Use of Optical Coherence Tomography to Monitor Multiple Sclerosis. A Review

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Summary. Multiple sclerosis is a lifelong autoimmune neurodegenerative central nervous system disease that often affects afferent visual system, resulting in optic neuritis. Although multiple sclerosis belongs to a group of demyelinating diseases, axonal damage is demonstrated in few postmortem studies, besides, axonal loss correlates with clinical disability and appears even in early stages of multiple sclerosis. Retina is the only place in human body where axonal tissue can be examined directly and retinal nerve fiber layer quantification with optical coherence tomography is a potential tool for evaluation of neurodegenerative process. In this review article, a deeper insight into optic nerve damage caused by multiple sclerosis and OCT will be proposed.

Keywords: multiple sclerosis, optic neuritis, optical coherence tomography.

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INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated lifelong inflammatory disease [1]. The French neurologist Jean-Martin Charcot was the first person who in 1868 documented multiple sclerosis as a separate disease [2] and since then numerous studies for a fuller examination of the disease were conducted.

Despite deep knowledge about immunological mechanisms involved, the reason of MS is still unknown, suspected causes are related to genetics and infections, environmental risks have also been proposed. MS results in a thinning or full loss of myelin and, as the disease progresses, the transsection of the axons. MS lesions most usually involve white matter regions close to the brain stem, basal ganglia and spinal cord, cerebellum, and the optic nerve.

The disease is associated with a variety of symptoms – a person with MS can suffer from almost any neurological symptom including visual problems such as optic neuritis [3, 4]. Multiple sclerosis is the most common neurological disease which leads to permanent neurological defects in young adults and around the world concern about its effective treatment has increased.

Besides, multiple sclerosis is quite unpredictable disease and that is why big attention is paid to its biological markers. Biological markers are measurable biological indicators that would help to predict a prognosis and the course of the disease. Biological markers are very useful for measurement of the treatment effectiveness and for outcome measure in clinical trials as well. Nowadays, the most popular biological markers are: clinical observation of relapses and assessment with different kind of scales, like Expanded Disability Status Scale. From imaging technique, magnetic resonance imaging (MRI) is a most helpful examination where the number of lesions, contrast enhancement, atrophies and etc. are observed.

Relatively recently a probably new biological marker, optical coherence tomography (OCT) was introduced. In this review article, a deeper insight into optic nerve damage caused by multiple sclerosis and OCT will be proposed.

OPTIC NEURITIS

The damage of optic nerve is closely associated with MS. Optic neuritis (ON) is an inflammation of one or both optic nerves resulting typically in temporary vision loss and it is more common in young adults. The optic nerve encompasses axons that come from the retina of the eye. These axons carry visual information to the primary visual nuclei, mainly relayed to the occipital cortex of the brain where it is processed into vision. Optic neuritis causes loss of vision typically due to swelling and damage of the myelin sheath casing the optic nerve. Axonal damage may also result in nerve obliteration. Main symptoms of ON are sudden complete or partial loss of vision, sudden loss of color vision, unclear vision, and pain on movement of the

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affected eye. Usually, the head of the optic nerve is examined using ophthalmoscope. Frequently, the nerve head in optic neuritis looks normal (in cases of retrobulbar optic neuritis), though it may be swollen in some cases (anterior papillitis or more widespread optic neuritis). In many cases, only one eye is affected. Vision in patients with ON is monitored by visual acuity, as well as by more sensitive methods contrast sensitivity and low-contrast letter acuity [4–6].

Optic neuritis is a sign of clinically definite multiple sclerosis (CDMS) in 15–20% of cases [7], and about 50% of patients with MS during their life experience an episode of optic neuritis. The detection of white matter lesions on brain MRI at the episode of optic neuritis is the strongest evidence for developing MS. About half of the patients with optic neuritis display white matter lesions; however, at five years follow-up, the general risk of developing MS is 30%, with or without MRI lesions. Patients without MRI lesions sometimes develop MS (16%), but to a smaller extent compared to persons with three or more lesions (51%). From the other point of view, 44% of patients without demyelinating lesions at ON episode will not have MS ten years later [8–11].

One of the largest studies in which optic neuritis is deeper investigated is optic neuritis treatment trial (ONTT). Data from the ONTT [12] collected during 15-years revealed that usually both eyes are involved. All visual fields (VF) from the affected eyes were anomalous. Also 75% of the fellow eyes were abnormal at baseline, and almost 40% were abnormal at year 15. During the acute attack and the first year of the study, the affected eyes had central diffuse VF defects that changed to more restricted nerve fiber bundle loss, including paracentral, partial arcuate, and arcuate defects. The majority of the fellow eyes in the beginning also had nerve fiber bundle defects that remained during all 15 years. So, affected and fellow eyes showed similar patterns of VF defects over time, the affected eye being more rigorously involved. As an explanation for why some patients had normal VFs, despite severe VA loss and other evidence of nerve damage was suggested redundancy of the optic nerve.

