonal bands, abnormal evoked potential and multifocal lesions in magnetic resonance imaging (MRI) enabled faster diagnosis [4,5].

The interdependence between focal inflammation, diffuse inflammation, and neurodegeneration as well as their relative contribution to clinical deficits remains ambiguous [6]. As the damage of oligodendrocytes would lead to the pathology of MS, its elimination is favourable for preventing axonal degeneration [7,8].

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https://doi.org/10.1016/j.pjnns.2017.10.009
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Optical coherence tomography (OCT) is a non-invasive tool used in MS as a potential marker of axonal retinal degeneration. Retinal nerve fibre layer (RNFL) thickness and total macular volume (TMV) are the most frequently investigated OCT parameters.

2. Retina and the optic nerve

The retina is a unique structure in a human visual system. It is developmentally related to the cerebrum, as it differentiates from the two layers of the optic cup, which is the prominence of the neural tube. Hence, considering the retina is a part of the CNS, it can be divided into two integral parts: the first, neuroepidermal one, which includes rods and cones forming the first neuron; and the second, cerebral one, which includes bipolar and ganglion cells forming the second and third neuron of the optic tract. The axial extensions of ganglion cells form the nerve fibre layer, stretching to the optic disc, where they leave the eye as an optic nerve consisting of 1.0–1.2 million of non-myelinated axons of retinal ganglion cells. It enters the orbit through the scleral lamina cribrosa, where the myelin sheaths of the nerve fibres originate. Histologically, the optic nerve, which contains axons of ganglion cells, astrocytes, oligodendrocytes and microglia, shows higher resemblance of the white matter of the brain rather than of the peripheral nerve [9]. The RNFL contains only the axons of ganglion cells and glia, without the myelin sheath, which contributes to its uniqueness. Hence, the RNFL thickness measurement detects the actual axonal injury and the results remain unaffected by the presence and thickness of the myelin sheath. That is why the RNFL may be the location of choice for the monitoring and assessment of neurodegeneration.

Axonal and neuronal damage are widely accepted as key events in the disease course of MS. In clinical practice, patients presenting with first clinical event that is highly indicative of MS are often diagnosed with clinically isolated syndrome (CIS). Oberwahrenbrock et al. shows that retinal neurodegeneration is already detectable in CIS patients and is dependent but importantly also independent of clinical relapses i.e. optic neuritis (ON). The present study is the first to investigate intraretinal layer changes or detect retinal neurodegeneration independent from ON in a larger cohort of CIS patients. Azevedo et al. indicates that the thalamus may be a location of early neurodegeneration in MS. Their data identified the presence of thalamic atrophy in radiologically isolated syndrome (RIS), which is highly indicative of early CNS demyelinating disease and should be investigated as a metric associated with neurodegeneration [10].

The post-mortem analyses report retinal pathology in MS beyond damage to the RNFL and the ganglion cell layer (GCL). They indicate that retinal pathology might not only develop as a consequence of inflammatory attack to the anterior optic pathway causing retrograde axonal and neuronal degeneration with RNFL thinning and retinal GCL, but retina itself may be a primary target of degenerative or inflammatory processes. Thus, OCT is increasingly being utilised as a marker of axonal loss in MS treatments trials [11].

3. Optical coherence tomography: biophysical basis of diagnostic imaging

The OCT is the method, which enables the imaging of axonal loss and injury to the retinal ganglion cells. It is a modern technique for tissue cross-sectional imaging first described in 1991 by Huang et al. from the Fujimoto Laboratory at the Massachusetts Institute of Technology, USA [12]. The subsequent development was rapid and spectacular — the first in vivo human cross-sectional retinal measurements were taken in 1993 at the University of Vienna, and in 1996, the Carl Zeiss Meditec company presented the first commercially available time-domain OCT (TdOCT). Then, the Institute of Physics at the Nicolaus Copernicus University, Poland entered the stage. Here, the first spectral domain optical coherence tomography (SOCT) for the in vivo retinal imaging was developed in 1999. In 2002, the first in vivo tomograms of the human eye were obtained by the same researchers [13,14]. OCT is basically similar to the ultrasonography examination. The difference, however, lies in using the light waves (instead of the sound wave) for tissue penetration. Like in ultrasound, the wave return time is measured, after it has been reflected and scattered throughout the imaged tissue. As the scanning beam velocity is very high (the light wave velocity is approx. 300,000 km/s, as compared to the velocity of the sound in water of 1500 m/s), a direct measurement of the wave return time is virtually impossible. Instead, wave interference is utilised for these measurements. OCT can be classified according to the measurement method into the originally developed TdOCT, and a newer SOCT. In TdOCT, the reference mirror is movable. By changing its distance from the photodetector it is possible to compare the light beam reflected by the mirror to the light beam returning from the eye. It enables a precise assessment of distances and a thickness of individual tissue structures. In SOCT, a movable reference mirror is absent and the diffractive grid is introduced and a light beam measurement is taken differently, utilising the Fourier transform [15]. As a result, the SOCT images yield much higher resolution, and the acquisition time of a single 1024-point line (a single A-scan) is only 19 microseconds, being 250-fold shorter as compared to TdOCT.

