• Original Article •

OCT as a monitoring tool for assessment of the stage and severity of multiple sclerosis

Yoav Yechezkel Pikkel[1], Muneer Abu Sneina[2], Vadim Igal[3], Yael Sara Pikkel Igal[3], Adi Nov-Sharabi[4,5], Ayelet Armon-Omer[4], Radi Shahien[2,6], Joseph Pikkel[6,7]

[1]Carmel Medical Center, Haifa 3436212, Israel
[2]Department of Neurology, Ziv Medical Center, Safed 13100, Israel
[3]Bar Ilan University, Safed 13100, Israel
[4]Tel-Hai Academic College 1220800, Israel.
[5]Research Wing, Ziv Medical Center, Safed 13100, Israel
[6]Faculty of Medicine, Bar Ilan University, Safed 13100, Israel
[7]Ophthalmology Department, Ziv Medical Center, Safed 13100, Israel
Correspondence to: Yoav Yechezkel Pikkel. Carmel Medical Center, Haifa 3436212, Israel. yoav.pikkel@mail.huji.ac.il
Received: 2017-09-21 Accepted: 2018-05-29

Abstract

• AIM: To identify a link between optical coherence tomography (OCT), length of multiple sclerosis (MS) and the expanded disability status scale (EDSS).

• METHODS: In a prospective double blind study, 29 patients with a diagnosis of MS were compared with 29 healthy patients, matched by age and sex. All participants underwent an OCT study and neurological EDSS test on the same day.

• RESULTS: The mean EDSS score was 3.2 in the MS group *vs* 0.03 in the control group, and the duration of MS is 11.7y. The mean retinal nerve fiber layer (RNFL) thickness was significantly thinner in those with MS (*P*<0.001). Correlation was found between duration of MS and RNFL thinning. EDSS and thinning of RNFL showed a tendency to correlate but without statistical significance.

• CONCLUSIONS: RNFL is thinner in MS patients than in the general population. MS duration has a direct statistically significant effect on RNFL thickness. There seems to be a tendency of a relationship between RNFL thinning and EDSS. OCT is suggested as a monitoring and evaluation tool of MS patients.

• KEYWORDS: multiple sclerosis; retinal nerve fibrous layer; optical coherence tomography; expanded disability status scale

DOI:10.18240/ier.2020.03.08

Citation: Pikkel YY, Abu Sneina M, Igal V, Pikkel-Igal YS, Nov-Sharabi A, Armon-Omer A, Shahien R, Pikkel J. OCT as a monitoring tool for assessment of the stage and severity of multiple sclerosis. *Int Eye Res* 2020;1(3):179-182

INTRODUCTION

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS). The disease manifests itself as a reaction against certain parts in the CNS, and eventually causes de-myelination and axonal damage[1]. Changes in brain tissue cause neurological deficits. A common manifestation of MS is acute phase accompanied by degenerative changes. In the acute phase, many gray matter components and white matter are damaged. MS damages all brain components and unmyelinated nerve tissue[2-5].

There are two common tools to monitor and assess the development of the disease and its stages-magnetic resonance imaging (MRI) and expanded disability status scale (EDSS). MRI is the main imaging study and is used to assess the magnitude and location of the inflammatory response[6]. EDSS is the main clinical scale, and enables the clinician to assess patients' condition and disease stage[7]. EDSS assess the clinical function of 8 different systems, *i.e.* pyramidal, cerebellar, cerebral, brainstem, gastrointestinal & urinary, sensory, visual, and other systems. A higher score implies a more damaged condition[8].

Major discrepancies exist between MRI studies and clinical condition. Due to the sporadic nature of inflammatory lesions, many have no clinical or functional significance. On the one hand, a patient may function well and be without a clinically detrimental condition in the midst of an acute inflammatory state. On the other hand, a small lesion may cause a major deficit. Thus, the contribution of MRI to clinical assessment is partial at most[9]. MRI equipment is also expensive and is not available in all neurological departments.

A major disadvantage of EDSS is the lack of correlation of the clinical condition with imaging studies or laboratory workup. Thus, patient evaluation does not reflect the progress of MS at the histological and molecular level. At present, there is no effective and reliable tool to diagnose and evaluate the stage of MS that will correlate with EDSS.