According to the ONTT in patients with 2 or more MRI white matter lesions at baseline [13], IV methylprednisolone (IVMP) considerably diminished the risk of development of MS for the first 2 years, but this positive effect was not maintained at 5 or more years [14–16]. The majority of patients developed a clinically definite multiple sclerosis (CDMS) within 5 years. The presence of a single white matter lesion on baseline MRI was the most definite predictor for conversion to CDMS. The ONTT also showed that in all patients with one or more white matter lesions on MRI, a history of ON in both eyes and mild neurological symptoms, such as sensory deficits, increased the risk of developing CDMS at 2 years. If patients had a normal brain MRI, absence of ocular pain and severe optic disc swelling, no light perception on baseline VA, no disc / peripapillary hemorrhage or retinal macular exudates, their risk of MS was low at 15 years.

OPTICAL COHERENCE TOMOGRAPHY

OCT Technique

Optical coherence tomography (OCT) is a method for acquirement and processing of an optical signal. It creates high resolution, three-dimensional images from biological tissues. OCT is an interferometric technique, usually employing near-infrared light penetrating into the scattering medium. With very wide-spectrum sources emitting over a ~100 nm wavelength range, optical coherence tomography has achieved sub-micrometer resolution. A relatively recent implementation of frequency-domain optical coherence tomography provides advantages in signal-to-noise ratio, permitting also a faster signal acquisition. Commercially available optical coherence tomography systems are employed in different applications, particularly in ophthalmology where they allow obtaining detailed images from within the retina [17, 18].

Light in an OCT system is divided into two parts. They are – a sample arm (containing the article of interest) and a reference arm (usually a mirror). The combination of reflected light from the sample arm and reference light from the reference arm forms an interference pattern. Reflectivity profile of the sample can be obtained by scanning the mirror in the reference arm (this is time domain OCT). Parts of the sample that reflect back much light will create greater interference than areas which do not. The method is capable to create images 1 to 2 mm below the surface in biological tissues. No special preparation of a biological sample is necessary, and images can be obtained without contact. They are available also through a transparent membrane. It is also important that no damage to the sample is possible as the laser output from the instrument is low and eye-safe near-infrared light is used.

In time domain OCT the path length of the reference arm is translated longitudinally in time. Interference is only achieved when the path difference lies within the coherence length of the light source.

In frequency domain OCT the broadband interference is acquired with spectrally separated detectors. The depth scan can be immediately calculated by a Fourier-transform from the acquired spectra, without movement of the reference arm [19, 20]. This feature improves imaging speed radically, while the diminished losses during a single scan improve the signal to noise proportionally to the number of detection elements.

Reproducibility of OCT

OCT is a reputable medical imaging technique. It is extensively used, to obtain high-resolution images of the retina and the anterior segment of the eye, with this method we may achieve like a biopsy of eye "in vivo". Reproducibility is an essential characteristic of longitudinal studies involving OCT techniques, including medical trials and observational studies. Earlier work by Cettomai et al. [21] demonstrated good levels of inter-rater and test–retest reliability

for OCT 3 (Stratus) measurements of RNFL thickness in MS patients and disease-free controls. A more recent investigation, however, showed that high-resolution frequency domain OCT techniques give an even better reproducibility of RNFL thickness and macular volume measurements [22] . The authors proposed that, besides to employing high-resolution frequency domain OCT technology, the exploitation of specific methods, such as the reading of algorithms and quality control, can serve to optimize the quality of OCT data [22]. Garcia-Martin and coauthors made a parallel investigation of MS patients' eyes using two different Fourier-domain instruments. They came to the decision that there are significant differences in RNFL thickness measurements between Cirrus and Spectralis despite a high correlation of measurement between the two instruments [23]. Recently first validated consensus quality control criteria for retinal OCT reading in MS were proposed [24].

Structures of eye examined with OCT

The retinal nerve fiber layer (RNFL) is formed by the expansion of the fibers of the optic nerve. As the nerve fibers pass through the *lamina cribrosa sclerae* they lose their medullary sheaths and are continued forward through the choroid and retina as cylinders. When they reach the internal surface of the retina they radiate from their point of entrance over this surface grouped in bundles and plexuses. Most of the fibers are centripetal, but some of them are centrifugal and branch in the inner plexiform and inner nuclear layers, where they end in enlarged extremities. The thickness of the RNFL decreases with age and this leads to a lower visual acuity [25]. RNFL is a sensitive structure. Some processes can cause its natural apoptosis. Damaging situations (such as inflammation, vascular illness, high intraocular pressure, changes of intraocular pressure, and hypoxia) can make some injury on RNFL.

Macula is an oval-shaped yellow spot in 5 mm diameter near the center of the retina of the human eye. It often has two or more layers of ganglion cells. As macula is yellow in color (containing xantophill carotenoids), it absorbs excess blue and ultraviolet light that enter the eye, and acts as natural sunglasses. Near its center is the fovea, a small cavity which is responsible for central, high resolution vision and contains the largest concentration of cone cells in the eye. A high density of photoreceptors with high acuity contains also another structure of macula – foveola.

USE OF OCT IN MULTIPLE SCLEROSIS

The first application of OCT technology to investigate MS was reported in 1999 [26]. In this valuable study, 14 patients with MS after recovery from ON attack were compared with 14 age-matched control individuals to compare RNFL thickness measures. The thickness of the RNFL was reduced by 46% in the affected eyes of the patients with MS versus the eyes of controls, and by 28% when affected eyes were compared with the 'fellow' eyes of the same patient. On the other hand, apparently unaffected eyes of the patients showed a 26% reduction in RNFL thickness when compared with eyes of control individuals.

