· 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]Department of Ophthalmology, 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

使用 OCT 评估多发性硬化症分期及其严重性

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]

(作者单位:[1]3436212 以色列,海法,Carmel 医疗中心;[2]13100 以色列,采法特,Ziv 医疗中心,神经病学科;[3]13100 以色列,采法特,Bar Ilan 大学;[4]1220800 以色列,Tel-Hai 学院;[5]13100 以色列,采法特,Ziv 医疗中心,研究部门;[6]13100 以色列,采法特,Bar Ilan 大学医学院;[7]13100 以色列,采法特,Ziv 医疗中心,眼科)
通讯作者:Yoav Yechezkel Pikkel. yoav.pikkel@mail.huji.ac.il

摘要

目的:评估光学相干层析成像(OCT)、多发性硬化病程(MS)和扩展伤残状态等级(EDSS)之间的联系。

方法:前瞻性双盲研究。29 例多发性硬化症确诊患者与 29 例正常人进行比较,年龄和性别匹配。所有受试者于同一天进行光学相干层析成像检查和神经扩展伤残状态等级测试。

结果:多发性硬化症患者平均扩展伤残状态等级指数为 3.2,健康对照组为 0.03,多发性硬化症患者病程为 11.7a。多发性硬化症患者视网膜神经纤维层(RNFL)厚度显著较薄($P<0.01$)。多发性硬化病程与视网膜神经纤维层变薄之间存在相关性。扩展伤残状态等级与视网膜神经纤维层变薄之间呈相关趋势但无统计学意义。

结论:较正常对照组,多发性硬化症患者 RNFL 较薄。多发性硬化症病程对 RNFL 厚度有直接影响。RNFL 厚度与扩展伤残状态等级之间可能存在相关性。建议使用 OCT 作为多发性硬化症患者的检测和评估工具。

关键词:多发性硬化症;视网膜神经纤维层;光学相干层析成像;扩展伤残状态等级

引用:Pikkel YY, Abu Sneina M, Igal V, Pikkel Igal YS, Nov-Sharabi A, Armon-Omer A, Shahien R, Pikkel J. 使用 OCT 评估多发性硬化症分期及其严重性. 国际眼科杂志 2018;18(12):2132-2136

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 was 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.

• CONCLUSION: 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; ocular coherence tomography; expanded disability status scale

DOI:10.3980/j.issn.1672-5123.2018.12.03

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. *Guoji Yanke Zazhi* (*Int Eye Sci*) 2018;18(12):2132-2136

INTRODUCTION

Multiplesclerosis (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.

Ocular 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 imagingof 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.

Table 1 Demographics of MS and control group

Parameters	Control (n=29)	MS (n=29)	P
Gender (F, %)	18 (62.1)	21 (72.4)	0.401
Age (y)	52.8±7.6	42.9±13.6	0.001
Duration of illness (a)	-	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.

Post-mortem investigations found CN2 sedimentations to correlate with MS in 90% - 94% of patients[10]. RNFL thickness is 110-120 micrometers in naive 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 affect of

other situation like peripapillary atrophy, myopic changes *etc*. that may occur nasal to the macula. Optic disc as devided 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.

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 weren't 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 significantwhen combining all parts of OD (Table 4).

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

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: Ocular 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 (a)			
	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.

scale[15-16]. EDSS is also somewhat insensitive to subtle changes in patients' clinical condition[17].

RNFL is an extension of the central nervous system (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.

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2018 眼科期刊学术影响力指数(CI)排名及分区

本刊讯 由中国科学文献计量评价研究中心和清华大学图书馆联合研制、《中国学术期刊(光盘版)》电子杂志社出版的 2018《中国学术期刊影响因子年报》于 2018 年 10 月 25 日在北京会议中心隆重发布。《年报》发布了反映学术期刊影响力的综合评价指标--学术期刊影响力指数,(Academic Journal Clout Index,简介 CI)。CI 是反映一组期刊中各刊影响力大小的综合指标。《年报》分区选择"影响力指数(CI)"这一综合指标为依据,对每个学科期刊按影响力指数(CI)降序排列,依次按期刊数量平均划分为 4 个区,即 Q1、Q2、Q3、Q4。Q1 区为本学科 CI 指数排名前 25% 的期刊。该指标可以更客观地反映期刊的学术影响力水平在本学科刊群中的相对位置。

2018 眼科期刊学术影响力指数(CI)排名及分区

排名	刊名	影响指数(CI)	分区
1	中华眼科杂志	834.134	Q1
2	眼科新进展	690.578	Q1
3	中华眼底病杂志	628.964	Q1
4	国际眼科杂志中文版	569.517	Q1
5	中华实验眼科杂志	523.491	Q2
6	临床眼科杂志	350.761	Q2
7	中国眼耳鼻喉杂志	324.388	Q2
8	中国中医眼科杂志	275.903	Q3
9	中华眼视光学和视觉科学杂志	233.998	Q3
10	中华眼科医学杂志(电子版)	228.396	Q3
11	眼科	196.298	Q3
12	中华眼外伤职业眼病杂志	195.573	Q3
13	中国斜视与小儿眼科杂志	169.619	Q4
14	眼科学报	150.435	Q4
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