Optical coherence tomography (OCT) is a non-invasive imaging study based on interferometry and infra-red spectrum light dispense. It produces 3-dimensional multi-layer high resolution images of biological tissue. The main application of OCT is the imaging of the retina and its layers[10]. OCT imaging can produce a retinal image with a resolution of less than 10 micrometer. Retinal nerve fibrous layer (RNFL) is composed of nerve cells that create the optic nerve (CN2). Good imaging of RNFL can be attained with OCT, without the need of X-ray radiation or an invasive procedure. It is a short, inexpensive, and effective imaging study.

Neural degeneration in the anterior pathway of CN2, manifested as optical damage, is one of the most common aspects of MS. About half (30%-70%) of patients have an acute optic neuritis (ON) event during their course of illness. Post-mortem investigations found CN2 sedimentations to correlate with MS in 90%-94% of patients[10]. RNFL thickness is 110-120 micrometers in naïve patients. Studies have shown changes in RNFL thickness in up to 46% of MS patients with an ON event, compared to a control group; change in up to 28% of RNFL thickness has been shown, when comparing affected and non-affected eyes of the same patient[11]. Thus, a change in RNFL thickness does not correlate with an acute ON effect but rather with the neurodegenerative course of illness.

In this study we examined if the RNFL thickness in the optic disk (OD) and macula correlates with disease duration and clinical condition. The aim is to determine if RNFL thickness, as measured in OCT, can be used to monitor MS patients more effectively than the methods that are currently used.

SUBJECTS AND METHODS

A prospective double-blind study was designed; technician and analyst were blind to the group the patients are assigned to. The MS group was comprised of 29 patients with a diagnosis of MS. The control group comprised 29 consecutive healthy patients of the ophthalmology department in Ziv Medical Center, who were treated for reasons other than MS, and whose known disease does not affect RNFL, mainly cataract. All control group patients underwent an ophthalmologist examination, including Snellen chart, in order to prevent bias. In both groups there were no patients with a diagnosis of optic neuritis. Mean ages and sex distribution of the two groups is presented on Table 1.

All participants underwent an OCT study and neurological EDSS test by a neurology consultant on the same day, in order to preclude changes between imaging time and clinical evaluation. Measurements were taken 500 μm temporal to the macula and around the OD. The temporal location was decided upon randomly and 500 μm was chosen in order to not measure the macula. The thickness was measured manually using a curser, using the horizontal scan line. The technician measured the thickness 3 times and the average was recorded. Radial line protocol was chosen in order to exam if the RNFL near the disk is affected by MS and if there is a certain segment that is more affected. In order to find if there is an impact of MS on other parts of the retina, we chose a spot, temporal to the macula in order to avoid the effect of other situation like peripapillary atrophy, myopic changes *etc*. that may occur nasal to the macula. Optic disc as divided into 12 parts, marked R for right and L for left, 1-12 respectively. The OCT used was the OCT SLO (OPKO instruments/OTI-Canada) and operated by a certified technician using a radial lines protocol. Patients registered their data on the same day with the research coordinator to assure correlation between EDSS and RNFL thickness.

Table 1 Demographics of MS and control group

Parameters	Control (*n*=29)	MS (*n*=29)	*P*
Gender (Female, %)	18 (62.1)	21 (72.4)	0.401
Age (y)	52.8±7.6	42.9±13.6	0.001
Duration of illness (y)		11.7±7.4	
EDSS score (0-10)	0.03±1.9	3.2±2.0	<0.001

MS: Multiple sclerosis; EDSS: Expanded disability status scale.

Statistical significance was $P<0.05$ in a two sample *T*-test in quantitative variables or in Pearson's correlations test between different parameters. The data was analyzed using the SPSS version 20.0.0.2 (SPSS Inc. Chicago, IL, USA).

The Institutional Review Board of Ziv Medical Center approved the study. All participants signed an informed consent to participate in this study.