Six years later, observations with OCT in 11 patients with MS and 14 patients with clinically isolated syndrome (CIS), everybody having a history of a single episode of optic neuritis were published. There was a cross-sectional analysis with follow-up lasting from 1 to 9 years after the ON event. In agreement with the previous findings of Parisi et al. [26], the investigators found a 33% reduction in RNFL thickness in the eyes of the patients when compared with the eyes of matched controls, and a 27% reduction when the affected and unaffected eyes of the same patient were compared ($p<0.001$). Trip et al. also showed that the macular volume (a reflection of retinal ganglion cell neuronal integrity) was reduced by 11% in eyes of patients with a history of ON when compared with control eyes ($p<0.001$), and by 9% in the affected *versus* the unaffected eye of the same patient ($p<0.001$). There were highly significant reductions ($p<0.001$) of RNFL thickness and macular volume in affected patient eyes compared with control eyes and clinically unaffected fellow eyes. So, it was shown that the apparently unaffected eyes of patients with MS were in fact considerably abnormal. There were significant relationships among RNFL thickness and visual acuity, visual field, color vision, and visual-evoked potential amplitude [27].

Visual function and OCT

Increasing evidence is collected showing that atrophy of axons in the retinal nerve fiber layer (RNFL), related to RNFL thickness on optical coherence tomography (OCT), is correlated to visual impairment [28, 29].

The advance of validated evaluation of visual performance has greatly facilitated the investigation for a structural indicator for neurodegeneration in MS. Balcer et al. [5] and Baier et al. [4] have employed performance on low-contrast letter acuity charts to compare retinal structure with visual function in patients with MS. Axonal and neuronal degeneration might be readily expected to occur in eyes with a history of ON, but in later studies, investigators using OCT to check RNFL thickness in mixed MS cohorts have also found that scores for low-contrast letter acuity might also reflect RNFL thinning in the eyes of MS patients who do not have a history of ON [30].

Low-contrast letter acuity scores also significantly correlated with overall average RNFL thickness in the eyes of MS patients, for every one-line change in low-contrast letter acuity score an average RNFL thickness variation of 4 m was observed.

Dasenbrock and colleagues investigated diffusion tensor imaging of the optic tracts in MS and its association with retinal thinning and visual disability. They found that optic-tract diffusion abnormalities are associated with retinal damage, suggesting that both may be related to optic-