4. TdOCT ver. SOCT in retinal evaluation

TdOCT is a method, which enables acquisition of lower resolution retinal tomograms, as compared to the SOCT, with the relatively longer procedure duration. The axial resolution of TdOCT devices used in ophthalmology is approx. 10 μm with the transverse resolution of 20 μm (Fig. 1), whereas the axial resolution of SOCT Copernicus HR (Optopol, Poland) is 3 μm with the transverse resolution ranging from 12 to 18 μm (Fig. 2.). The number of A-scans per second obtained using TdOCT is usually up to 500, whereas Copernicus HR acquires 52,000 A-scans per second [16]. Owing to the high resolution of SOCT, as well as a short examination time, which implies elimination of the eye movement-related artefacts, it is possible to obtain the high quality scans which enable the precise morphological assessment of the analysed tissue and
The first measurements of RNFL thickness using the TdOCT were taken as a single peripapillary scan along a ring with a diameter of 3.4 mm. Due to low precision of measurements and the low reproducibility of the results, triple circular scans of the same size were introduced in 2002. The final outcome of the examination was the mean of the three measurements. Since the SOCT launch, the entire optic disc and the peripapillary area is scanned and after the automated centration, the acquired images are precisely analysed. This imaging and result processing technique significantly increased the reliability and reproducibility of the test, which contributed to the common use of SOCT in all conditions involving nerve fibre loss. Due to the possibility of optic disc analysis and a precise RNFL measurement, SOCT is particularly useful in diagnosis and monitoring of optic nerve diseases. It is utilised in glaucoma, MS and other diseases causing optic nerve damage, including ischaemia, post-traumatic injuries, brain tumours, Alzheimer and Parkinson disease. The innovative spectral domain imaging is superior to the conventional technique with respect to data acquisition speed, resolution and reproducibility. Bock et al. compared of the two techniques in 55 MS patients. The result from the two devices is not interchangeable [17].

5. TdOCT and SOCT in RNFL evaluation in MS

The first report on evaluating the RNFL in patients with MS using the TdOCT was published in 1999. Parisi et al. [18] examined 14 patients diagnosed with MS, with the history of previous retrobulbar ON and 14 healthy subjects. The RNFL was assessed in MS patients both in eyes with the history of previous retrobulbar ON and in eyes without previous ON episodes. The mean RNFL thinning in eyes with the history of ON as compared to the control group and as compared to the patients with MS without the history of ON was 46% and 28%, respectively. At the same time, the RNFL thickness in these patients was lower by 26%, as compared to the same measurements in healthy controls. Trip et al. found in their studies that the RNFL thinning in eyes with the history of ON can be attributed to the axonal loss in an optic nerve [19,20]. Other authors confirmed the peripapillary RNFL thinning in eyes with the history of ON as compared to both healthy individuals and MS patients without the history of ON [21–24]. Different publications report also the RNFL thinning in patients with MS who did not have previous retrobulbar ON [21,25]. Our results also show that during the natural course of MS statistically significant RNFL reduction occurs both in eyes.
with and without the history of previous ON (Fig. 3). Fig. 3 presents the SOCT report showing the mean peripapillary RNFL thickness (TSNIT), the RNFL thickness in individual sectors (expressed both as numbers and on the graph with the indicated normative values), and the optic disc parameters. The noticeable abnormalities include the decreased TSNIT graph and the RNFL thinning in particular sectors of the right eye with the history of ON and the decreased TSNIT in the left eye. The mean RNFL thinning in case with and without the history of ON was 23.3% and 9.5%, respectively [26].