RESULTS

Mean EDSS score was 3.2 in MS group in comparison to 0.03 in control group, and duration of MS illness was 11.7y. Measured thickness of the temporal point in the inner part of the retina (in relation to the vitreous body), the RNFL, was significantly thinner in the MS group: 25.3 and 26.5 μm (right and left eyes, respectively), compared to the control group-95.0 and 91.2 μm ($P<0.001$). Such difference between the MS and control groups was not observed in the thickness of the outer parts of the retina (Table 2). Other parts of the retina were not measured due to the nature of MS which insults the nerve fibers.

Correlation was found between the duration of MS and RNFL thinning. Correlation between EDSS and duration of illness was found, but EDSS and thinning of RNFL showed a tendency to correlate, without statistical significance. Full results appear in Table 3.

Both left and right OD showed a statistically significant difference between the cohort and control groups. The difference was more noted in the temporal side but was statistically significant when combining all parts of OD (Table 4).

Table 2 RNFL thickness, as measured by OCT (μm) mean±SD

Parameters	Control (*n*=29)	MS (*n*=29)	*P*
OCT-right			
RNFL	95.0±25.7	25.3±3.8	<0.001
Retina[a] outer	78.8±5.9	79.5±4.7	0.625
OCT-left			
RNFL	91.2±29.5	26.5±4.3	<0.001
Retina[a] outer	77.2±8.1	79.5±4.5	0.197

MS: Multiple sclerosis; RNFL: Retinal nerve fiber layer; OCT: Optical coherence tomography. [a]Outer retina-Bruch's membrane, retinal pigmented epithelium and photoreceptors.

Table 3 Pearson's correlations between duration of illness, EDSS and RNFL

Group	Critteria	Duration of illness	EDSS score	RNFL-right
MS	Duration of illness (y)			
	EDSS (0-10)	0.528[a]		
	RNFL-right	-0.321	-0.239	
	RNFL-left	-0.663[b]	-0.275	0.616[b]
Control	RNFL-left			0.700[b]

EDSS: Expanded disability status scale; RNFL: Retinal nerve fiber layer; MS: Multiple sclerosis. [a]*P*<0.01, [b]*P*<0.001.

Table 4 Right (R) and left (L) optic disk (OD) values mean±SD

Section	MS (*n*=29)	Control (*n*=29)	*P*
R1	52.1±11.5	62.1±8.9	0.001
R2	77.6±19.9	88.0±13.4	0.022
R3	124.9±26.0	127.1±19.1	0.710
R4	130.7±25.6	119.8±23.4	0.090
R5	115.1±20.4	122.1±21.8	0.214
R6	95.7±15.9	89.6±9.6	0.084
R7	76.9±13.4	75.2±10.9	0.600
R8	83.1±13.9	75.2±8.6	0.011
R9	103.2±21.3	106.5±11.2	0.467
R10	121.1±30.0	122.7±20.1	0.806
R11	123.7±26.4	134.0±16.1	0.078
R12	74.2±21.2	97.2±31.3	0.002
L1	51.0±10.7	57.9±8.9	0.009
L2	68.9±13.5	58.9±15.6	0.000
L3	111.8±19.6	123.4±22.6	0.041
L4	118.7±29.9	118.4±22.9	0.961
L5	118.7±20.1	118.8±21.8	0.990
L6	94.9±22.5	91.2±9.9	0.420
L7	70.8±15.6	76.4±10.6	0.119
L8	76.2±17.2	75.4±9.2	0.828
L9	101.5±20.8	105.9±10.8	0.317
L10	127.8±30.4	117.0±17.3	0.102
L11	126.2±26.0	132.3±17.7	0.300
L12	70.8±14.1	83.9±27.0	0.035

MS: Multiple sclerosis.

DISCUSSION

MS is a chronic and progressive disease with several subtypes, such as relapsing-remitting, primary or secondary progressive, and benign MS. While the patients with each subtype may change in their course and natural history of the disease, they are all evaluated according to the same scales and treated by the same physicians. Such as, it is important to identify an assessment and follow-up tool for MS patients that will comply with the first rule of medicine-Primum non nocere.

A clinical scale such as EDSS is a relatively easy to apply, cost-effective and non-harmful way to examine patients and to follow-up on the clinical state of MS. EDSS validity is not questionable[12-15]. Nevertheless, as with any clinical scale, its inter- and intra-evaluator reliability is debatable, and reliability seems especially lacking in the lower range of the scale[15-16]. EDSS is also somewhat insensitive to subtle changes in patients' clinical condition[17].