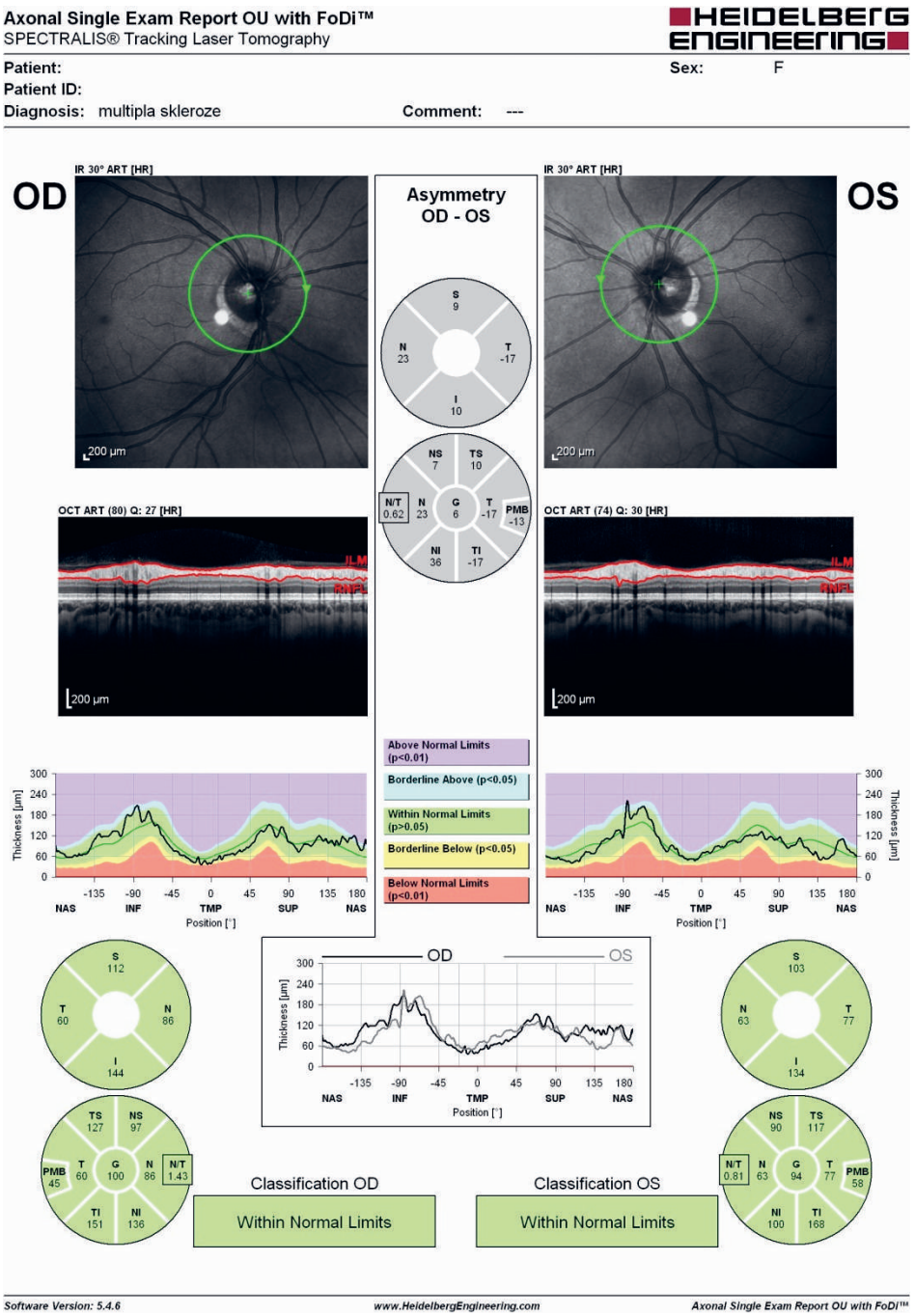

Fig. 1. **OCT report with normal RNFL thickness** (from personal archive)

nerve injury, but do not appear to contribute strongly to visual disability in MS [31]. Saidha et al. [32] provided evidence that visual dysfunction and disability in MS correlates better with OCT derived estimates of macular ganglion cell layer thickness than with usually determined peripapillary RNFL thickness.

Fragoso and co-authors were interested in sight-dependent quality of life and ophthalmic findings in a group of Brazilian patients with multiple sclerosis. The Visual Function Questionnaire (VFQ-25) was used to assess the visual quality of life. They found that VFQ-25 did not correlate with patients' ages, with disability (EDSS), disease duration or medication use. Visual acuity showed a relatively poor (<60%) correlation to VFQ-25, while no correlation could be established between visual fields, OCT and disc cupping with VFQ-25 [33].

Villoslada and others found that color vision is strongly associated with retinal thinning in multiple sclerosis. They studied the association between high-contrast visual acuity (HCVA), low-contrast visual acuity (LCVA), color vision and OCT. They discovered that MS patients have impairments in HCVA and LCVA, but that suffer from even more profound abnormalities in color discrimination. They found strong correlation between color vision and SD-OCT measures of RNFL thickness and papillomacular bundle thickness [34].