In one of their first reports, Reich et al. observed a correlation between the optic radiation damage shown in MRI and RNFL atrophy in the respective eye [27]. The authors claim that it is the evidence of a secondary, trans-synaptic damage to the ganglion cell axons and the peripapillary RNFL thinning due to the degenerative process, which involves the optic tract even in eyes without clinical episodes of ON. In another study, Gordon-Lipkin et al. examined 40 patients diagnosed with MS and found an association between the MRI-confirmed cerebral atrophy and the peripapillary RNFL atrophy [28]. The authors suggested, that the RNFL thickness assessment using OCT enables obtaining reliable information regarding the neurodegenerative brain lesions, which develop in MS. These results correspond with the findings of other investigators, who confirmed that the peripapillary RNFL atrophy occurs both in eyes after previous ON and in eyes of patients with MS with no history of ON and that it correlates with the MRI-confirmed brain atrophy [20,24,25,29–33]. However, in MS, data on the relation of OCT measures and grey and white matter volumes are contradictory. Young et al. suggests that in early MS, OCT measures of retinal atrophy are related to volumetric changes in the white but not grey matter compartment as assessed by MRI [34]. Dorr et al. in large prospective study on 104 relapsing-remitting MS (RRMS)

![Porównywanie 2010-04-12](image)

**Fig. 3** – SOCT Copernicus HR: analysis of peripapillary RNFL thickness in a patient with previous retrobulbar optic neuritis in the right eye.
patients evaluated the associations of RNFL thickness and TMV with brain parenchymal fraction (BPF) [35]. RNFL thickness (RNFL-T) was furthermore linked to disease duration but neither to disease severity nor patients age. Contrarily BPF was rather associated with severity than disease duration and was confounded by age. TMV was not associated with any of these parameters. RNFL-T might be better parameter for monitoring axonal damage longitudinally. Gabilondo et al. evaluated the association between the damage to the anterior and posterior visual pathway as evidence of the presence of trans-synaptic degeneration in MS [36]. The voxel-based morphometry (VBM) showed that RNFL-T was specifically associated with atrophy of the visual cortex and with lesions in optic radiation of study inclusion. Patients with severe prior ON had a lower adjusted mean visual cortex volume than patients without ON. Zimmermann et al. investigated the association of white and grey matter brain volume with peripapillary RNFL and GCL in 63 patients with RRMS [37]. Both parameters – RNFL and GCL in eyes without previous ON are comparably linked to whole brain as well as white and grey matter atrophy. An event of ON interferes with this relation. Sinnecker et al. studied 75 MRI, OCT, optic radiation volume, optic radiation thickness and visually evoked potentials in 30 patients (26 RRMS and 4 CIS). The authors confirmed that both anterior visual pathway damage and optic radiation integrity loss detectable by MRI are common findings in MS patients [38]. Saidha et al. investigated dynamic changes including OCT (including automated macular segmentation), MRI (including brain structure volumetrics) in 107 MS patients biannually (median follow-up 46 months) [39]. The ganglion cell plus inner plexiform layer (GCCP) and whole-brain (as well as grey and white matter) atrophy rates were more strongly associated in progressive MS than RRMS. They support the utility of OCT for clinical monitoring in investigative trials. Scheel et al. investigated the association of RNFL thickness with white matter damage assessed by diffusion tensor imaging in MS. They demonstrated that RNFL changes indicate white matter damage exceeding the visual pathway [40]. Owing to precision and reproducibility of the peripapillary RNFL thickness measurement, SOCT offers a reliable evaluation of RNFL atrophy progression (Fig. 4). As a result, it is possible to assess both the pace of neurodegeneration and the response to treatment.

It should be emphasised that the RNFL thinning is not pathognomonic for the optic nerve atrophy secondary to MS. As confirmed by Choi et al. [41], all types of optic neuropathy – either ischaemic, toxic, post-traumatic or inflammatory unrelated to MS – are associated with the peripapillary RNFL thinning.

### 6. SOCT for macular evaluation

Another point of interest for the neuroophthalmologists studying MS is the retinal area located temporally to the optic disc.
disc referred to as the macula. It involves the central portion of the retina (diameter about 2.85 mm) and has the natural pit in the middle, which is referred to as the fovea (Fig. 5). The perifoveal area of 0.5 mm is the only part of the retina where the GCL is composed of 5–7 cell layers rather than a single cell layer, which is the case in other portions of the retina [42]. That is why it makes this region an ideal target site for assessing neurodegeneration processes.