RNFL is an extension of the CNS, located in a relatively accessible site. Thus, it is a likely place to examine the long-lasting effect of MS on the CNS, and also to follow-up on disease status and complications.

RNFL thickness in patients with MS was the subject of several studies, as well as a Meta-analysis[18]. RNFL gets thinner with age, and RNFL thinning is currently recognized as part of the pathophysiology of MS, and probably plays a role in the clinical deterioration of patients with MS[19]. Our cohort, in comparison to the control group, showed a statistically significant thinner RNFL, even with the control group statistically significant older. This data allowed us to proceed to the next step in our study and to seek a connection between MS duration and the clinical manifestation, as is observed in EDSS, to RNFL thickness.

Our cohort showed a pattern of increasing RNFL thinning with the duration of MS. The natural history of MS is of a continuous insult to the white and gray matter. This occurs whether the inflammation relapses without returning to the baseline condition, progresses without a remitting phase or even in the benign form of MS, in which a consistent insult takes a toll on the RNFL. Indeed, this unique RNFL behavior has been described in MS[20]. The authors do not have an explanation why the correlation is better in the left eye rather the right eye and have chosen to bring forward the data as is.

MS group showed a tendency to correlate EDSS and RNFL thickness, as measured in OCT. However, this correlation did not reach statistical significance. We suggest a number of reasons for the lack of statistical significance. First, despite the observed tendency, the correlation may be only coincidental. Second, the cohort may not have been large enough and a larger cohort would possibly support our hypothesis. Third, since MS is generally a progressive disease, EDSS may be a confounder in the correlation between MS duration and RNFL thinning.

If the correlation of RNFL thickness and EDSS can be proven, the authors believe that OCT should be strongly considered

as a follow-up and assessment tool for MS patients. It is as unharmful for patient as MRI, but much more accessible and easier to apply. OCT is an objective tool, with its sensitivity only limited by technology, and it is constantly improving. Some have claimed that OCT is better for the detection of MS than for its follow-up[21], However, the findings of the current study and the possible correlation between RNFL thickness and EDSS can be supported, the authors believe, may lead to a new and improved tool to be used by neurologists.

A limitation of this study is the small number of patients in the cohort, which may be the reason for the non-statistically significant trend observed between EDSS and RNFL thinning.

In this study we have found data supporting our hypothesis that MS patients have a thinner RNFL and that MS duration has a direct effect on RNFL thickness. The data collected is statistically significant. There seems to be a tendency of a relationship between RNFL thinning and EDSS; further investigations might show a statistically significant difference. Until such a relationship is proven beyond all doubt, the data collected here supports the hypothesis that RNFL thinning is in a close relationship to MS progression and duration. OCT is suggested as monitoring and evaluation tool of MS patients.

ACKNOWLEDGEMENTS

Conflicts of Interest: Pikkel YY, None; **Abu Sneina M,** None; **Igal V,** None; **Pikkel-Igal YS,** None; **Nov-Sharabi A,** None; **Armon-Omer A,** None; **Shahien R,** None; **Pikkel J,** None.

Peer Review File: Available at: http://ier.ijo.cn/gjykier/ch/reader/download_attache_file.aspx?seq_id=20210325152956001&flag=1&journal_id=gjykier&year_id=2020&issue=3

REFERENCES

1 Saidha S, Syc SB, Ibrahim MA, Eckstein C, Warner CV, Farrell SK, Oakley JD, Durbin MK, Meyer SA, Balcer LJ, Frohman EM, Rosenzweig JM, Newsome SD, Ratchford JN, Nguyen QD, Calabresi PA. Primary retinal pathology in multiple sclerosis as detected by optical coherence tomography. *Brain* 2011;134(2):518-533.

2 Horakova D, Kalincik T, Dusankova JB, Dolezal O. Clinical correlates of grey matter pathology in multiple sclerosis. *BMC Neurol* 2012;12:10.