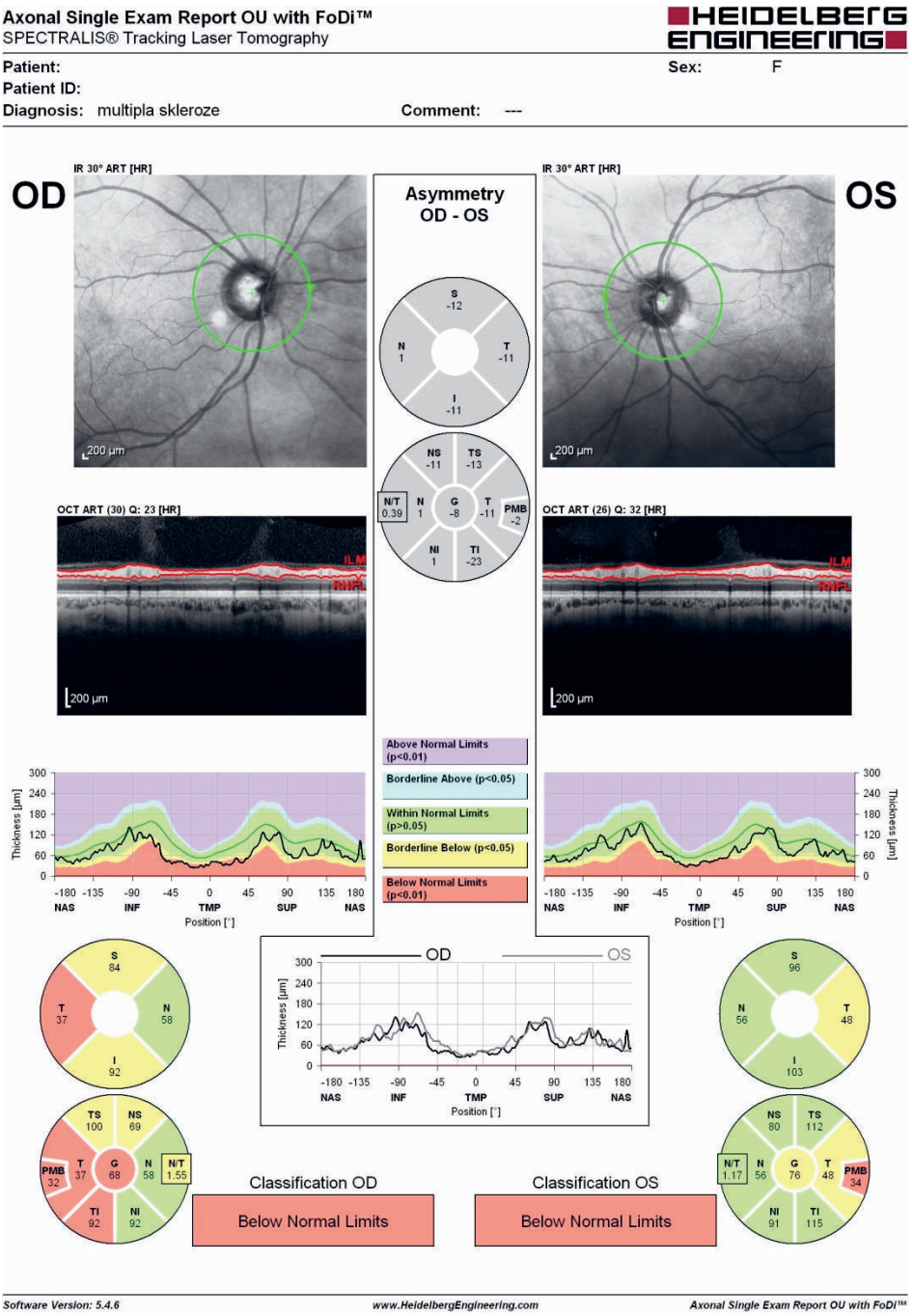

Fig. 2. **OCT scan report of multiple sclerosis patient with reduced RNFL in right eye and reduced papillomacular bundle thickness in left eye** (from personal archive)

The measurements of ETDRS VA and VF defects are correlated with the RNFL thickness values found by OCT. Trip et al. (2005) demonstrated that a loss of 1 m in RNFL forecasted a significant decrease in VA of 0.01 logMAR on the ETDRS chart and a 10% reduction in RNFL significantly correlated with a progression of VF defects and only macular volume (RGCs) significantly correlated with worsening of colour vision on Farnsworth–Munsell 100-Hue test. Decrease of thickness of superior and inferior, as opposed to nasal and temporal, RNFL quadrants was associated with deterioration of corresponding VF defects [27].

Costello et al. [28] found that VA correlated with RNFL measurements smaller than 70 m. Visual field defects may be a more responsive measure of visual function than VA in ON. In 54 ON patients, the main part of patients developed VF defects 3 to 6 months after the ON attack and were correlated with smaller than 75 m RNFL thickness. Following attack of ON 11% of patients had decreased RNFL thickness after 3 months and 85% after 6 months. RNFL thickness and macular volume also significantly correlated with VA (ETDRS), low-contrast acuity and VF mean deviation in patients with RRMS, SPMS and PPMS [35, 36]. Low-contrast letter acuity and contrast sensitivity

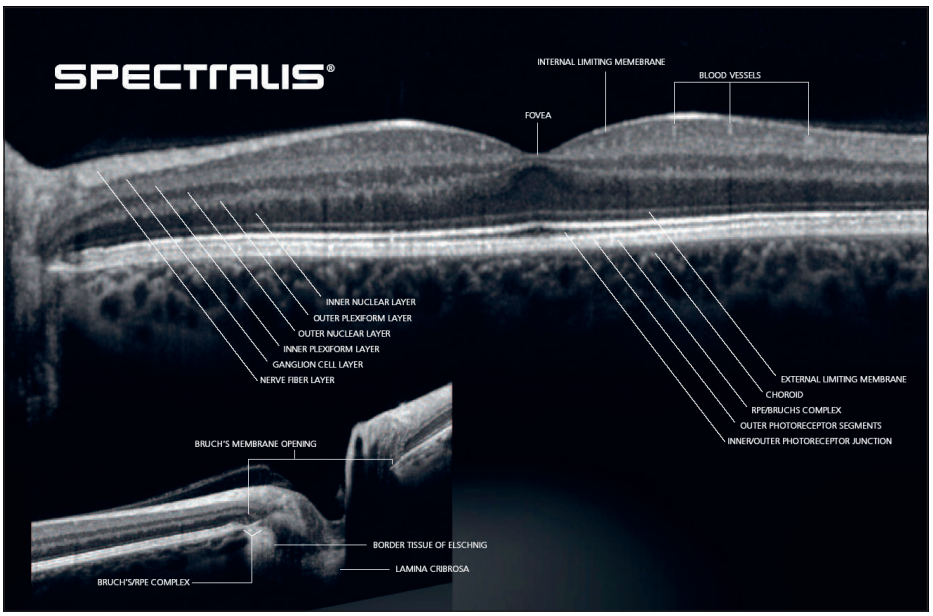

Fig. 3. **OCT picture of retinal transsection** (www.heidelbergengineering.com)