The TMV is one of the parameters evaluated by SOCT in the perimacular area. Fig. 6 shows the TMV, as well as retinal thickness and volume in individual measurement sectors (expressed both as numbers and on the graph). The noticeable abnormalities involve a significant TMV decrease and retinal thinning in the peripheral measurement rings of the right eye with the history of previous ON. The first reports on TMV were published in 2005. Trip et al. examined 25 patients with the history of ON followed by an incomplete visual recovery. They found that the TMV was statistically significantly lower in eyes with the history of ON, as compared to the eyes without previous ON or controls [20]. Our results also indicate that MS causes TMV reduction, which is the largest in eyes with the history of previous ON. However, this decrease is also present and remains statistically significant even in eyes without previous ON [26]. These results correspond with the findings of other investigators, who confirmed that the TMV reduction occurs both in eyes after previous ON and in eyes of patients with MS but without a history of ON [25,27,30,32,43]. The highly heterogeneous disease course in MS may be explained by diverse pathologi-cal processes, such as the amounts of de- and remyelination but also the degree of axonal and neuronal damage. Some previous studies have compared the RNFL thickness and TMV between the different MS disease types. More recent studies reported the most severe atrophy of the RNFL and GCC in secondary progressive MS (SPMS) rather than in primary progressive MS (PPMS) [44–46]. Saidha et al. identified a unique subset of patients with MS in whom there appears to be disproportionate thinning of the inner and outer nuclear layers which may be occurring as a primary process independent of optic nerve pathology [47]. Patients with greater inner and outer pathology appear to have a predilection towards a more accelerated rate of disability progression. Brandt et al. analysed their datasets from a large cohort of 370 patients with MS (262 RRMS, 61 SPMS, 36 PPMS and 11 CIS) and 71 healthy controls, investigated with a latest generation SOCT system (Spectralis OCT, Heidelberg Engineering, Germany) at three large academic MS centres in Germany [48]. They examined whether the proposed macular thinning predominant phenotype and its frequency were also observed in their cohort. Interestingly only 6/17 (35.3%) of patients with PPMS fulfilled the macular thinning predominant criteria, in contrast to Saidha et al., who did not find the macular thinning predominant phenotype among their PPMS cohort. This results do not support the conclusion of a distinct macular thinning predominant OCT phenotype in MS. Patients displaying the macular thinning predominant phenotype when measured with Cirrus OCT (Carl Zeiss Meditec, Germany), could be re-evaluated with Spectralis OCT to determine whether differences in instruments and scanning methodologies might be of importance. Balk et al. confirmed that thinning of the inner retinal layers (RNFL, GCC and inner nuclear layer) is significantly influenced by the heterogeneous disease course in MS [49]. Oberwahrenbrock et al. pointed out the effect size of the association of disease duration and RNFL thickness or TMV in MS-NON (no optic neuritis) eyes only. They showed the strongest and highly significant changes for RNFL thickness and TMV (for SPMS not significant correlation in TMV change). However, correlation of RNFL and TMV with disease duration were not significant for PPMS-NON eyes [46]. Considering the specific histology of the retina in the perimacular area, an assumption that the changes in retinal thickness and TMV reflect not only the retinal nerve fibre loss but also ganglion cell loss, appears reasonable. Some authors claim that the TMV reduction shows that the primary damage in MS involves the retinal ganglion cells and is later followed by the nerve fibre damage (axons). Owing to further development of SOCT, the research is being conducted into potential segmentation of retinal layers in the perifoveal area and the possibility to assess the macular ganglion cell complex (GCC) composed of ganglion cells and the inner plexiform layer (GCIP) (Fig. 7). Walter et al. [50] observed a statistically significant GCC thinning in MS patients as compared to the controls, which correlated with their visual acuity and the subjectively assessed quality of life. Syc et al. [51] showed that the GCC atrophy commonly found in patients with MS and NMO (neuromyelitis optica) was also present in individuals without the history of ON. This appears to confirm the hypothesis that the degenerative process in these diseases causes both axonal and neuronal injury within the retina, regardless of previous ON, which may only lead to the deterioration of pre-existing pathology. Another essential finding from this study was the absence of oedema during the retrobulbar ON within the ganglion cell and inner plexiform layers. The oedema usually develops within the RNFL in acute stage of ON and significantly limits the neurodegeneration assessment based on the peripapillary RNFL thickness measurement. However, the assessment of the GCC thickness is not subject to this limitation. Hence, it is superior to RNFL.