3 Ruffoli R, Biagioni F, Busceti CL, Gaglione A, Ryskalin L, Gambardella S, Frati A, Fornai F. Neurons other than motor neurons in motor neuron disease. *Histol Histopathol* 2017;32(11):1115-1123.

4 de Wit NM, Vanmol J, Kamermans A, Hendriks J, de Vries HE. Inflammation at the blood-brain barrier: The role of liver X receptors. *Neurobiol Dis* 2017;107:57-65.

5 Rovira A, Auger C, Alonso J. Magnetic resonance monitoring of lesion evolution in multiple sclerosis. *Ther Adv Neurol Disord* 2013;6(5):298-310.

6 Kurtzke JF. On the origin of EDSS. *Mult Scler Relat Disord* 2015;4(2):95-103.

7 Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;33(11):1444-1452.

8 Britze J, Frederiksen JL. Optical coherence tomography in multiple sclerosis. *Eye* 2018;32(5):884-888.

9 Barkhof F. MRI in multiple sclerosis: correlation with expanded disability status scale (EDSS). *Mult Scler* 1999;5(4):283-286.

10 Talebi M, Nikanfar M, Sorkhabi R, Sharifipour E, Bahrebar M, Kiavar A, Andalib S, Khanli HM. Optic coherence tomography findings in relapsing-remitting multiple sclerosis patients of the northwest of Iran. *Iran J Neurol* 2013;12(3):81-86.

11 Khanifar AA, Parlitsis GJ, Ehrlich JR, *et al*. Retinal nerve fiber layer evaluation in multiple sclerosis with spectral domain optical coherence tomography. *Clin Ophthalmol* 2010;4:1007-1013.

12 Meyer-Moock S, Feng YS, Maeurer M, *et al*. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC Neurol* 2014;14:58.

13 Cao H, Peyrodie L, Boudet S, Cavillon F, Agnani O, Hautecoeur P, Donzé C. Expanded Disability Status Scale (EDSS) estimation in multiple sclerosis from posturographic data. *Gait Posture* 2013;37(2):242-245.

14 Bin Sawad A, Seoane-Vazquez E, Rodriguez-Monguio R, Turkistani F. Evaluation of the Expanded Disability Status Scale and the Multiple Sclerosis Functional Composite as clinical endpoints in multiple sclerosis clinical trials: quantitative meta-analyses. *Curr Med Res Opin* 2016;32(12):1969-1974.

15 Rudick RA, Polman CH, Cohen JA, *et al*. Assessing disability progression with the multiple sclerosis functional composite. *Mult Scler* 2009;15(8):984-997.

16 Rabadi MH, Vincent AS. Comparison of the Kurtkze expanded disability status scale and the functional independence measure: measures of multiple sclerosis-related disability. *Disabil Rehabil* 2013;35(22):1877-1884.

17 Goldman MD, Motl RW, Rudick RA. Possible clinical outcome measures for clinical trials in patients with multiple sclerosis. *Ther Adv Neurol Disord* 2010;3(4):229-239.

18 Petzold A, de Boer JF, Schippling S, Vermersch P, Kardon R, Green A, Calabresi PA, Polman C. Optical coherence tomography in multiple sclerosis: a systematic review and meta-analysis. *Lancet Neurol* 2010;9(9):921-932.

19 Sriram P, Wang CY, Yiannikas C, Garrick R, Barnett M, Parratt J, Graham SL, Arvind H, Klistorner A. Relationship between optical coherence tomography and electrophysiology of the visual pathway in non-optic neuritis eyes of multiple sclerosis patients. *PLoS One* 2014;9(8):e102546.

20 Kimbrough DJ, Sotirchos ES, Wilson JA, Al-Louzi O, Conger A, Conger D, Frohman TC, Saidha S, Green AJ, Frohman EM, Balcer LJ, Calabresi PA. Retinal damage and vision loss in African American multiple sclerosis patients. *Ann Neurol* 2015;77(2):228-236.

21 Balk LJ, Cruz-Herranz A, Albrecht P, Arnow S, Gelfand JM, Tewarie P, Killestein J, Uitdehaag BM, Petzold A, Green AJ. Timing of retinal neuronal and axonal loss in MS: a longitudinal OCT study. *J Neurol* 2016;263(7):1323-1331.