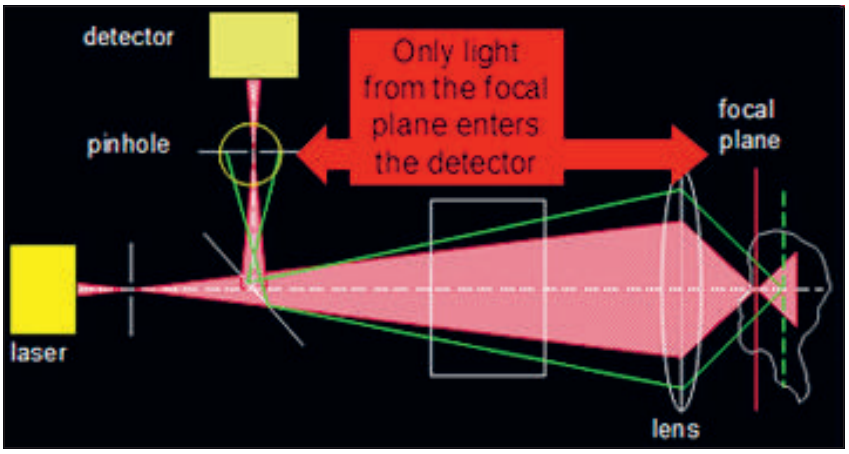

Fig. 4. **Principles of OCT technique** (www.heidelbergengineering.com)

have been shown to correlate with RNFL thickness, sustaining legitimacy for these assessments as secondary clinical effect measures for MS trials.

The nervous system of MS patient responds slower to stimulation of the optic and sensory nerves due to demyelination of them. These responses can be investigated using visual and sensory evoked potentials [37]. Retinal and visual pathway function was assessed by simultaneously recording pattern electroretinograms (PERGs) and visual evoked potentials (VEPs) using high-contrast (80%) checkerboard stimuli subtending 15 minutes and 60 minutes of the visual arc (min arc) and reversed at the rate of two reversals per second. In PERG and VEP experiments with patients' eyes there was found a significant delay in latency and reduction in amplitude. RNFL values were significantly correlated to the PERG P50 latency and P50 to N95 amplitude recorded with 15-min arc checks [26]. As a confirmation of the axonal origin of OCT metrics in the RNFL, Trip and colleagues [27] demonstrated that measures of the RNFL thickness correlated better with VEP P100 amplitudes (a measure of axonal integrity or function) than with P100 latency (normally a reflection of myelin integrity). As known, loss of myelin sheath has a direct impact on the function and protection of axons [38]. Also Wang and colleagues studied the photopic negative response of the flash electroretinogram in multiple sclerosis, including use of OCT and GDx-VCC. They concluded that photopic ERG PhNR amplitudes in MS patients were significantly reduced in eyes with and without a history of ON [39].

Correlation with EDSS and MRI

Some studies have witnessed that the RNFL thickness does correlate with brain lesions and atrophy in multiple sclerosis (MS) without ON, but does not in MS patients with ON [40, 41]. Information concerning the connection of neurological disability [Expanded Disability Status Scale (EDSS)] and RNFL thickness has been contradictory. While in the Early Treatment Diabetic Retinopathy Study (ETDRS) scores correlate with the EDSS [4] and multiple sclerosis functional composite (MSFC) scores and MRI lesion load [42], RNFL thickness does not correlate [42, 43]. An essential discovery of these investigations was that the apparently unaffected eyes of patients with MS were actually considerably abnormal when compared with the eyes of matched control persons, but were less abnormal than the eye of a MS patient with a history of ON. This finding indicates that ON causes accelerated and more severe histopathological consequences on the retina, in contrast to a more subtle and less

observable changes in persons without a history of an acute syndrome.

Pfueller and colleagues in their article described evidence that metabolic changes in the visual cortex are linked to RNFL thinning in MS. Patients with relapsing-remitting MS were subjected to RNFL thickness (RNFLT) measurement by OCT, to a routine MRI scan including the calculation of the brain parenchymal fraction (BPF), and to magnetic resonance spectroscopy, quantifying N-acetyl aspartate (NAA) concentrations in the visual cortex and normal-appearing white matter. RNFLT correlated significantly with BPF and visual cortex NAA, but not with normal-appearing white matter NAA. These results suggest a strong interrelationship between damage to the anterior and the posterior visual pathway [44].

In another study [30] average overall RNFL thickness also declined with rising degrees of overall neurological impairment and disability in the MS cohort, and it was significantly associated with the Expanded Disability Status Scale score and duration of the disease.

OCT findings as prognostic factor

In 2006, Costello and colleagues [28] described in their article that the greater part of patients with MS who have ON (about 75%) will get 10–40 m of RNFL loss within a period of only about 3–6 months following the initial inflammatory event. This finding is outstanding given that the RNFL is only about 110–120 m thick by the age of 15 years and that the majority of individuals (without a history of macular degeneration or glaucoma) will lose only about 0.017% per year in retinal thickness, which results in approximately 10–20 m over a 60-year period [45]. Costello et al. [28] also presented convincing evidence that identifies an injury threshold within the RNFL of about 75 m; thinning of the RNFL below this level led to a corresponding loss in visual function, as measured by automated perimetry.