![Fig. 5 – Fundus colour photograph showing the optic disc and the macula (encircled area) with the centrally located fovea.](image-url)
Fig. 6 – Total macular volume (TMV) obtained by SOCT Copernicus HR in a patient with a history of ON of the right eye 2 years earlier.

Fig. 7 – SOCT Copernicus HR: cross-sectional image of the macula with the marked ganglion cell layer and the inner plexiform layer which form the ganglion cell complex (GCC).
thickness measurement in assessing retinal neurodegeneration. Schneider et al. investigated retinal changes in eyes of NMO spectrum disorders patients and compared them to matched RMS patients and healthy controls [52]. RNFL thickness was more severely reduced in NMO compared to MS following ON. In MS-ON eyes, RNFL thinning showed a clear temporal preponderance, whereas in NMO-ON eyes RNFL was more evenly reduced. The inner nuclear layer and the outer retinal layers were thicker in NMO-ON patients compared to NMO without ON, while these differences were primarily driven by microcystic macular oedema (MNO). However, OCT is still insufficient to help with the clinically relevant differentiation of both conditions in an individual patient. Numerous studies showed that ON in NMO typically results in more severe RNFL and GCL thinning and more frequent development of MMO than in MS [53]. RNFL thinning also occurs in the absence of ON in MS, subclinical damage seems to be rare in NMO. OCT might be useful in differentiating NMO from MS. Ratchford et al. showed a significant GCC thinning in patients with early, active MS. They suggest that the MS-related retinal lesions reflect the severity of neurodegeneration within the CNS [44]. The current studies also show that thinning of the RNFL and other retinal layers shown in SOCT correlate with the brain volume changes secondary to MS, observed in brain MRI [54]. Therefore, they can be a sensitive marker of progression for the assessment of neurodegeneration in patients with MS. However, the SOCT showed not only retinal layers atrophy but also other abnormalities in patients with SM. Gelfand et al. [55] observed MNO in about 5% of patients with MS (unrelated to MS-induced uveitis). Tiny pseudocystic lesions were located within the inner nuclear layer that is composed of bipolar, amacrine, horizontal and Muller cells, mainly in patients with the history of ON. The presence of MNO may be indicative of the inflammatory and degenerative type of demyelination in patients with MS. They were associated with greater disease severity and decreased visual acuity. According to Saidha et al. the increased thickness of the inner nuclear layer and the presence of MNO observed in SOCT correlate with the activity and relapses of MS, the onset of enhancing Gd+ focal lesions in MRI as well as disability progression [56]. The recent discovery that antibodies to myelin oligodendrocyte glycoprotein (MOG) are detected in some NMO IgG-seronegative patients manifesting clinical and neuroimaging signs of NMO or NMO spectrum disorders (NMOSD) represents a variant of opticospinal MS or acute disseminated encephalomyelitis. This poses the question whether the MOG-IgG positive, AQP4-seronegative phenotype patients should be classified as NMOSD? [57] Ramathan et al. confirmed the presence of MOG antibodies in 9/23 AQP4 antibody negative patients with NMO/NMOSD, compared to 1/17 patients with MS and 0/52 controls. MOG-antibody-positive patients had prominent optic disc swelling and were more likely to have a rapid response to steroid therapy and relapse on steroid cessation than MOG antibody-negative patients. MOG antibodies have a strong association with bilateral and/or recurrent ON [58]. Chalmoukou et al. confirmed that anti-MOG antibodies are frequently associated with recurrent forms of ON or chronic relapsing inflammatory ON [59].

7. Conclusions

The SOCT studies show, that regardless of previous retrobulbar ON, each case of MS involves the peripapillary RNFL thinning, accompanied by the reduced TMV. With the course of the disease, the severity of these abnormalities increases, which reflects the progressive degeneration of retinal ganglion cells and nerve fibres. The changes of the abovementioned parameters can be a sensitive, non-invasive indicator useful in assessing the progression of inflammation and degeneration in MS, being the additional marker for treatment monitoring, which is currently used in patients with relapsing-remitting MS treated with disease modifying drugs.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

References