Though MS is classically considered as a disorder involving the white matter of the CNS, recent pathologic and MRI studies of brain tissue have established that also gray matter degeneration happens in MS. Besides, the results of a postmortem analysis of 82 MS patients demonstrated retinal atrophy with shrunken neurons [46]. In patients with MS, there was a deficiency of retinal ganglion cells (RGC) in 79% of eyes and inner nuclear layer atrophy in 40% of eyes. The harshness of the retinal atrophy was significantly linked with postmortem brain weight, with a trend towards an association with disease duration. This report by Green and colleagues [46] presents the first depiction of inner nuclear layer cell loss in MS and supports a role for forthcoming OCT studies that incorporate segmentation technologies to determine the thicknesses of specific retinal layers and structures. Dörr et al. investigated association of retinal and macular damage with brain atrophy in MS, concluding that in RRMS patients with relatively short disease duration and rather mild disability RNFL and total macular volume (TMV) reflect brain atrophy and are thus promising parameters to evaluate neurodegeneration in MS. Furthermore, their data suggested that RNFL and brain parenchymal fraction (BPF) reflect different aspects of MS. Whereas BPF best reflects disease severity, RNFL might be the better parameter for monitoring axonal damage longitudinally [47]. Particularly, patients with greater brain atrophy, as measured by validated metrics (like the brain parenchymal fraction), have a more significant retinal involvement, as measured by RNFL loss [42, 48]. Consequently, the eye seems to be able to correctly model the process of neurodegeneration and could even be utilized to identify and monitor neuroprotection in MS. On the contrary, Kallenbach and co-authors tried to evaluate retinal and brain atrophy and possible associations at the earliest possible stages of MS investigating untreated patients with monosymptomatic ON. VEP latency was significantly prolonged in patients with white matter lesions compared to those without lesions. However, neither OCT measurements nor brain volume measures revealed signs of localized or generalized atrophy in patients compared with healthy volunteers. These findings suggest that atrophy does require time to evolve and indicate the complexity of the relationship between local and general structural measures [49].

Serbecic et al. investigated also MS patients in a traditional way and found no correlation between RNFL reduction and disease duration (range 9–540 months). Thus it remained unclear if RNFL analysis is an appropriate method for monitoring disease progression [50].

Correlation with different MS subtypes

When MS is segregated into its various subtypes a RNFL thickness stratification can be realized [43, 51, 52]. In particular, OCT can be used to determine the integrity of both neurons and their axonal projections within the retina. Furthermore, the rigorousness of retinal injure straightforwardly correlates with visual dysfunction, and with both the severity of MS-related brain atrophy and stratified by disease progression status MS clinical subtype designations [52]. In some studies, RNFL thickness and macular volume were significantly reduced in SPMS, but not in PPMS patients comparing with control. Thinning was greater in the temporal quadrant of the RNFL – in SPMS patients more than in PPMS patients, and even less in RRMS patients when compared with control [43, 51]. Considerable global reductions in RNFL and macular volume were detected in SPMS eyes without a history of ON, but not in PPMS eyes [43].

While prior studies have highlighted the relationship between inferior visual function and decrease in OCT-measured RNFL thickness [30] and macular volume [53] at a single time point, longitudinal studies have also established that thinning of the RNFL takes place over time in MS, even in eyes with no history of acute ON [54]. In that way this study afforded convincing proof that progressive RNFL thinning happens as a function of time in MS, even in the lack of a history of ON, and is coupled with clinically

significant visual loss. These discoveries are consistent with sub-clinical axonal loss in the anterior visual pathway in MS and support the use of OCT and low-contrast acuity as means to assess the usefulness of presumed neuroprotection procedures [54]. More recent studies show that retinal axonal loss is increasingly prominent in more advanced stages of disease, but begins early in the course of MS. Besides, RNFL thinning is nearly identical between progressive MS subtypes [55].

ARGUMENTS SUPPORTING USE OF OCT IN MS [56]

(1) Optical coherence tomography is a comparatively rapid, reproducible, noninvasive, office-based imaging examination that is less expensive than MRI and suitable to quantify atrophy of axons in eyes of MS patients. OCT of the RNFL allows direct visualization and quantification of the atrophy of unmyelinated axons in eyes with a history of ON as well [26–28]. It can be used to study the time dependant RNFL changes at various recovery stages of ON.

(2) As retinal ganglion cell (RGC) loss in the macula occurs in parallel with RNFL axonal degeneration, OCT can also quantify macular volume and RGC loss, which is related to the grey matter atrophy in MS brains. More advanced OCT techniques can also be applied to quantify macular volume and RGC loss in addition to the RNFL measures. It was supposed that preferential loss of central macular thickness in non-ON eyes might indicate primary neurodegenerative processes, such as apoptosis. To further characterize the association and timing of RGC degeneration in the inner and outer macular volumes with RNFL thinning longitudinal studies in more patients with MS are required.

(3) Optical coherence tomography can without difficulty identify sub-clinical atrophy which is difficult to notice on MRI, especially the RNFL thinning that occurs in eyes not attacked by ON before. RNFL thinning can happen also in eyes of MS patients not previously affected by ON.

(4) As OCT has a good correlation with visual function, in categories of high-contrast VA testing, low-contrast letter acuity testing and contrast sensitivity testing, it can be incorporated as a secondary clinical outcome measure for MS trials in evaluating disease-modifying therapies. Use of this method may be considered for the evaluation of visual outcomes of MS clinical trials in the future.

(5) At establishing of diagnosis, optical coherence tomography can help in discerning ON from neuromyelitis optica (NMO). Since more severe retinal damage occurs after ON in NMO than in MS, OCT has been shown to be useful in distinguishing between these two illnesses [57]. RNFL loss of >15 m after ON in a patient should suggest an NMO syndrome [58].

ARGUMENTS DENYING USE OF OCT IN MS [56]

(1) The future risk of MS cannot be foreseen by optical coherence tomography of the RNFL at ON. While OCT can predict visual recovery after ON (a lower RNFL value is correlated with impaired visual function) [28], it has not been shown to have predictive importance in the estimation of future possibility of MS. The RNFL thickness does not consistently discriminate patients at higher risk of converting to CDMS after ON. The progressive RNFL thinning in CDMS patients is most likely associated to persistent sub-clinical ON events. At the clinically isolated syndrome (CIS) stage, OCT does not notice sub-clinical RNFL thinning and does not forecast change to MS in 6 months [59]. No trustworthy indicator yet exists for alteration to CDMS, and it is still doubtful whether conversion even occurs from the CIS step.

(2) The possibilities of OCT in monitoring MS are still uncertain because RNFL thinning progression may occur linearly or nonlinearly over time in RRMS, SPMS and PPMS. Consequently, the role of OCT in evaluating disease development in each subtype of MS nowadays is still doubtful. The doubt of whether RNFL thinning happens linearly or nonlinearly will need to be clarified with higher-resolution OCT techniques in future clinical studies expanding over 2 years to observe the progression of the disease from RRMS to SPMS stages. Hopefully that future OCT techniques will provide a better resolution in clinical studies. No consensus yet has been recognized on how to obtain and analyze longitudinal OCT data in MS regardless topographic change analysis and statistical image mapping have been tried [60].

(3) It was not been shown that optical coherence tomography data definitively correlates with brain atrophy. As stated in the article by Gordon-Lipkin et al. [48], decreased brain parenchymal fraction was correlated with RNFL loss, based on an MS population in which 50% had a history of ON prior to joining to the study, and this RNFL thinning can occur following ON when no brain was investigated at the onset of MS [61]. As PPMS patients appeared to have severe ongoing RNFL thinning apart from history of ON, it remains uncertain whether or not ON calls forth the rigorousness of RNFL thinning [51]. It could be supposed that early RNFL thickness reduction could forecast faster brain atrophy, but the strict timing of RNFL thinning in relation to brain atrophy is still uncertain, as explained above.

(4) Optical coherence tomography has not been reliably correlated with more universal neurological disability records. Data regarding the relationship between neurological disability (EDSS) and RNFL thickness have been contradictory. EDSS has drawbacks in CIS and early MS as it evaluates mobility and motor functions that are not outstanding in the early stages of MS.

(5) Visual evoked potentials have been found to be more perceptive for detecting clinical and sub-clinical ON than OCT. The sensitivity of OCT measuring RNFL after

ON was 60%, diminishing further with mild inception and good recuperation. Sensitivity of visual evoked potentials was better at 81%. Visual evoked potentials identified 75% of sub-clinically affected eyes while OCT identified less than 20% [62].

CONCLUSION

Information from many studies have shown that anomalous retinal architecture assessed with OCT can be used as a noninvasive method to monitor the course of disease in patients with MS and to detect and monitor the efficiency of new therapies targeting mechanisms that might support neuroprotective effects on retinal axons and ganglion cell neurons. Hopefully, progress in OCT development and reliable quality control criteria may facilitate studying of the relationship between atrophy of retina or optic nerve and brain atrophy in different MS stages and subtypes.

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IŠSĖTINĖS SKLEROZĖS EIGOS MONITORAVIMAS PANAUDOJANT OPTINĖS KOHERENCIJOS TOMOGRAFIJĄ. APŽVALGA

Santrauka

Išsėtinė sklerozė yra lėtinė neišgydoma autoimuninė ir neurodegeneracinė centrinės nervų sistemos liga, kuri dažnai pažeidžia aferentinę regos sistemą, sukeldama regos nervo uždegimą. Nors išsėtinė sklerozė priklauso demielinizuojančių ligų grupei, aksonų degeneracija pasireiškia jau ankstyvose ligos stadijose, yra įrodyta patomorfologiniais tyrimais ir gerai koreliuoja su bendros negalios rodikliais. Tinklainė yra vienintelė žmogaus kūno struktūra, kurioje aksonų būklė gali būti tiriama juos tiesiogiai vizualizuojant ir vertinant kiekybiškai. Optinės koherencijos tomografijos erdvinė skiriamoji geba yra nepalyginamai didesnė nei magnetinio rezonanso tomografijos, todėl optinės koherencijos tomografijos panaudojimas aksonų būklei įvertinti potencialiai yra labai vertingas metodas neurodegeneraciniam išsėtinės sklerozės aspektui tirti. Šiame apžvalginiame straipsnyje bandoma giliau pažvelgti į regos nervo patologiją, sukeltą išsėtinės sklerozės, ir optinės koherencijos tomografijos panaudojimą šiai patologijai vertinti.

Raktažodžiai: išsėtinė sklerozė, regos nervo neuritas, optinės koherencijos tomografija.